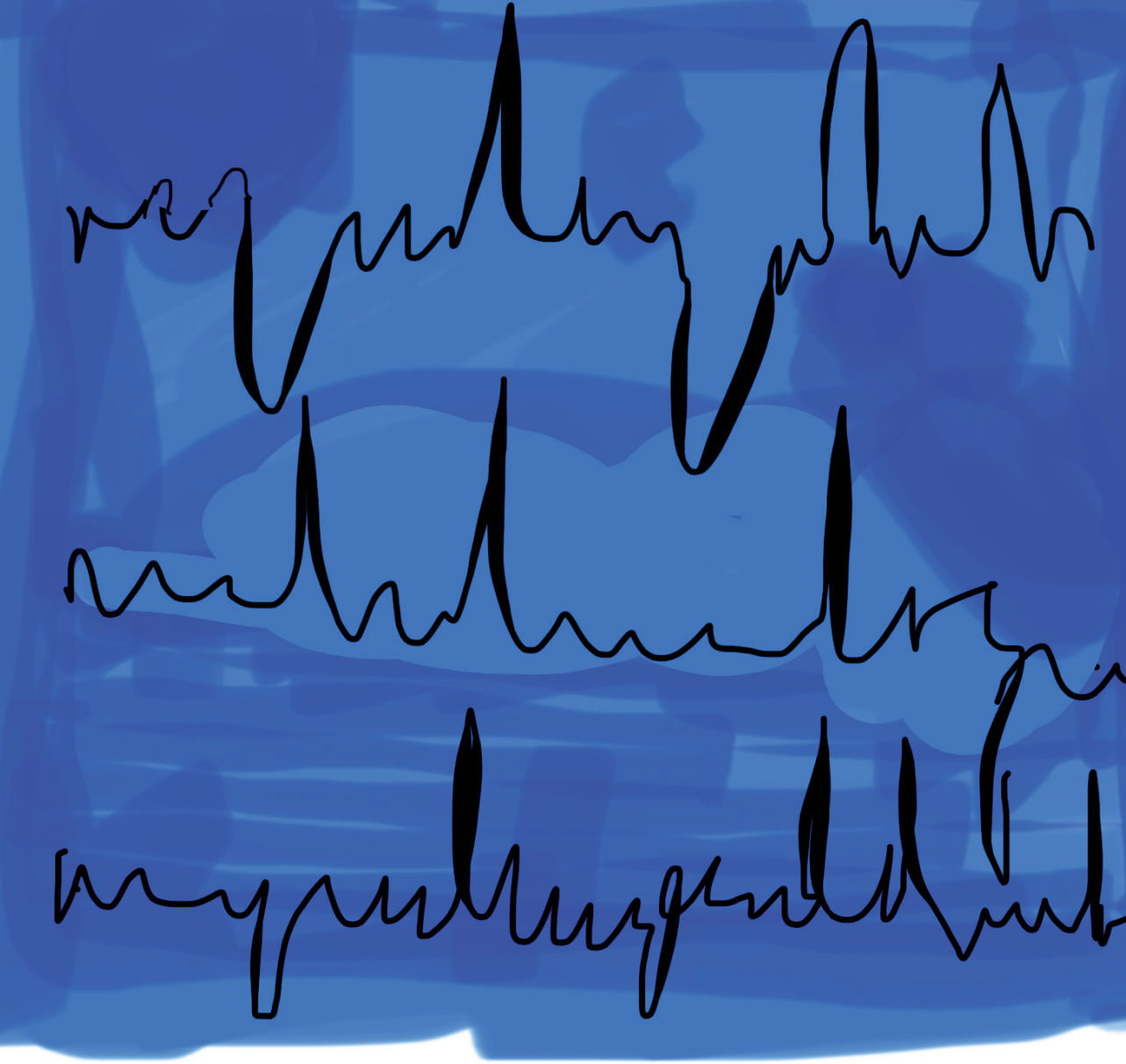
Left ventricular reconstruction in ischemic cardiomyopathy

Klein, P.



Left Ventricular Reconstruction in Ischemic Cardiomyopathy

Patrick Klein

Left Ventricular Reconstruction in Ischemic Cardiomyopathy

Patrick Klein

Layout and printing by Optima Grafische Communicatie
Cover en tekeningen door S.C.D. Klein

Left Ventricular Reconstruction in Ischemic Cardiomyopathy

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 15 december 2022
klokke 16.15 uur
door

Patrick Klein

geboren te Oegstgeest
in 1977

Promotores:	prof. dr. R.J.M. Klautz
	prof. dr. J. Braun
Co-promotor:	dr. M.J. Swaans
Thesis committee members:	prof. dr. J.W Jukema (secretary)
	prof. dr. M. Mariani
	prof. dr. W.J.M. Suyker
	prof. dr. K. Zeppenfeld

TABLE OF CONTENTS

Chapter 1

General introduction

INTRODUCTION

The major advances in medical therapy that have occurred over the past few decades have not diminished the impact of heart failure as one of the leading causes of death and disability in the developed countries of the world [ref. 1]. Mortality rates have decreased, but remain high in patients with left ventricular (LV) systolic dysfunction, even among those receiving evidence-based medical therapies. In the Framingham Study, median survival was only 1.7 years for man and 3.2 years for women, with only 25% of man and 38% of women surviving 5 years [ref. 2]. A more recent large study from the Mayo Clinic Hospitals found a survival rate of 32% at 5 years in patients admitted for decompensated heart failure with reduced ejection fraction [ref. 3]. A Dutch population-based cohort study in patients 55 years and older "The Rotterdam Study" found a cumulative survival at 2 years of 51% (95% CI 47-55%) and 35% at 5 years (95% CI 31-39%) [ref. 4]. Differences in patient selection and definitions of heart failure leading to inclusion of milder cases might be of influence in these differences in survival. The poor survival in patients with heart failure is despite a decrease in the incidence of cardiovascular disease over time. Conventional explanations include an ageing population and advances in the treatment of acute myocardial infarction [ref. 5]. Stewart and colleagues suggested that heart failure was more 'malignant' than cancer in a study of over 30,000 patients hospitalised for heart failure, myocardial infarction, or four common cancers in Scotland; with the exception of lung cancer, heart failure was associated with the worst 5-year adjusted mortality [ref. 6].

The prevalence of heart failure in the general population is 2-3% and increases with age [ref. 7]. In 2018 in the Netherlands 242.300 people were living with heart failure and 37.600 new patients were registered. In 2017 the expenditures were 816.6 million euro, of which 367 million for hospital care [ref. 8].

ISCHEMIC AND NON-ISCHEMIC HEART FAILURE

The term ischemic cardiomyopathy describes a state of left ventricular systolic dysfunction due to coronary artery disease [ref. 9]. Coronary artery disease or ischemic heart disease is thought to be the most important cause of heart failure [ref. 10-11]. In the 7 to 8 years after a myocardial infarction, more than one-third of patients will develop heart failure, particularly those with LV dysfunction noted at the time of their myocardial infarction [ref. 12]. Ischemic cardiomyopathy accounts for approximately 60% of the aetiology of the patients with heart failure [ref. 57]. In

epidemiological surveys and large-scale therapeutic trials, the prognosis of ischemic heart failure is worse then in patient with a non-ischemic aetiology. The term non-ischemic heart failure includes various subgroups such as hypertensive heart disease, myocarditis, alcoholic cardiomyopathy and cardiac dysfunction due to atrial fibrillation with rapid ventricular response. Some of these causes are reversible. Interesting, the therapeutic effect of essential drugs such as angiotensin-converting enzyme inhibitors, beta-blockers and diuretics, in general does not significantly differ between ischemic and non-ischemic heart failure [ref. 13]. In patients with ischemic heart failure and non-contracting ischemic viable myocardium, myocardial contractility may improve following revascularization. Patients with irreversible loss of myocardial tissue are recommended pharmaceutical management according to the Guideline Dericted Medical Therapies (GDMT) [ref. 7].

MYOCARDIAL INFARCTION AND CARDIAC REMODELLING

The term myocardial infarction reflects cell death of cardiac myocytes caused by ischaemia, which is the result of a perfusion imbalance between supply and demand [ref. 14]. As a result of this injury, molecular, cellular and interstitial changes occur that manifest clinically as changes in size, mass, geometry and function of the heart called remodelling [ref. 15]. The term remodelling was used for the first time in 1982 by Hockman and Buckey in a myocardial infarction model. They used this term to characterize the replacement of infarcted tissue with scar tissue. Pfeffer first described the term remodelling in the current context: as a progressive increase in left ventricular cavity in experimental model of myocardial infarction in rats [ref. 16]. Following, the term remodelling was used in scientific articles on morphological changes following acute myocardial infarction. Pfeffer and Braunwald published a review on cardiac remodelling following myocardial infarction in 1990 and the term was adopted to characterize morphological changes after infarction and in particular increase of the left ventricular volume [ref. 17]. Unfortunately, in following years the term remodelling also has been used to describe different clinical situations and pathophysiological changes. Therefore, an international forum published a consensus which defined cardiac remodelling as a group of molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart resulting from cardiac injury [ref. 18]. The forum also recognised two types of cardiac remodelling: physiological (adaptive) remodelling and pathological remodelling.

Remodelling of the LV following myocardial infarction has been divided into stages [ref. 19]. Following interruption of arterial perfusion from occlusion of a coronary vessel, death of cardiac myocytes immediately ensues. In the next stage of infarct healing, dying cardiac myocytes release intracellular proteins into the circulation and trigger an inflammatory response. Inflammatory cells, including neutrophils, monocytes, macrophages, and lymphocytes, infiltrate the tissue. These immune cells remove dead myocytes and pave the way for healing. After the resolution of the inflammatory response, cardiac fibroblasts proliferate and secrete extracellular matrix proteins, such as collagen I, to form a fibrotic scar that replaces dead myocytes. The resulting tightly cross-linked, fibrotic scar with significant tensile strength serves to prevent rupture. This remodelling of the LV continues progressively in response to increases in wall stress, provoking cardiac myocyte hypertrophy in the infarct border zone, wall thinning, and chamber dilation. This global adverse remodelling response leads to increases in both LV end-diastolic and end-systolic volumes and reduced ejection fraction [ref. 19].

In addition to the sequence of pathophysiological changes that occur in the infarcted myocardium, there is also increasing evidence that pathological changes also take place in the remote (non-infarcted) myocardium. Remote myocardial zones have been associated with the activation of pro-inflammatory pathways and infiltration of leukocytes, responses which are increasingly recognised as important in post-infarct LV remodelling [ref. 20,21]. The remodelling proces is also mediated by differences in mechanical behaviour between the infarcted area itself, the adjacent and remote non-infarcted regions [ref. 22].

CLINICAL CHARACTERISATION OF PATHOLOGICAL CARDIAC REMODELLING

The clinical diagnosis of pathological remodelling is based on the detection of morphological changes: changes in cavity diameter or volume, mass (hypertrophy and atrophy), geometry (wall thickness and shape), areas of scar and wall motion abnormalities after myocardial infarction, fibrosis and inflammatory infiltrate [ref. 23]. Currently, the most used imaging modalities to detect these morphological changes are echocardiography, ventriculography, magnetic nuclear resonance and computed tomography.

CLINICAL IMPLICATIONS OF PATHOLOGICAL CARDIAC REMODELLING

Cardiac dysfunction

The primary consequence of pathological cardiac remodelling is the onset and progression of cardiac dysfunction. As a result of genetic changes in response to cardiac injury, there is re-expression of fetal genes [ref. 19]. Consequently, cellular and molecular changes occur, leading to progressive loss of ventricular contractile function. This can be asymptomatic at first, but can lead to the clinical syndrome of heart failure. Although not fully clarified, a number of processes have been identified that play important roles in cardiac dysfunction caused by pathological remodelling.

Cardiac cell death

Cardiac myocytes carry out the contractile function of the myocardium, and they are largely incapable of replication. Therefore, their survival is crucial. Progressive loss of myocytes in response to pathophysiological stimuli seem to play an important role in remodelling. Three main mechanisms involved in myocyte death are identified: apoptosis or programmed cell death, necrosis and autophagy. Following myocardial injury, cardiac myocytes undergoing necrosis lyse, releasing intracellular contents, some of which can be detected in the blood and used as markers of injury (e.g. creatine kinase, cardiac troponins). Apoptosis, an energy-dependent, programmed cell death response, does not entail release of intracellular contents and does not trigger an inflammatory response; it is reversible up to a "point of no return". Emerging literature suggests that necrosis may itself be a programmed cellular process, rather than uncontrolled disintegration of the cell. The exact role of apoptosis and necrosis in cardiac injury and dysfunction have been subject of intense debate, but recent evidence actually suggests that these mechanisms are closely related and may be different phases of the same proces called necroptosis [ref. 19,24] . Often, dying cells manifest evidence of up-regulated autophagy, an evolutionarily ancient process of ordered recycling of intracellular contents. Autophagy is an intracellular process characterised by the destruction of unnecessary or dysfunctional cytoplasmatic components by lysosomes. Protein homeostasis, or proteostasis, depends on a delicate balance between protein synthesis, transport, post-translational modification and degradation. A disturbance on such balance may lead to accumulation of defective proteins and a process known as proteotoxicity. Therefore, autophagy exerts a crucial role in proteotoxicity prevention, with the participation of the ubiquitin system and chaperones, also known as heat shock protein-HSP. Considerable debate has centred around whether this autophagic cascade reflects the cellular response to stress, serving to promote cell survival, or represents a process which, itself,

contributes to cell death. Consensus has emerged recently, however, that at least in some instances, autophagic cell death (programmed cell death type II) exist also in heart muscle [ref 25]. Irrespective of whether autophagy can trigger cardiomyocyte death, considerable evidence indicates that progression of ventricular dysfunction may be associated with changes in the process of autophagy, which can be either adaptive or deleterious [ref. 26].

Energy metabolism

Energy deficit is another mechanism potentially involved in alterations of the cardiac function after remodelling. This is caused by the imbalance between oxygen supply and consumption. In normal conditions, free fatty acids are the major energy substrate for the heart, accounting for 60%-90% of energy supply. Fatty acid and glucose metabolites enter the citric acid cycle by β-oxidation and glycolysis, respectively, to generate FADH2 and NADH, which, in turn, participate in the electron transport chain. The generated energy is then stored and transported in the form of phosphocreatine [ref. 27].

Altered energy metabolism has been reported in cardiac remodelling, with decreased free fatty acids oxidation and increased glucose oxidation. A decrease in β-oxidation may result in accumulation of triglycerides and lipotoxicity, and mitochondrial atrophy and altered mitochondrial function have been also described in cardiac remodelling. All these processes result in low energy availability for myocardial proteins with ATPase activity, and generation of reactive oxygen species, oxidative stress and its consequences.

Oxidative stress

Oxidative stress caused by reactive oxygen species can be produced by several sources in the heart, including the mitochondrial electron transport chain, NADPH oxidase system, activity of the enzymes cyclooxygenase, cytochrome P450, glucose oxidase, xanthine oxidase, lipoxygenase, as well as by catecholamine degradation. In physiological conditions, there is a balance between reactive species production and antioxidant defence; the oxidative stress occurs when excess reactive oxygen species are generated that cannot be neutralised by antioxidant systems [ref. 28].

Strong evidence supports an association between cardiac remodelling and oxidative stress resulting from increased reactive species production and decreased antioxidant defence. This would lead to several conditions, such as lipid peroxidation, protein oxidation, DNA damage, cellular dysfunction, proliferation of fibroblasts, activation of metalloproteinases, induction of apoptosis, changes in calcium-transport

proteins, activation of hypertrophy signalling pathways, among others. Therefore, the oxidative stress seems to play a significant pathophysiological role in cardiac remodelling.

Inflammation

In response to cardiac injury both adaptive and innate immune responses can be activated The innate system generates a more nonspecific inflammatory response, the adaptive system - mediated by B and T cells- induces a more specific response [ref. 25]. Experimental evidence has shown that inflammatory mediators induce the re-expression of fetal genes, cellular growth, activation of metalloproteinases, proliferation of fibroblasts, and progressive loss of myocytes by apoptosis. Similarly, antagonism of innate response (antagonists to toll-like receptors, TNF, IL-1 and IL-8) attenuated the cardiac remodelling after myocardial infarction. Also, adaptive response modulation (macrophages, regulatory T cells and B cells) may induce a more favourable remodelling, particularly in myocardial ischaemia model. Ref 28,29].

Collagen

The human heart contains a complex collagen network. Cardiac interstitium consists mainly (95%) of type I and type III collagen fibers. The main functions of this network are to regulate apoptosis, restore pathological deformations, maintain the alignment of structures, regulate the distensibility of the heart muscle and transmission of strength during fiber shortening, and express cytokines and growth factors [ref. 30]. Collagen fibers are cross-linked by chemical bonds and are resistant to degradation of most proteases. Some enzymes, however, including metalloproteinases, have collagenolytic activity. The rupture of the collagen network could lead to several consequences for ventricular architecture and function. Therefore, in the acute myocardial infarction model, increased metalloproteinase activity was associated with progressive ventricular dilation and cardiac dysfunction.

The abnormal accumulation of type III collagen and especially type I collagen (harder, longer and more stable) was detected in different models of cardiac injury, induced by several signaling pathways including TGF-β, endothelin-1, angiotensin II, connective tissue growth factor, and platelet-derived growth factor. In this context, fibrosis was associated with increased myocardial stiffness, diastolic dysfunction, weakened contraction, impaired coronary flow and malignant arrhythmias. In addition, fibrosis has been found to be a predictor of mortality in patients with cardiac dysfunction [ref. 31]. Therefore, collagen plays a critical role in the maintenance of cardiac architecture and function. In the remodelling process, however, the balance

between collagen synthesis and degradation may be affected with many adverse effects.

Contractile proteins

Ventricular remodelling is characterised by alterations in the main contractile protein - myosin - composed of one pair of heavy chains (α and β) and two pairs of light chains. Depending on the myosin chain composition, three isomyosins (V1, V2 e V3) may be identified in the myocardium of different species. These isoenzymes possess the same pairs of light chains and differ by their heavy chain compositions (αα in V1, αβ in V2, and ββ in V3). The myosin ATP-ase activity relies on active sites located on heavy chains, and α-fraction has the highest activity. Hence, the composition of isoenzymes determine the contractile capacity of myocytes. In addition to the predominance of the fetal form of myosin light chain, a decrease in V1 isoform accompanied by an increase in V3 isoform is commonly observed in remodelling. Additionally, increased troponin T type 2 and reduced phosphorylation of troponin I have been found after remodelling. [ref. 32].

Calcium transport

Calcium transport through the sarcoplasmic reticulum is an active, complex process, involving many components. Membrane and intracellular systems (L-type calcium channels, ryanodine receptor, calsequestrin) regulate the supply of calcium to contractile proteins during contraction. Also, stimulation of calmodulin kinase and phosphorylation of phospholamban activates enzymes (SERCA-2a) that mediate calcium uptake by the sarcoplasmic reticulum, and enhances cardiac relaxation.

Evidence suggests that alterations in the calcium transport system occur in ventricular remodelling and dysfunction, including a decrease in L-type calcium channels, and ryanodine receptors, and decreased calsequestrin and calmodulin kinase activity. Hence, cardiac remodelling leads to reduced calcium release during systole and increased release during diastole. Therefore, alterations in proteins involved in calcium transportation may contribute to cardiac dysfunction in remodelled hearts.

Changes in cardiac geometry

It has been proposed that the ventricular myocardium, both right (RV) and left (LV), exists as a continuous muscle band. The band is oriented spatially as a helix formed by basal and apical loops. [ref. 33, 34]. It is reasoned that sequential contraction of the ventricular muscle band, spatially distributed as a helicoid, results in successive shortening and lengthening of the ventricles. These movements may determine the ejection and suction of blood [ref. 35]. Alterations in geometry, including changes in

the wall thickness, cavity diameter, and normal configuration of the left ventricle (from elliptical to spherical), may have functional consequences. This can be caused by difference in load and geometrical distortions impacting on ventricular rotation and torsion, For example, in rat infarct models, the animals developed increased ventricular cavity associated with depressed global systolic function, and yet preserved myocyte contractile function [ref. 36]. Chances in geometry by affecting cardiac load could affect the global ventricular function [ref. 37].

Additionally there is the influence of ventricular rotation and torsion on cardiac function. The normal ventricular function requires coordination between electrical and mechanical activities. The left ventricular wall is first activated in the endocardial region of the septum and then on the ventricular free wall, from ventricular apex to the base, following the Purkinje fiber network. The mechanical response, however, is characterised by a physiological dyssynchrony between the subendocardial and subepicardial regions [ref. 38].

"Rotation" is defined as a circumferential movement around the longitudinal axis. During isovolumetric contraction, the apex shows a brief clockwise rotation followed by a continued counterclockwise rotation during LV ejection. Parallel to this movement, a shortening of endocardial fibers and expansion of epicardial fibers occur, followed by simultaneous shortening of both types during ejection. In contrast, the base rotates counterclockwise and clockwise during isovolumetric contraction and ejection, respectively, to a lesser extent than the apex. The term torsion refers to the gradient between the base and the apex. Torsion, then, describes the degree of myocardial deformation, which is restored during diastole. The first consequence of systolic torsion is the increase in the intracavitary pressure with minimum shortening, which reduces the energy demand. In addition, torsion induces a more uniform distribution of LV fiber stress and fiber shortening across the wall. Also, the simultaneous presence of subendocardial and subepicardial vectors (i.e. shortening and lengthening vectors) during diastolic torsion, which initiates during isovolumetric relaxation, facilitates the recoil forces and restoration of ventricular architecture. Therefore, the loss of torsion affects systolic and diastolic function of the LV [ref. 39].

Neurohormonal activation

The main two systems involved in cardiac remodelling are the sympathetic system and the renin-angiotensin-aldosterone system. Activation of both systems activates intracellular signalling pathways that stimulate the synthesis of protein in myocytes and fibroblasts, causing cellular hypertrophy and fibrosis. Other effects reported include activation of growth factors and metalloproteinases, hemodynamic over-

load by vasoconstriction and water retention, increase in oxidative stress and direct cytotoxic effect, leading to cellular death by necrosis or apoptosis [ref. 40].

Cardiac arrhythmias

Cardiac remodelling is associated with malignant ventricular tachyarrhythmias, including both sustained ventricular tachycardia and ventricular fibrillation. Different mechanisms caused by different changes are involved. There are changes in ion channels that include inactivation of sodium channels, changes in calcium and potassium channels and alterations in the sodium/calcium exchanger function [ref. 41,42]. Also, there are changes in the gap junctional intercellular communication, which are responsible for the contact between adjacent cells and hence for the electrical coupling. Gap junction proteins are called connexins and the most prominent expressed connexin in the heart is connexin 43, mainly located in the intercalated discs in normal hearts. In remodelling, both a decrease in labelling intensity and a redistribution of connexin along the long sides of the myocytes are observed. This would lead to prolongation of QT intervals and arrhythmias. Last, cardiac remodelling is associated with an increase in collagen content or fibrosis of both the epi- peri and endomysium in addition to the areas of scar tissue. This leads to blockage of electrical conduction and re-entry arrhythmia.

RATIONALE FOR SURGICAL VENTRICULAR RECONSTRUCTION

Surgical reconstruction of akinetic or dyskinetic segments reduces LV volume and this has three important effects. First, based on the Laplace equation, which relates wall stress inversely to wall thickness and directly to chamber radius, volume reduction diminishes wall stress and thereby reduces myocardial oxygen consumption. Minimising the mass of abnormal myocardium improves wall compliance, reduces filling pressure, and further enhances diastolic coronary flow. Second, reduction of wall stress, as a critical determinant of afterload, enhances contractile performance of the ventricle by increasing the extent and velocity of systolic fibre shortening [ref. 43]. Third, the ineffective shifting of blood volume within the LV caused by nonuniform contraction and relaxation or ‘internal flow fraction’ is reduced by the exclusion of a- and dyskinetic wall segments [ref 44]. Clearly, this effect is more pronounced in the exclusion of dyskinetic segments in true LV aneurysms, than in akinetic segments of the more globally remodelled LV’s.

Historically, already in the CASS study (Coronary Artery Surgery Study) 30% of surgical treated patients with severe LV dysfunction (LVEF <36%) underwent concomitant LV reconstruction procedures. These reconstructions were either linear plications or resections of aneurysmatic segments, which were not anatomic and commonly led to a box-like deformation of the LV [ref. 45]. Moreover, these procedures do not consistently improved ventricular performance [ref. 46]. More anatomic reconstructions were developed such as the intraventricular or endocardial ventricular reconstructions (with or without a patch) that would reduce LV volume but maintained a more elliptical shape [ref. 47]. Dor described an original surgical technique built on prior contributions by Cooley, Keith, and Jatene [47-50]. The Dor procedure excludes akinetic or dyskinetic portions of the ventricle, reshapes the ventricle with a stitch that encircles the transitional zone between contractile and non-contractile myocardium, and uses a small patch to reestablish ventricular wall continuity at the level of the purse-string suture. To diminish the risk of creating a ventricle that is either to small - and which would lead to catastrophic physiology of restrictive cardiomyopathy - or too large and which would have a limited benefit on ventricular performance, Dor introduced the use of an intraventricular balloon filled to a known volume of 60 mL/m2 BSA, to guide the restoration and to leave an adequate residual chamber. The volume 60 mL/m2 was chosen after study of postoperative angiograms. Dor et al. advocated the use of surgical ventricular reconstruction (SVR) not only for patients with aneurysm's or dyskinetic wall segments, but also for patients with dilated LV and akinetic wall segments [ref. 51]. In these patients with akinetic myocardial wall segments, preserved epicardial covering of largely transmural fibrosis make these akinetic zone appear normal at the time of cardiac surgery, but in the unloaded / decompressed heart the thinning of these wall segment can be easily appreciated by palpation.

Not like earlier LV aneurysmectomies or the Batista procedure in which wall segments were excised to reduce LV volume [ref. 52], the objective of SVR was to reshape and decrease LV volume by decreasing the circumference of the endocardial scar. The scar tissue or a patch can be used to decrease linear wall tension and close the ventriculotomy and avoid the restrictive physiology of undersizing the LV. Immediate reduction of LV end-systolic volume (ESV) by as much as 30% or more is typically achieved by SVR, far greater than the degree of reverse remodelling achieved with any other heart failure treatment. Furthermore, SVR also results in an immediate reduction in chamber radius, which decreases myocardial systolic and diastolic wall stresses (Laplace's Law) and therefore has potential, similar to pharmacologic therapies that reduce myocardial afterload and preload, to induce myocellular and molecular reverse remodelling. Several theoretic and experimental studies explored

the impact of SVR on LV pump function [ref. 53-58]. Although LV ejection fraction consistently increases after SVR, it has been shown that this does not have the usual meaning of an increase in LV pump function [ref. 59,60] Indexes of pump function can be load-independent (eg. end-systolic pressure-volume relations) and load-dependent (eg. stroke volume). Regardless which of these indexes was examined, the results suggested that pump function could be increased, unchanged, or decreased, depending on the relative characteristics (dyskinetic, akinetic, or hypokinetic, respectively) and amount of the LV wall excluded during SVR. The RESTORE registry group published their combined experience of 1,198 SVR procedures in 11 centres, with 5.1% in-hospital or operative mortality and 88% 18-months survival [ref. 61].

THE STICH-TRIAL

In 2002, the National Heart, Lung, and Blood Institute (NHLBI) funded the Surgical Treatment for IsChemic Heart failure (STICH) trial to address 2 pressing clinical and policy questions regarding the management of HF patients with surgically revascularizable coronary artery disease and LV dysfunction: 1) is contemporary CABG surgery superior to contemporary medical/secondary prevention therapy in prolonging survival in these patients; and 2) among patients with significant anterior wall dysfunction, does the addition of surgical ventricular reconstruction (SVR) to CABG improve hospitalization-free survival? [ref. 43].

The STICH trial was designed to enrol at least 2000 men and women aged ≥18 years who have coronary artery disease amenable to revascularization and LV dysfunction defined by a clinically-determined LVEF of ≤35%. Patients awaiting a planned PCI to treat symptomatic CAD within the next 30 days are not eligible, although previous PCI is not an exclusion. While planned operative treatment of the aortic valve excludes potential candidates, the decision to pursue operative management of any other valves, specifically the mitral valve, is left to the discretion of responsible physicians and surgeons [ref. 43]. In the Hypothesis 2 (H2) arm of the trial, the minimum requirement for certification is evidence of 25 CABG patients with LVEF ≤40% who were operated on with ≤5% mortality. Before cardiac surgeons are certified to perform SVR on a randomised patient, they are required to perform at least 5 SVR procedures without a perioperative death and demonstrate consistent LV volume reduction after operation. A composite endpoint of survival free of cardiac hospitalisation was chosen for H2 since no data existed to suggest that adding SVR to CABG improves survival over CABG alone. Moreover, this composite endpoint has validity for patients who would be likely to consent to adding SVR to a planned

CABG. The planned enrolment of 1000 patients into H2 provides a 90% power to detect a 20% reduction in mortality and cardiac hospitalisation by the addition of SVR to CABG, assuming that the 3-year event rate for those treated with CABG alone is 45% or higher.

The published results of this trial were as follows: SVR reduced the end-systolic volume index by 19%, as compared with a reduction of 6% with CABG alone [ref. 62]. Cardiac symptoms and exercise tolerance improved from baseline to a similar degree in the two study groups. However, no significant difference was observed in the primary outcome, which occurred in 292 patients (59%) who were assigned to undergo CABG alone and in 289 patients (58%) who were assigned to undergo CABG with surgical ventricular reconstruction (hazard ratio for the combined approach, 0.99; 95% confidence interval, 0.84 to 1.17; P=0.90). The conclusions were that adding SVR to CABG reduces LV volume, as compared with CABG alone. However, this anatomical change was not associated with a greater improvement in symptoms or exercise tolerance or with a reduction in the rate of death or hospitalisation for cardiac causes

The 490 patients who underwent SVR in the STICH trial was predicated on favourable reports of recovery in >5000 patients worldwide and registry data from approximately 1200 patients that decreased LV end-systolic volume index (LVESVI) 40% (ranging 30–58%), but had different results [ref. 61, 63], The questions were raised whether *SVR was an improper concept or was the STICH trial improperly executed?* Although the trial results suggest equivalency of these therapies, important shortcomings have been identified which cast critical doubt regarding the generalisability of the trial findings. Eligibility for STICH required that 'all patients will be evaluated further for appropriateness of SVR indicated by evidence of absent viability in the anterior ventricle by nuclear scan determination, LVESVI ≥60 ml/m2, and akinesia ≥35% of the anterior wall [ref. 64]. Echocardiography was specifically excluded for measuring LV volume because of its inaccuracy when regional asynergy is present [ref. 65]. Selection of STICH centres was based on capability to measure volume by cardiac magnetic resonance (CMR) imaging. However, STICH enrolled a quite different group of patients, namely those with NYHA Class II–IV CHF (within 3 months of entry), coronary artery disease that was amenable to CABG, an EF ≤35% [defined by echocardiogram, left ventriculogram, CMR, or gated single photon (SPECT) studies], and 'dominant anterior left ventricular dysfunction'. Accurate viability and LV volume were not done in all patients as planned. STICH required that all patients have dyskinesia or akinesia with evidence of non-viability in 35% of the anterior ventricular wall. Dyskinesia is caused by no reperfusion of the LV after infarction.

Akinesia accompanies early thrombolysis or angioplasty and results in a dilated but thick LV. STICH, however, reports that only half of patients had akinesia or dyskinesia and 13% had no prior history of infarction. Surgical ventricular reconstruction has never been reported or recommended in patients with regional dysfunction alone and absent scar. The STICH surgical therapy committee specifically defined SVR as 'any ventricular reconstruction method that consistently results in a low operative mortality, an average EF increase of ≥10%, and an average LVESVI decrease of ≥30% as assessed on the four-month post-operative CMR measurement'. STICH, however, measured LVESVI in only 212 of 490 patients (43%) in the CABG-only group and in 161 of 490 patients (33%) in the CABG plus SVR group by echocardiography. The number of CMR measurements is not given. STICH reported that SVR lowered LVESVI an average of only 19%. Patients should be excluded from the analysis if the originally defined goals were not met. Patients in the SVR trial underwent SVR based on qualitative rather than quantitative assessment. Perhaps they had hibernation of ischaemic areas or post-infarction stunning, both of which are clearly not indications for SVR. Surgeons cannot know when SVR should be performed without accurate viability and volume information. The STICH patients cannot be compared with previously reported patients with SVR. Dor's 1000 patients and the 1198 patients in the RESTORE group had prior history of MI, akinesia, or dyskinesia involving ≥35% of the LV, reduced EF, and LVESVI ≥60 mL/m2 [ref. 61, 66]. Furthermore, only 49% of patients in STICH had NYHA class III or IV CHF vs. >66% in the RESTORE registry. Above all, during the trial, another protocol deviation was that also NYHA-class I patients were considered eligible. So one can pose the questions whether the STICH trial really still concerned symptomatic heart failure patients *and whether the SVR procedures were performed appropriately?* Michler et al. performed an interesting analysis of the STICH trial data, in which they examined left ventricular volumes at baseline and 4 months after surgery to determine whether any magnitude of postoperative reduction in end-systolic volume affected survival after coronary artery bypass grafting alone compared with bypass grafting plus surgical ventricular reconstruction [ref. 67]. He found that SVR resulted in improved survival compared with coronary artery bypass grafting alone when the postoperative end-systolic volume index was 70 mL/m2 or less. However, the opposite was true for patients achieving a postoperative volume index greater than 70 mL/m2. A reduction in the end-systolic volume index of 30% or more compared with baseline was an infrequent event in both treatment groups.

SVR AFTER THE STICH-TRIAL

The question is valid whether or not SVR still represents a valuable treatment option in the surgeon's armamentarium for patients with ischemic heart failure in the post-STICH era? [ref. 68]. Expert-centres continue to publish excellent results with SVR in selected patients and also less-invasive hybrid transcatheter techniques to reconstruct the pathologically remodelled LV have emerged [ref. 69,70].

Dor et al. published the favourable effects of SVR in patients who were excluded from the STICH trial [ref. 71]. They describe the outcome in 274 patients, 117 of these patients would not have been eligible for the STICH trial. Reasons for exclusion included 12 patients with no coronary vessel suitable for coronary artery bypass grafting; 17 patients within a month of myocardial infarction, including 11 with acute heart failure (8 septal ruptures and 3 cases of ventricular tachycardia); 48 patients receiving intravenous inotropes, intra-aortic balloon pumping, or both; 15 patients with bifocal or posterior scarring; 4 patients scheduled for heart transplantation. Four in-hospital and 2 delayed deaths occurred during the first year. In 101 patients with chronic heart failure, magnetic resonance imaging revealed that ejection fraction improved from 26% ± 4% preoperatively to 40% ± 8% at 1 month and 44% ± 11% at 1 year postoperatively. At these same time points, the LV end-diastolic volume index was reduced from 130 ± 43 mL/m(2) to 81 ± 27 (-38%) and 82 ± 25 mL/m(2) (-37%), respectively, and the LV end-systolic volume index was reduced from 96 ± 45 mL/m(2) to 50 ± 21 (-48%) and 47 ± 20 mL/m(2) (-51%,) respectively.

Contreras et al. reported on SVR results in 34 patients with end-stage heart failure of ischemic origin that were candidates for heart transplantation [ref. 72]. Overall mortality of 14.7%, with hospital admission being 8.82% and late death being 5.88%. Total survival rate at five years of 85.3%.

Isomura et al. demonstrated SVR to be more effective when 33% of ventricular reduction is obtained and LVESVI < 90 ml/m2, as well as that there is no long-term benefit when SVR induces a left ventricular volume reduction <15% and leaves a residual LVESVI > 90 ml/m2 [ref. 73].

Calafiori et al. published his SVR results of a group of 113 patients with a mean LVEF of 26%, 90% with functional mitral regurgitation and 78% of the patients were in NYHA-class III or IV [ref 74]. Five patients (4.4%) died while in hospital, all from cardiac causes. After a median follow-up of 12 (95% CI: 6, 18) months, 22 patients died, 17 from cardiac causes. Five-year freedom from death any from cause was

73 ± 5%, emergency status and MR Grade 4 being the only risk factors. Five-year freedom from death from any cause and NYHA class III/IV was 61 ± 6%. After a median follow-up of 31 (95% CI: 19, 38) months, 91 patients underwent postoperative echocardiography. EF increased by 20%, but stroke volume remained unchanged. Postoperatively, patients with severe left ventricular diastolic dysfunction had lower EF and higher end-systolic volumes than patients without left ventricular diastolic dysfunction.

The postoperative left ventricular end-systolic volume index and ejection fraction are benchmarks of surgical ventricular reconstruction but remain unpredictable. An analysis into the relationships between surgical ventricular reconstruction, postoperative end-systolic volume index, ejection fraction, and survival to identify responders to the therapy was performed by Wakasa et al. [ref. 75]. They aimed to identify who could be associated with a higher long-term survival by adding surgical ventricular reconstruction to coronary artery bypass grafting than coronary artery bypass grafting alone (responders to surgical ventricular reconstruction) in a study with 293 patients in 16 cardiovascular centers in Japan. Surgical ventricular reconstruction was performed in 165 patients (56%). The LV end-systolic volume index and LV ejection fraction significantly improved (LV end-systolic volume index, 91 to 64 mL/m2; LV ejection fraction, 28% to 35%) for all patients. The postoperative LV end-systolic volume index and ejection fraction were estimated, and surgical ventricular reconstruction was found to be significantly associated with both LV end-systolic volume index reduction (-14.5 mL/m2) , $P < .001$) and LV ejection fraction increase (+3.1%, $P = .003$). During the median follow-up of 6.8 years, 69 patients (24%) died. Only the postoperative LV ejection fraction was significantly associated with survival (hazard ratio, 0.925; 95% confidence interval, 0.885-0.968), although this effect was limited to those with postoperative LV end-systolic volume index of 40 to 80 mL/m2 in the subgroup analysis (hazard ratio, 0.932; 95% confidence interval, 0.894-0.973). This same research group published earlier a simple prognostic risk model to predict mortality after surgical ventricular reconstruction [ref. 76] . They did this based on the outcome of an analysis of 596 patients who underwent surgical ventricular reconstruction for chronic ischemic heart failure in 11 Japanese cardiovascular hospitals between 2000 and 2010. Forty-one patients died before discharge, and 81 patients died during a mean follow-up time of 2.9 years. Four independent predictors of mortality were identified: age, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, left ventricular ejection fraction, and severity of mitral regurgitation. Each variable was assigned a number of points proportional to its regression coefficient. A risk score was calculated using the point scores for each patient, and 3 risk groups were developed: a low-risk group (0-4

points), an intermediate-risk group (5-6 points), and a high-risk group (7-12 points). Their 3-year survival-rates were 93%, 81%, and 44%, respectively (log-rank P < .001). Harrell's C-index of the predictive model was 0.69.

Song et al. reported on the results of SVR in 523 patients (75 who underwent SVR plus mitral valve surgery and 448 who underwent SVR) with concomitant moderate mitral regurgitation [ref. 77]. The median follow-up time among all patients was 41 months. There was no significant difference between SVR plus mitral valve surgery and SVR groups with regard to all-cause mortality (*P* = .208) and major adverse cardiovascular and cerebrovascular events (*P* = .817) after adjustment for covariates.

These post-STICH publications continue to demonstrate that SVR is effective in dilated ventricles, provided the procedure achieves >30% volume reduction. Suma and Anyanwu concluded in a review on the current status of SVR in ischemic cardiomyopathy *"that (it) is critical that surgeons continue their work in SVR, and continue to analyse their data, to enable better clarification of the indications and future role for this procedure" [ref. 78]*.

AIMS OF THIS THESIS

This thesis had the following aims:

To assess the early and late outcome of (early, late and current) LV reconstruction surgery in ischemic heart disease

To develop better tools (than standard preoperative TTE and EuroSCORE risk score calculators) for risk stratification / predictors for (functionally good and poor) outcome after LV reconstruction in ischemic heart failure

To describe the management of Functional Mitral Regurgitation (FMR) during LV reconstruction for in ischemic heart failure

To evaluate the late impact of preoperative important FMR and mitral repair during LV reconstruction surgery

To test LVEF as criterium for ICD implantation after LV reconstruction for ischemic heart failure

To evaluate novel hybrid LV reconstruction technique as an alternative treatment option for patients with ischemic cardiomyopathy

OUTLINE OF THIS THESIS

This thesis is the result of several studies into the clinical and echocardiographic outcome of both open and hybrid surgical ventricular reconstruction for the treatment of ischemic cardiomyopathy. Additionally, predictors for a favourable outcome and important associated issues such as management and late outcome of functional mitral regurgitation and the use of LV ejection fraction as a selection criterium for indication for a implantable cardioverter defibrillator for the primary prevention of ventricular arrhythmias after surgical ventricular reconstruction were studied. In chapter 2 the early and late outcome of different types of open left ventricular reconstruction surgery by means of a meta-analysis are presented. Chapter 3 describes the use of echocardiographic wall motion score index to predict mortality and functional results after surgical ventricular reconstruction for advanced ischemic heart failure. In chapter 4 the management of functional mitral regurgitation during left ventricular reconstruction is presented followed by a landmark analysis into the 10-year outcome of functional mitral regurgitation after left ventricular reconstruction. Chapter 5 discusses the use of the improved LV ejection fraction after SVR as an indication for a implantable cardioverter defibrillator for the primary prevention of ventricular arrhythmias after surgical ventricular reconstruction in heart failure patients. Chapter 6 discusses the early experience with a minimal-invasive hybrid transcatheter surgical ventricular reconstruction technique. First the technique of hybrid transcatheter left ventricular reconstruction is described. Followed by the preliminary results of this technique from 2 cardiac centres in the Netherland. Finally, the multicenter European results of hybrid less invasive reconstruction on clinical, functional and echocardiographic outcome are presented.

LIST OF ABBREVIATIONS

SVR	Surgical ventricular reconstruction
LVR	Left ventricular reconstruction
CABG	Coronary artery bypass grafting
LV	Left ventricle / left ventricular
LVEF	Left ventricular ejection fraction
ECC	Extracorporeal circulation

MI	Myocardial infarction
HF	Heart failure
ICMP	Ischemic cardiomyopathy
CT	Computed tomography
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
FMR	Functional mitral regurgitation

REFERENCES

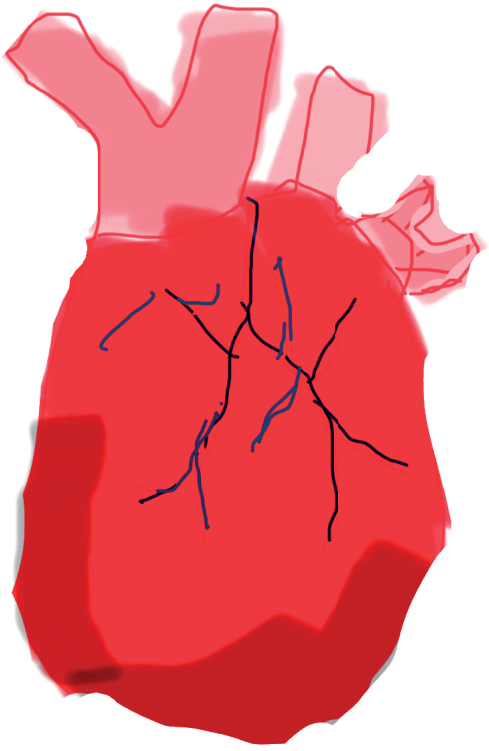
1. Braunwald, E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N. Engl. J. Med. 1997; 337:1360–1369 (1997)
2. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev. 2000 Jun;5(2):167-73
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. Engl J Med. 2006 Jul 20;355(3):251-9
4. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. The Rotterdam Study. Eur Heart J. 2004;25:1614–1619.
5. Buckberg G, Athanasuleas C, Conte J. Surgical ventricular restoration for the treatment of heart failure. Nat Rev Cardiol. 2012 Dec;9(12):703-16.
6. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail. 2001 Jun; 3(3):315-22.
7. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC.Eur J Heart Fail. 2016 Aug;18(8):891-975
8. www.volksgezondheidenzorg.info
9. Felker GM, Shaw LK, O'Connor CM. A standardised definition of ischemic cardiomyopathy for use in clinical research. Journal of the American College of Cardiology. 2002;16(39):210-218
10. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol. 2008 Apr 1; 101(7):1016-22.
11. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol. 2000 May; 35(6):1628-37.
12. Hellermann JP, Goraya TY, Jacobsen SJ, Weston SA, Reeder GS, Gersh BJ, Redfield MM, Rodeheffer RJ, Yawn BP, Roger VL . Incidence of heart failure after myocardial infarction: is it changing over time? Am J Epidemiol. 2003 Jun 15; 157(12):1101-7.
13. Follath F. Ischemic versus non-ischemic heart failure: should the etiology be determined? Heart Fail Monit. 2001;1(4):122-5
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72(18):2231-2264.

15. Azevedo PS, Polegato BF, Minicucci MF, Paiva SA, Zornoff LA. Cardiac Remodeling: Concepts, Clinical Impact, Pathophysiological Mechanisms and Pharmacologic Treatment. Arq Bras Cardiol. 2016 Jan;106(1):62-9.
16. J.M. Pfeffer. Inlfuence of chronic captopril. Circ Res. 1985
17. Pfeffer MA, Braunwald E.Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990 Apr;81(4):1161-72.
18. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35(3):569-82
19. Burchfield JS, Xie M, Hill JA. C Pathological ventricular remodeling: mechanisms: part 1 of 2. Circulation. 2013 Jul 23; 128(4):388-400.
20. Lee WW, Marinelli B, van der Laan AM, Sena BF, Gorbatov R, Leuschner F, et al. PET/MRI of inflammation in myocardial infarction. J Am Coll Cardiol. 2012;59(2):153–163
21. Frangogiannis NG, Smith CW, Entman ML. The inflammatory response in myocardial infarction. Cardiovasc Res. 2002;53(1):31–47
22. Kramer CM, Lima JA, Reichek N, Ferrari VA, Llaneras MR, Palmon LC, Yeh IT, Tallant B, Axel L .Regional differences in function within noninfarcted myocardium during left ventricular remodeling. Circulation 1993;88:1279–1288
23. Anand IS. Non-invasive assessment of left ventricular remodelling. J Card Fail 2002
24. Vandenabeele P, Galluzzi L, Vanden Berghe T, Kroemer G. Molecular mechanisms of necroptosis: an ordered cellular explosion. Nat Rev Mol Cell Biol. 2010 Oct; 11(10):700-14
25. Miyata S, Takemura G, Kawase Y, Li Y, Okada H, Maruyama R, Ushikoshi H, Esaki M, Kanamori H, Li L, Misao Y, Tezuka A, Toyo-Oka T, Minatoguchi S, Fujiwara T, Fujiwara H Autophagic cardiomyocyte death in cardiomyopathic hamsters and its prevention by granulocyte colony-stimulating factor. Am J Pathol. 2006 Feb; 168(2):386-97
26. Matsui Y, Takagi H, Qu X, Abdellatif M, Sakoda H, Asano T, Levine B, Sadoshima J. Distinct roles of autophagy in the heart during ischemia and reperfusion: Roles of amp-activated protein kinase and beclin 1 in mediating autophagy. Circ Res. 2007;100:914–922
27. Doenst T, Nguyen TD, Abel ED. Cardiac metabolism in heart failure: implications beyond ATP production. Circ Res. 2013 Aug 30; 113(6):709-24
28. Takimoto E, Kass DA Role of oxidative stress in cardiac hypertrophy and remodeling. Hypertension. 2007 Feb; 49(2):241-8
29. Mann DL Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res. 2015 Mar 27; 116(7):1254-68.
30. Frieler RA, Mortensen RM. Immune cell and other noncardiomyocyte regulation of cardiac hypertrophy and remodeling. Circulation. 2015 Mar 17; 131(11):1019-30.
31. Zannad F, Rossignol P, Iraqi W. Extracellular matrix fibrotic markers in heart failure. Heart Fail Rev. 2010 Jul; 15(4):319-29.
32. Leask A. Getting to the heart of the matter: new insights into cardiac fibrosis. Circ Res. 2015 Mar 27; 116(7):1269-76.
33. Torrent-Guasp F. Anatomía funcional del corazón. Madrid: Paz- Montalbo, 1957.
34. Torrent-Guasp F. An experimental approach in heart dynamics physiology and pharmacology. Eugene Talmadge Hospital. Augusta (GA). Madrid: S. Aguirre Torre, 1959.

35. Torrent-Guasp F, Ballester M, Buckberg GD, Carreras F, Flotats A, Carrió A, Ferreira A, Samuels LE, Narula J, Spatial orientation of the ventricular muscle band: Physiologic contribution and surgical implications I J Thorac Cardiovasc Surg 2001;122:389-92
36. Anand IS. Ventricular remodelling without cellular contractile dysfunction. J Card Fail. 2002 Dec; 8(6 Suppl):S401-8.
37. Norton GR, Woodiwiss AJ, Gaasch WH, Mela T, Chung ES, Aurigemma GP, et al. Heart failure in pressure overload hypertrophy. The relative roles of ventricular remodeling and myocardial dysfunction. J Am Coll Cardiol. 2002;39(4):664–671
38. Buckberg GD, Hoffman JI, Coghlan HC, Nanda NC. Ventricular structure-function relations in health and disease: Part I. The normal heart. Eur J Cardiothorac Surg. 2015;47(4):587–601.
39. Buckberg GD, Hoffman JI, Coghlan HC, Nanda NC. Ventricular structure-function relations in health and disease: Part II. Clinical considerations. Eur J Cardiothorac Surg. 2015;47(5):778–787
40. Sayer G, Bhat G. The renin-angiotensin-aldosterone system and heart failure. Cardiol Clin. 2014;32(1):21–32
41. R. Coronel. Electrophysiological changes in heart failure. Biochim Biophys Acta 2013
42. Y. Wang. Electrophysiological remodeling in heart failure. J Mol Cell Cardiol. 2010
43. Eric J. Velazquez, Kerry L. Lee, Christopher M. O'Connor, Jae K. Oh, Robert O. Bonow, Gerald M. Pohost, Arthur M. Feldman, Daniel B. Mark, Julio A. Panza, George Sopko, Jean L. Rouleau, Robert H. Jones, STICH Investigators. The Rationale and Design of the Surgical Treatment for IsChemic Heart failure (STICH) Trial. J Thorac Cardiovasc Surg. 2007 Dec; 134(6): 1540–1547
44. Steendijk P. Tulner S.A. Schreuder J.J. Bax J.J. van Erven L. van der Wall E.E. et al. Quantification of left ventricular mechanical dyssynchrony by conductance catheter in heart failure patients. Am J Physiol Heart Circ Physiol. 2004; 286: H723-H730
45. Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS) Circulation. 1983;68:785–95
46. Froehlich RT, Falsetti HL, Doty DB, Marcus ML. Prospective study of surgery for left ventricular aneurysm. Am J Cardiol. 1980;45:923–31
47. Jatene AD. Left ventricular aneurysmectomy. Resection or reconstruction. J Thorac Cardiovasc Surg. 1985;89:321–31
48. Cooley D. Ventricular endoaneurysmorrhaphy: a simplified repair for extensive postinfarction aneurysm. J Cardiac Surg. 1989; 4: 200-205
49. Dor V Kreitmann P Jourdan J et al. Interest of physiological closure (circumferential plasty on contractile areas) of left ventricle after resection and endocardectomy for aneurysm of akinetic zone: comparison with classical technique about a series of 209 left ventricular resections [abstract]. J Cardiovasc Surg. 1985; 26: 73
50. Loop FD Effler DB. Left ventricular aneurysm.in: 3rd ed. Gibbon's surgery of the chest. WB Saunders, Philadelphia1976: 1384
51. Dor V, DiDonato M, Sabatier M, Montiglio F, Civaia F, RESTORE Group Left ventricular reconstruction by endoventricular circular patch plasty repair: a 17-year experience. Semin Thorac Cardiovasc Surg. 2001;13:435–47
52. Batista RJ, Santos JL, Takeshita N, Bocchino L, Lima PN, Cunha MA. Partial left ventriculectomy to improve left ventricular function in end-stage heart disease. J Card Surg. 1996;11:96–7

53. Di Donato M, Fantini F, Toso A, Castelvecchio S, Menicanti L, Annest L, Burkhoff D. Impact of surgical ventricular reconstruction on stroke volume in patients with ischemic cardiomyopathy. J Thorac Cardiovasc Surg. 2010 Dec;140(6):1325-31.e1-2
54. Artrip J.H. Oz M. Burkhoff D. Left ventricular volume reduction surgery for heart failure: a physiologic perspective. J Thorac Cardiovasc Surg. 2001; 122: 775-782
55. Burkhoff D. Wechsler A.S. Surgical ventricular remodeling: a balancing act on systolic and diastolic properties.J Thorac Cardiovasc Surg. 2006; 132: 459-463
56. Ratcliffe M.B. Guy T.S. The effect of preoperative diastolic dysfunction on outcome after surgical ventricular remodeling. J Thorac Cardiovasc Surg. 2007; 134: 280-283
57. Tulner S.A. Steendijk P. Klautz R.J. Tops L. Bax J.J. Versteegh M.I. et al. Clinical efficacy of surgical heart failure therapy by ventricular restoration and restrictive mitral annuloplasty. J Card Fail. 2007; 13: 178-183.
58. Tulner S.A. Bax J.J. Bleeker G.B. Steendijk P. Klautz R.J. Holman E.R. et al. Beneficial hemodynamic and clinical effects of surgical ventricular restoration in patients with ischemic dilated cardiomyopathy. Ann Thorac Surg. 2006; 82: 1721-1727
59. Annest L. Burkhoff D. Jorde U. Wechsler A.S. Stroke volume alterations in patients undergoing left ventricular reconstructive surgery: a meta-analysis of 2,131 cases. J Card Fail. 2007; 3: S118
60. Menicanti L. Di Donato M. The Dor procedure: what has changed after fifteen years of clinical practice?.J Thorac Cardiovasc Surg. 2002; 124: 886-890
61. Athanasuleas CL, Buckberg GD, Stanley AW, et al. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. J Am Coll Cardiol. 2004;44:1439–45
62. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens P, Rouleau JL, Lee KL; STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med. 2009 Apr 23;360(17):1705-17
63. Di Donato M, Castelvecchio S, Kukulski T, Bussadori C, Giacomazzi F, Frigiola A, Menicanti L. Surgical ventricular restoration: left ventricular shape influence on cardiac function, clinical status, and survival. Ann Thorac Surg 2009; 87:455-461
64. http://clinicaltrials.gov/archine/NTC00023595/2005_06_23
65. Bellenger BN, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, Pennell DJ. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000; 21:1387-1396
66. Dor V. Left ventricular reconstruction: the aim and the reality after twenty years J Thorac Cardiovasc Surg 2004;128(1):17-20
67. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, Holly TA, Oh JK, Dagenais F, Milano C, Wrobel K, Pirk J, Ali IS, Jones RH, Velazquez EJ, Lee KL, Di Donato M; STICH Trial Investigators. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg. 2013 Nov;146(5):1139-1145
68. Santarpino G, Melone M, Specchia L, Albano A, Nicoletti A, Gregorini R. Does surgical ventricular restoration still represent a valuable option in the surgeon's armamentarium in the post-STICH era? J Cardiovasc Surg (Torino). 2018 Jun;59(3):305-306

69. Cheng Y, Aboodi MS, Annest LS, Wechsler AS, Kaluza GL, Granada JF, Yi GH. Off-pump epicardial ventricular reconstruction restores left ventricular twist and reverses remodeling in an ovine anteroapical aneurysm model.J Thorac Cardiovasc Surg. 2014 Jul;148(1):225-3
70. Wechsler AS, Sadowski J, Kapelak B, Bartus K, Kalinauskas G, Rucinskas K, Samalavicius R, Annest L. Durability of epicardial ventricular restoration without ventriculotomy. Eur J Cardiothorac Surg. 2013 Sep;44(3):e189-92; discussion e192
71. Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg. 2011 Apr;141(4):905-16
72. Contreras CAM, Orellana PX, Almeida AFS, Finger MA, Rossi JM Neto, Chaccur P. Left Ventricular Reconstruction Surgery in Candidates for Heart Transplantation. Braz J Cardiovasc Surg. 2019 Jun 1;34(3):265-270
73. Isomura T, Hoshino J, Fukada Y, Kitamura A, Katahira S, Kondo T, Iwasaki T, Buckberg G, RESTORE Group. Volume reduction rate by surgical ventricular restoration determines late outcome in ischaemic cardiomyopathy.Eur J Heart Fail. 2011 Apr; 13(4):423-31
74. Calafiore AM, Iaco' AL, Kheirallah H, Sheikh AA, Al Sayed H, El Rasheed M, Allam A, Awadi MO, Alfonso JJ, Osman AA, Di Mauro M Outcome of left ventricular surgical remodelling after the STICH trial.Eur J Cardiothorac Surg. 2016 Oct; 50(4):693-701
75. Wakasa S, Matsui Y, Kobayashi J, Cho Y, Yaku H, Matsumiya G, Isomura T, Takanashi S, Usui A, Sakata R, Komiya T, Sawa Y, Saiki Y, Shimizu H, Yamaguchi A, Hamano K, Arai H. Estimating postoperative left ventricular volume: Identification of responders to surgical ventricular reconstruction. J Thorac Cardiovasc Surg. 2018 Dec;156(6):2088-2096
76. Wakasa S, Matsui Y, Isomura T, Takanashi S, Yamaguchi A, Komiya T, Cho Y, Kobayashi J, Yaku H, Kokaji K, Arai H, Sawa Y. Risk scores for predicting mortality after surgical ventricular reconstruction for ischemic cardiomyopathy: results of a Japanese multicenter study. J Thorac Cardiovasc Surg. 2014 Jun;147(6):1868-74, 1874
77. Song Y, Hu S, Sun H, Song Y, Wang L, Wang W, Pan S, Wang S, Feng W, Zheng Z. Results of Left Ventricular Reconstruction With and Without Mitral Valve Surgery. Ann Thorac Surg. 2020 Mar;109(3):753-761
78. Suma H, Anyanwu AC. Current status of surgical ventricular restoration for ischemic cardiomyopathy. Semin Thorac Cardiovasc Surg. 2012 Winter;24(4):294-301



Chapter 2

Early and late outcome of left ventricular reconstruction surgery in ischemic heart disease

Patrick Klein [a], Jeroen J. Bax [c], Leslee J. Shaw [b], Harm H.H. Feringa [a], Michel I.M. Versteegh [a], Robert A.E. Dion [a], Robert J.M. Klautz [a]

[a] Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Atlanta Cardiovascular Research Institute, Atlanta, GA, USA
[c] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

European Journal of Cardio-thoracic Surgery 34 (2008) 1149—1157

SUMMARY

A systematic review of the literature was performed to determine early and late mortality associated with left ventricular (LV) reconstruction surgery and to assess the influence of different surgical techniques, concomitant surgical procedures, clinical and hemodynamic parameters on mortality. The MEDLINE database (January 1980—January 2005) was searched and from the pooled data, hospital mortality and survival were calculated. Summary estimates of relative risks (RR) were calculated for the techniques that were used and for concomitant coronary artery bypass grafting (CABG) and mitral valve surgery. The risk-adjusted relationships between mortality and clinical and hemodynamic parameters were assessed by meta-regression. A total of 62 studies (12,331 patients) were identified.Weighted average early mortality was 6.9%. Cumulative 1-year, 5-year and 10-year survival were 88.5%, 71.5% and 53.9%, respectively. Endoventricular reconstruction (EVR) showed a reduced risk for both early (RR = 0.79, $p < 0.005$) and late (RR = 0.67, $p < 0.001$) mortality compared to the linear repair (early: RR = 1.38, $p < 0.001$; late: RR = 1.83, $p < 0.001$). Early and late mortality were mainly cardiac in origin, with as predominant cause heart failure in respectively 49.7% and 34.5% of the cases. Ventricular arrhythmias caused 16.6% of early deaths and 17.2% of late deaths. Concomitant CABG significantly decreased late mortality (RR = 0.28, $p < 0.001$) without increasing early mortality (RR = 1.018, $p = 0.858$). Concomitant mitral valve surgery showed both an increased risk for early (RR = 1.57, $p = 0.001$) and late mortality (RR = 4.28, $p < 0.001$). No clinical or hemodynamic parameters were found to influence mortality. It is noteworthy that only one third of patients included in the current analysis were operated for heart failure (14 studies, 4135 patients). In this group we noted an early mortality of 11.0% with a late mortality (3-year) of 15.2%. This analysis of pooled literature data showed that LV reconstruction surgery is performed with acceptable mortality and EVR may be the preferred technique with a reduced risk for early and late mortality. Concomitant CABG improved outcome, whereas the need for mitral valve surgery appeared an index of gravity. No clinical or hemodynamic parameters were found to influence mortality; specifically LV ejection fraction and LV volumes both did not predict outcome.

Keywords: Left ventricular reconstruction surgery; Aneurysmectomy; Surgical ventricular restoration; Dor procedure; Ischemic heart disease; Heart failure

1. INTRODUCTION

The formation of scar tissue after myocardial infarction leads to changes in left ventricular (LV) shape and function (remodeling) [1]. The normally elliptical LV tends to sphericity and chamber dilatation, while the transmurality of the myocardial scar determines whether or not a true LV aneurysm (dyskinetic segment) will develop [2]. Likoff and Bailey described the first aneurysmectomy in 1952 [3], subsequently followed by the first aneurysmectomy with linear repair using cardio-pulmonary bypass reported by Cooley in 1958 [4]. A number of different surgical techniques and modifications have since developed to restore LV shape and to improve LV function [4—9]. The most commonly used techniques are the endoventricular repair (EVR), with or without the use of an endoventricular patch, introduced by Dor in 1985 [4] and the aforementioned linear repair. Dor et al. demonstrated the feasibility of his procedure not only for the true LV aneurysms with a dyskinetic segment, but also for remodeled left ventricles with extensive akinesia [2]. Surgeons who advocate the different surgical techniques, all report on good short- and long-term results. Only a few reports are available that compare different surgical techniques, particularly in respect to long-term results [10—15,75]. The aims of this study were:

1. to compare early and late mortality in LV reconstruction surgery using different surgical techniques, based on pooled analysis of literature studies,
2. to evaluate the causes of early and late mortality in LV reconstruction surgery,
3. to evaluate the influence of factors including concomitant surgical procedures, clinical and hemodynamic parameters on early and late mortality.

LV reconstruction surgery is increasingly being employed as an alternative surgical therapy for patients with ischemic heart failure. In these patients the issues listed above are particular important and therefore a sub-analysis was conducted for this category of patients.

2. METHODS

2.1. Review of published reports

The studies were identified by means of several combined search strategies: (1) A search of the MEDLINE database (January 1980—January 2005) was conducted using the following Keywords: ‘left ventricular aneurysm’, ‘left ventricular restoration’, ‘surgical ventricular restoration’, ‘left ventricular remodeling surgery’, ‘aneurysmectomy’, and ‘Dor procedure’. (2) A manual search of six cardiothoracic surgery and cardiology journals (Annals of Thoracic Surgery, Journal of Thoracic and

Cardiovascular Surgery, European Journal of Cardiothoracic Surgery, Thoracic and Cardiovascular Surgery, Circulation and Journal of the American College of Cardiology). (3) The reference lists of the reports obtained through these searches were screened for additional articles that may have been missed. Only articles in English were considered, and reviews, editorials, animal or in vitro experimental studies, abstracts and articles concerning LV reconstruction surgery for non-ischemic heart disease were disregarded. The most recent publication or the publication concerning the largest patient population was included for analysis if multiple publications were available from the same institute to avoid double counting.

2.2. Statistical analysis

The following parameters were extracted from each article and entered into the database: pooled, average and median rates of in-hospital mortality and survival, specified causes of death (whether cardiac, subdivided in heart failure, ventricular arrhythmias, acute myocardial infarction and other, non-cardiac or unknown), follow-up duration, mean age, gender, interval post myocardial infarction, patients with ischemic heart failure (defined as LV ejection fraction (EF) ≤35% and New York Heart Association (NYHA) class III or IV), surgical technique used, mortality and survival with concomitant CABG and mitral valve surgery, LVEF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), LV end-diastolic dimension (LVEDD) and LV end-systolic dimension (LVESD). From the data, pooled, median and weighted-average early and late mortality were calculated. Cumulative survival was calculated from the pooled late mortality. Using comprehensive meta-analysis software (Borrestein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis Version 2, Biotstat, Englewood, NJ (2005)), the summary estimates of relative risks (RR) were calculated for the different surgical techniques that were used and for concomitant CABG and mitral valve surgery. The relative risk (with 95% confidence intervals, CI) was calculated using a random effects model. The riskadjusted relationship between mean age, time from infarction, LVEF, LVEDVI, LVESVI, LVEDD and LVESD and hospital mortality and survival was assessed by meta-regression. A sub-analysis on survival in patients with heart failure was conducted. A Chi-square test from homogeneity was calculated and Fisher's exact test was used for comparing events. A p value <0.05 was considered significant.

3. RESULTS

Two hundred and eight citations were returned and the articles scrutinized. After excluding non-English articles, reviews, editorials, animal or in vitro experimental

studies, abstracts and articles concerning LVRS for non-ischemic heart disease, 121 articles were evaluated. After exclusion of all but the most recent publication from the same institute and those not reporting deaths, 62 articles [10—70] were entered into the pooled analysis.

3.1. Early and late mortality in LV reconstruction surgery

Pooling of all data from the 62 studies [10—70] (12,331 patients) showed a pooled early mortality (defined as inhospital or 30-day mortality) of 6.8% and a median early mortality of 7.9%. Weighted average early mortality is 6.9%. Forty-seven studies also reported on long-term survival [11—53,71—74], following 8571 patients for a median of 49 months. Cumulative 1-, 5- and 10-year survival was 88.5%, 71.5% and 53.9%, respectively (Fig. 1).

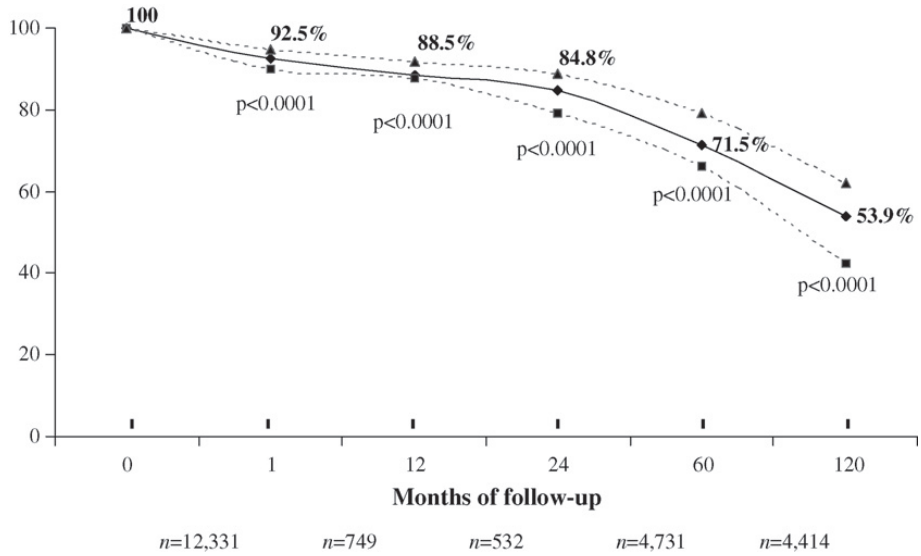


Fig. 1. Cumulative survival after LV reconstruction surgery calculated from 62 published reports (*n* = 12,331 patients) that reported on early mortality and 47 published reports following 8571 patients for a median of 49 months (25th, 75th percentile = 23, 62 months). Cumulative 1-, 5- and 10-year survival were 88.5%, 71.5% and 53.9%, respectively. Straight line: weighted average cumulative survival; dotted lines: 95% confidence intervals.

3.2. Different surgical techniques versus early and late mortality

The different techniques for LV reconstruction surgery, reported between January 1980 and January 2005, can be grouped into five main types of surgery: (1) direct reconstruction of the LV wall using a circular patch, (2) endoventricular reconstruction of the LV with or without the use of an endoventricular patch (EVR) as described by Jatene and Dor [9,60], (3) linear repair, (4) linear repair with septoplasty as described by Mickleborough et al. [5] and (5) septo-exclusion technique as described

by Guilmet et al. [7] and Stoney et al. [6]. Fig. 2 shows the summary estimates of the relative risks for the different surgical techniques for early mortality. Comparing the two main techniques, EVR shows a reduced risk for early mortality (RR = 0.79, $p = 0.002$) compared to the linear repair (RR = 1.38, $p < 0.001$). In Fig. 3, the summary estimates of the relative risks for the different surgical techniques are shown for late mortality. Again, considering the two main techniques EVR shows a significantly reduced risk on late mortality (RR = 0.67, $p < 0.001$) compared to linear repair (RR = 1.83, $p < 0.001$).

Type of Surgery	Death/ Total *n*	RR	95% CI	p value
Circular	40 / 880	0.60	(0.44 – 0.81)	0.001
EVR	237 / 3,759	0.79	(0.68 – 0.92)	0.002
Linear	416 / 4,769	1.38	(1.21 – 1.58)	<0.0001
Linear with septoplasty	96 / 1,265	1.03	(0.84 – 1.27)	0.77
Septo-exclusion	8 / 117	0.93	(0.47 – 1.81)	0.82
Pooled Deaths	797 / 10,790			

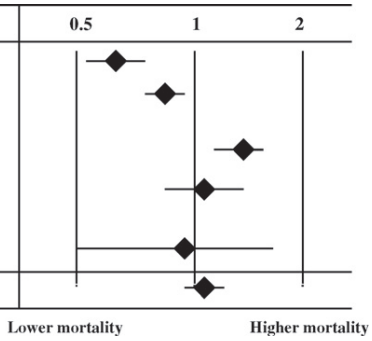


Fig. 2. Summary estimates of the relative risks for the different surgical techniques for early mortality. Comparing the two main techniques, EVR showed a reduced risk for early mortality (RR = 0.79, $p = 0.002$) compared to the linear repair (RR = 1.38, $p < 0.001$). LVRS: LV reconstruction surgery; Circular: direct reconstruction of LV wall using a circular patch; EVR: endoventricular reconstruction of the LV with or without a patch; linear: linear repair; linear with septoplasty: linear repair with a plasty of the interventricular septum; septo-exclusion: septo-exclusion technique.

Type of Surgery	Death/ Total *n*	RR	95% CI	p value
Circular	53 / 309	0.72	(0.56 – 0.93)	0.007
EVR	625 / 3,379	0.67	(0.61 – 0.73)	<0.0001
Linear	903 / 2,772	1.83	(1.68 – 1.98)	<0.0001
Linear with septoplasty	117 / 756	.634	(0.53 – 0.75)	<0.0001
Septo-exclusion	3 / 29	0.44	(0.15 – 1.29)	0.095
Pooled Deaths	1,701 / 7,245			

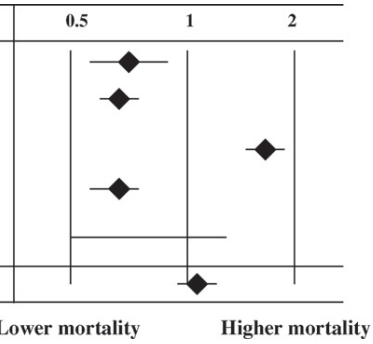


Fig. 3. Summary estimates of the relative risks for the different surgical techniques for late mortality. Comparing the two main techniques, EVR showed a significantly reduced risk on late mortality (RR = 0.67, $p < 0.001$) compared to the linear repair (RR = 1.83, $p < 0.001$). LVRS: LV reconstruction surgery; Circular: direct reconstruction of LV wall using a circular patch; EVR: endoventricular reconstruction of the LV with or without a patch; linear: linear repair; linear with septoplasty: linear repair with a plasty of the interventricular septum; septo-exclusion: septo-exclusion technique.

3.3. Causes of early and late mortality in LV reconstruction surgery

A total of 20 studies (n = 3729 patients) were identified that specified causes of early mortality. In Table 1, the causes of early mortality are shown. Early mortality was mainly cardiac in origin (84.7%), with as predominant cause heart failure in 49.7% of the cases. Ventricular arrhythmias were responsible for 16.5% of early mortality.

Table 1
Causes of early mortality after LVRS (20 studies, n = 3729 patients)

Cause of death	No. of patients	% of cardiac early mortality	% of total early mortality
Cardiac early mortality	261		84.7
Heart failure/LCO	153	58.6	49.7
VT/VF	51	19.5	16.6
AMI	34	13.0	11.0
Other	23	8.8	7.5
Non-cardiac early mortality	47		15.3
Total early mortality	308		

Early mortality was mainly cardiac in origin (84.7%), with as predominant cause heart failure in 49.7% of the cases. Ventricular arrhythmias were responsible for 16.6% of early mortality.
LCO: low cardiac output; VT/VF: ventricular tachycardia/ventricular fibrillation; AMI: acute myocardial infarction.

A total of 13 studies (n = 2702 patients) were identified that specified causes of late mortality. In Table 2, the causes of late mortality are summarized. Late mortality was also mainly cardiac in origin (70.2%). Heart failure constituted 34.5% and ventricular arrhythmias 17.2% of the late deaths. In 12.6% of late deaths, the cause was unknown.

Table 2
Causes of late mortality after LVRS (13 studies, n = 2702 patients)

Cause of death	No. of patients	% of cardiac late mortality	% of total late mortality
Cardiac late mortality	368		70.2
Heart failure/LCO	181	49.2	34.5
VT/VF	90	24.5	17.2
AMI	88	23.9	16.8
Other	9	2.5	1.7
Non-cardiac late mortality	90		17.2
Unknown	66		12.6
Total late mortality	524		

Late mortality was also mainly cardiac in origin (70.2%). Heart failure constituted 34.5% and ventricular arrhythmias 17.2% of the late death. In 12.6% of late deaths, the cause was unknown.
LCO: low Cardiac output; VT/VF: ventricular tachycardia/ventricular fibrillation; AMI: acute myocardial infarction.

3.4. Concomitant surgical procedures potentially influencing mortality

Seven studies (1525 patients) reported on concomitant CABG and early mortality in LV reconstruction surgery, and three studies (497 patients) reported on concomitant CABG and late mortality. Concerning concomitant mitral valve surgery (mitral valve repair or replacement): eight studies (524 patients) reported on early mortality in LV reconstruction surgery, two studies (84 patients) reported on late mortality. In Fig. 4, the summary estimates of the relative risks for concomitant CABG and mitral valve surgery for both early and late mortality are provided. Concomitant CABG was not associated with an increased risk for early mortality (RR = 1.018, $p = 0.858$), but was associated with a significantly lower risk for late mortality (RR = 0.28, $p < 0001$). Concomitant mitral valve surgery was associated with both an increased risk for early (RR = 1.57, $p = 0.001$) and late mortality (RR = 4.28, $p < 0.001$).

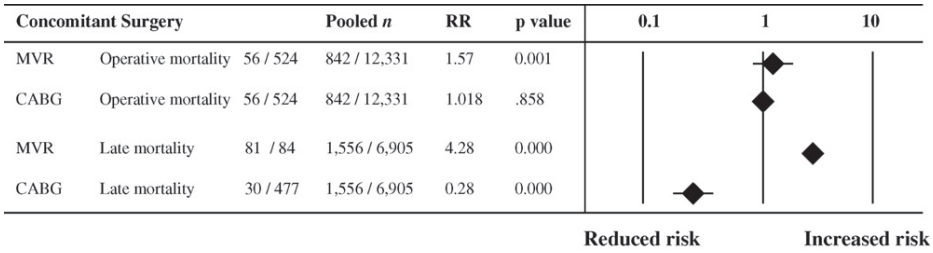


Fig. 4. Comparison of left ventricular reconstruction surgery with concomitant CABG or mitral valve surgery on early (inhospital or 30-day mortality) and late (5-year) mortality. Concomitant CABG was not associated with an increased risk for early mortality (RR = 1.018, $p = 0.858$), but was associated with a significantly lower risk for late mortality (RR = 0.28, $p < 0001$). Concomitant mitral valve surgery was associated with both an increased risk for early (RR = 1.57, $p = 0.001$) and late mortality (RR = 4.28, $p < 0.001$). MVR: mitral valve surgery (repair or replacement); CABG: coronary artery bypass grafting.

3.5. Factors potentially influencing mortality

The following parameters were evaluated: mean age, gender, interval post myocardial infarction, LVEF, LVEDVI, LVESVI, LVEDD and LVESD. None of the parameters were significantly related to early or late mortality. In particular, LVEF and indexed LV volumes were not related to early or late mortality.

3.6. Heart failure

Fourteen of the 62 (22.6%) reports included LV reconstruction surgery in patients with heart failure, with a total of 4135 patients. The pooled, median and average weighted early mortality patients with heart failure were 5.2%, 12.9% and 11.6%, respectively. Ten studies (802 patients) also reported on late mortality after LV reconstruction surgery showing a pooled, median and average weighted late mortal-

ity at 3-year follow-up of 15.7%, 14.7% and 15.7%, respectively (Fig. 5). Eight studies (n = 2376 patients) reported on EVR and early mortality in ischemic heart failure patients, four studies (1045 patients) reported on linear repair and early mortality in ischemic heart failure patients. Comparison of these two techniques for the relative risk of early mortality, revealed a significantly reduced risk for early mortality with EVR (RR = 0.66, p = 0.004, Fig. 6). There were no statistical significant relationships for any of the parameters postulated to possibly influence early and late mortality.

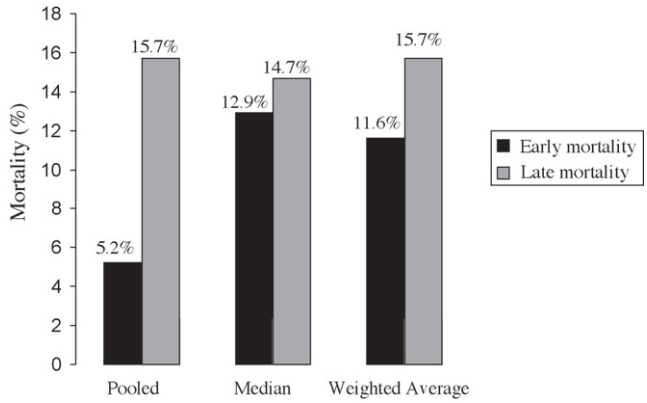


Fig. 5. Early (inhospital or 30-day mortality) and late (3-year) mortality in patients with heart failure. The pooled, median and average weighted early mortality (14 studies, n = 4135 patients) were 5.2%, 12.9% and 11.6%, respectively. The pooled, median and average weighted late mortality (10 studies, n = 802 patients) were 15.7%, 14.7% and 15.7%, respectively.

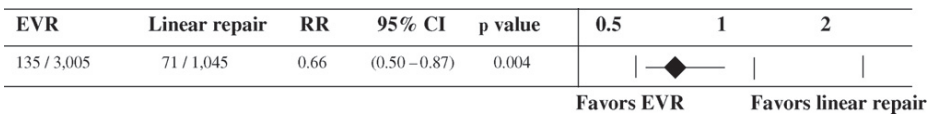


Fig. 6. Summary estimates of the relative risk for EVR (8 studies, n = 2376 patients) versus linear repair technique (4 studies, n = 1045 patients) in patients with heart failure. EVR shows a significantly reduced risk for early mortality (RR = 0.66, p = 0.004). EVR: endoventricular reconstruction of the LV with or without a patch; linear: linear repair.

4. DISCUSSION

In this pooled analysis of available studies in the literature, we found that surgical treatment of a LV aneurysm has an acceptable early mortality of 6.9% and a good longterm outcome (10-year survival 53.9%). This compared favorably to the natural history of LV aneurysms with a reported 5-year survival of 12% to 47% [76,77]. Improved medical treatment of ischemic heart disease has since then undoubtedly improved survival and delayed hemodynamic decompensation, but

survival in patients with a LV aneurysm is still limited. Faxon et al. demonstrated in the Coronary Artery Surgery Study (CASS) that patients with a LV aneurysm and three-vessel coronary artery disease and patients with clinical heart failure have improved survival with surgical therapy [74]. To date there have been no results from prospective randomized controlled trials comparing modern medical and surgical treatment. Historically, only a few patients with heart failure were considered for cardiac surgery in the absence of a clear need for coronary revascularization or valve repair or replacement. Indications for LV reconstruction have evolved over time from aneurysmectomy for thromboembolic complications or progressively enlarging aneurysms to LV reconstruction for improvement of ventricular function in the treatment of heart failure. One third of patients included in the current analysis were operated for heart failure (14 studies, 4135 patients). In this group we noted an early mortality of 11.0% with a late mortality (3-year) of 15.2%. Tertiary referral centers for cardiovascular care with large experience in LV reconstruction surgery for heart failure, like the Centre Cardio-Thoracique in Monaco and the San Donato Hospital in Milan, reported an early mortality ranging between 10% and 13% with survival at 3 years ranging from 62.7% to 77.2% [28,39,89]. It is noteworthy in this respect that the 'realworld' application of LV reconstruction surgery, as reported by Hernandez et al. in their study from the data of the STS National Cardiac Database shows higher operative risks, especially in specific subgroups of patients [95].

4.1. Surgical techniques and mortality

Comparing the two most used and reported techniques, endoventricular reconstruction of the LV with or without a patch (EVR) and linear repair, EVR shows a significantly reduced risk for early mortality (RR = 0.79, $p = 0.002$). The linear repair technique cannot exclude the septal scar, and also carries the risk of creating a restrictive residual LV cavity, especially in large aneurysms, leading to diastolic dysfunction and LV failure [27,78,79]. Sizing of the residual LV cavity in EVR, either by an intracavitary balloon or a commercially available shaper device to a volume of 50—60 ml/m^2 BSA avoids creating a residual LV cavity that is restrictive [9,29,39]. Another explanation for EVR to show better results could be that EVCPP patients were operated in a more recent era with improved myocardial protection, anesthesiological techniques, and perioperative care. Because of the limited number of patients in the currently available reports, the relative risks for early mortality calculated for the linear repair with septoplasty, and the septo-exclusion techniques did not reach statistical significance. The reconstruction of the LV wall using a circular patch did however show a significantly reduced risk for early mortality (RR = 0.60, $p = 0.001$), but again patient numbers for this technique are limited. In the meta-analysis by Parolari et al. concerning the early outcomes following

different LV reconstruction techniques, the authors also concluded that geometric reconstruction carries a reduced risk for early mortality compared to linear repair [90]. In contrast, in a sub-analysis comparing geometric and linear reconstruction techniques that were carried out in the same time lag, a difference in early mortality could not be demonstrated. Mukaddirov et al. recently published a study advocating a tailored approach (linear or patch plasty repair) in LVR depending on the specific anatomy of individual patients [99].

In the current pooled analysis, EVR also showed a significantly reduced risk for late mortality (RR = 0.67, $p < 0.0001$). Possibly, the complete exclusion of the septal scar and the more anatomical reconstruction leading to a more efficient myocardial fiber orientation and systolic function contributed to this reduction in late mortality [9,80]. Also the fact that grafting the left anterior descending coronary artery is more feasible in the EVR technique and may play a role [11,81,78]. The linear repair with septoplasty and direct reconstruction of the LV wall using a circular patch also both showed a significantly reduced risk for late mortality (RR = 0.72, $p = 0.007$ and RR = 0.63, $p < 0.0001$, respectively), but for both techniques available patient numbers are limited.

The factors that may have contributed to the reduced risk for mortality with the EVR technique in the pooled analysis of all patient categories may be even more important in patients with heart failure. Generally, these patients often have severely enlarged LV volumes, associated with depressed contractile function of the remote myocardium [88,89]. Indeed, we noted that in heart failure patients both early and late mortality were less with the EVCPP technique.

4.2. Fatal-failure modes of LVR

It was noted that 50% of early deaths and 30% of late deaths were caused by heart failure. With respect to the technique of reconstructing the LV cavity, three possible explanations exist for early and late LV failure: first, the aforementioned problem of creating a restrictive residual LV cavity, leading to diastolic dysfunction and LV failure; second, leaving a too large residual LV cavity only partially reverses the remodeling process and may lead to redilatation of the left ventricle. Also a residual large akinetic area has been mentioned as possible cause for redilatation. Ueno et al. demonstrated redilatation and increasing sphericity after Dor- and SAVE-procedures at intermediate follow-up, resulting in increased wall tension with reduced compliance as possible causes for late heart failure [92]. Raman et al. associated the use of a stiff and relatively big patch in EVR as cause for some adverse long-term outcomes [94]. Patch size, shape and orientation may prove to be important in preventing

adverse ventricular remodeling over time, as Cirillo et al. have shown in a small group with an EVR technique using a small, obliquely oriented and oval-shaped patch [93]. Third, insufficient residual remote myocardium to survive the procedure and to translate the surgically induced morphological changes to functional improvement leads to LV failure. No data are available on preoperative assessment of the functional capacity of the remote myocardium and used as predictor of outcome after LV reconstruction surgery.

Early and late mortality due to ventricular arrhythmias in this study were 16.5% and 17.2%, respectively (of note, it is unknown whether these patients already had ventricular arrhythmias preoperatively). Early ventricular arrhythmias after LV reconstruction surgery can be ascribed to electrolyte abnormalities, tissue edema and inflammation. Late ventricular arrhythmias have been related to ventricular dilatation with high wall stress and stretch [96]. It has been postulated that LV reconstruction surgery due to volume reduction reduces arrhythmogenicity. Exclusion of the myocardial scar, concomitant complete revascularization and mechanical resynchronization further reduces the trigger for electrical instability and may render the need for an implantable cardioverter-defibrillator (ICD) unnecessary [96,97]. Some authors like Dor et al. [79] and Mickleborough et al. [5] advocate routine use of concomitant endocardiectomy of the border zone of viable and non-viable myocardium and cryotherapy to further decrease the risk of ventricular arrhythmias. These authors have reported a low late incidence of ventricular arrhythmias with this strategy. The relatively high incidence of death due to ventricular arrhythmias observed in the present pooled analysis raises the question whether LV reshaping with volume reduction, scar exclusion and revascularization is sufficient antiarrhythmogenic to make adjunctive device therapy of little use. O'Neill et al. demonstrated a high incidence of ventricular arrhythmias after LV reconstruction surgery and advocate the use of predischarge electrophysiological studies and/or ICD implantation before hospital discharge [98]. More studies are needed to clarify the need for device therapy after LV reconstruction surgery.

4.3. Concomitant surgical procedures potentially influencing mortality

We found that concomitant myocardial revascularization with LV reconstruction surgery improved late survival without increasing the risk for early mortality. Besides symptomatic relief of angina, revascularization of viable, remote myocardium in non-scarred segments may improve compensatory contractile function [82]. Also, revascularization of the proximal left anterior descending coronary artery to improve septal perfusion may contribute favorably [11]. Another contributing

factor could be that revascularization further reduced the risk for late ventricular arrhythmias. These factors probably outweigh the increase in operative and extracorporal circulation time and thus did not result in higher early mortality. This finding underlines the importance of (complete) revascularization in these patients.

Concomitant mitral valve surgery, whether repair or replacement, shows an increased risk for early (RR = 1.57, $p = 0.001$) and late mortality (RR = 4.28, $p < 0.001$). In patients with previous anterior myocardial infarction, functional mitral regurgitation occurs mainly in the setting of LV dilatation, with tethering of the mitral valve leaflets, displacement of the subvalvular apparatus and dilatation of the mitral annulus causing secondary incompetence of the mitral valve. Functional mitral regurgitation therefore mainly reflects a more advanced stage of disease, and has been shown to be associated with an increased mortality, independent of the degree of underlying LV dysfunction [85—87]. The need for mitral valve surgery in LV reconstruction surgery is therefore an index of gravity. This is by no means an argument not to perform mitral valve surgery in these patients, since mitral regurgitation-related volume overload has been shown to promote further LV remodeling and progression of heart failure. Correcting mitral regurgitation improves clinical functional class and may prevent LV redilatation [39,72,91]. However, this analysis does not permit any conclusion on the benefits of mitral valve surgery, since no comparison between treated and non-treated patients was available in the literature.

4.4. Factors potentially influencing mortality

Besides the surgical technique and concomitant procedures, a number of parameters have been traditionally identified that influence early and late mortality. A low LVEF has been reported in earlier reports to be a predictor of higher early and late mortality [12,49,51,80]. The observation that LV dilatation is more closely related to outcome than (decreased) LVEF was first described by White at al., showing the correlation between increased LV volumes after myocardial infarction with increased mortality [83]. This work was subsequently confirmed by DiDonato et al. and Dor et al. for ventricular restoration procedures [26].

These authors have published that mortality after EVR procedures increased with larger preoperative LV volumes, irrespective of baseline LVEF [82]. Interestingly, we could neither confirm the relationship of LVEF with mortality, nor that of LV volumes in the current pooled analysis. An important explanation for this phenomenon may be the heterogeneity in the functional capacity of the residual remote myocardium. Since stroke volume is relatively constant at rest, LVEF is mainly determined by

the LV enddiastolic volume. If the LVend-diastolic volume is large due to a localized (dyskinetic) scar tissue, the improvement in LVEF after a LVR procedure will parallel improvement in function. On the other hand, if the LV end-diastolic volume is large due to remodeling or cardiomyopathy, a reduction will not be accompanied by improvement in LV function. Therefore neither LVEF, nor LV volumes per se can predict improvement in LV function and outcome [84]. The failure of LVEF, LV volumes, age, gender and time interval post-myocardial infarction in predicting outcome, questions the use of these parameters in risk stratification for these patients. Newer models using advanced imaging techniques that can test for the functional capacity of the remote myocardium, like (contrast-enhanced) magnetic resonance imaging or (3D) echocardiographically derived wall motion score indexes, may prove useful for improved risk stratification.

5. LIMITATIONS

A pooled analysis, when well designed and appropriately performed, is a powerful tool to combine in a single conclusion the results of different studies conducted on the same topic. Random effect models were used to control for within-study and between-study variability (random effects modeling). In addition, meta-regression analysis was used to adjust for the influence of patient demographics and prognostic indicators that covaried with the dependent variable. Despite the advantages of a pooled analysis, such as increased statistical power of a comparison and improved estimation of the effect of a treatment, several limitations of the current analysis should be addressed. Publication bias may have influenced our results, since observational studies with a poor outcome may not have been published in fulllength papers. Second and most important, surgical techniques and approaches have improved over time, which affects the current results. Third, since to date no prospectively randomized controlled trials have been published concerning LV reconstruction surgery, all studies included in this analysis were observational reports.

REFERENCES

[1] Gaudron P, Eilles C, Ertl G, Kochsiek K. Compensatory and non-compensatory left ventricular dilatation after myocardial infarction: time course and hemodynamic consequences at rest and during exercise. Am Heart J 1992;123:377—85.

[2] Di Donato M, Sabatier M, Dor V, Toso A, Maioli M, Fantini F. Akinetic versus dyskinetic postinfarction scar: relation to surgical outcome in patients undergoing endoventricular patch plasty repair. J Am Coll Cardiol 1997; 29:1569—75.

[3] Likoff W, Bailey CP. Ventriculoplasty: excision of myocardial aneurysm. Report of a successful case. JAMA 1955;158:915—20.

[4] Cooley DA, Collins HA, Morris GC, Chapman DW. Ventricular aneurysm after myocardial infarction: surgical excision with the use of temporary cardiopulmonary bypass. JAMA 1958;167:557—60.

[5] Mickleborough LL, Carson S, Ivanov J. Repair of dyskinetic or akinetic left ventricular aneurysm: results obtained with a modified linear closure. J Thorac Cardiovasc Surg 2001;121:675—82.

[6] Stoney WS, Alford Jr WC, Burrus GR, Thomas Jr CS. Repair of anteroseptal ventricular aneurysm. Ann Thorac Surg 1973;15:394—404.

[7] Guilmet D, Popoff G, Dubois C, Tawil N, Bachet J, Goudot B, Guermonprez JL, Brodaty D, Schlumberger S. Nouvelle technique chirurgicale pour la cure des aneurysmes du ventricle gauche. Archivie des maladie du coeur 1984;77:953—8.

[8] Dor V, Kreitmann P, Jourdan J. Interest of ''physiological'' closure (circumferential plasty on contractile areas) of left ventricle after resection and endocardectomy for aneurysm or akinetic zone: comparison with classical technique about a series of 209 left ventricular resections [abstract]. J Cardiovasc Surg 1985;26:73.

[9] Dor V, Saab M, Coste P, Kornazewska M, Montiglio F. Left ventricular aneurysm: new surgical approach. J Thorac Cardiovasc Surg 1989;37: 11—9.

[10] Sinatra R, Macrina F, Braccio M, Melina G, Luzi G, Ruvolo G, Marino B. Left ventricular aneurysmectomy: comparison between two techniques; early and late results. Eur J Cardiothorac Surg 1997;12:291—7.

[11] Lundblad R, Abdelnoor M, Svennevig JL. Surgery for left ventricular aneurysm: early and late survival after simple linear repair and endoventricular patch plasty. J Thorac Cardiovasc Surg 2004;128:449—56.

[12] Tavakoli R, Bettex D, Weber A, Brunner H, Genono M, Pretre R, Jenni R, Turina M. Repair of postinfarction dyskinetic LV aneurysm with either linear or patch technique. Eur J Cardiothorac Surg 2002;22: 129—34.

[13] Calafiore AM, Gallina S, Di Mauro M, Pano M, Teodori G, Di Giammarco G, Contini M, Iaco` AL, Vitolla G. Left ventricular aneurysmectomy: endoventricular circular patch plasty or septoexclusion. J Card Surg 2003; 18:93—100.

[14] Doss M, Martens S, Sayour S, Hemmer W. Long term follow up of left ventricular function after repair of left ventricular aneurysm. A comparison of linear closure versus patch plasty. Eur J Cardiothorac Surg 2001; 20:783—5.

[15] Vural KM, Sener E, Ozatik MA, Tas¸demir O, Bayazit K. Left ventricular aneurysm repair: an assessment of surgical treatment modalities. Eur J Cardiothorac Surg 1998;13:49—56.

[16] Akins CW. Resection of left ventricular aneurysm during hypothermic fibrillatory arrest without aortic occlusion. J Thorac Cardiovasc Surg 1986;91:610—8.

[17] Alloni A, Rinaldi M, Gazzoli F. Left ventricular aneurysm resection with port-access surgery: a new mini-invasive surgical approach. Ann Thorac Surg 2003;75:786—9.

[18] Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donato M, Menicanti L, Almeida de Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy PM, Oz MC, Fontan F, Scott ML, Accola KA, RESTORE group. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilatation. J Am Coll Cardiol 2004;44:1439—45.

[19] Barratt-Boyes BG, White HD, Agnex TM, Pemberton JR, Wild CJ. The results of surgical treatment of left ventricular aneurysm: an assessment of risk factors affecting early and late mortality. J Thorac Cardiovasc Surg 1984;89:87—8.

[20] Matthias Bechtel JF, To¨lg R, Graf B, Richardt G, Noetzold A, Kraatz EG, Sievers HH, Bartels C. High incidence of sudden death late after anterior LV-aneurysm repair. Eur J Cardiothorac Surg 2004;25:807—11.

[21] Brawley RK, Magovern Jr GJ, Gott VL, Donahoo Js, Gardner TJ, Watkins Jr L. Left ventricular aneurysmectomy: factors influencing postoperative results. J Thorac Cardiovasc Surg 1983;85:712—7.

[22] Cherniavsky AM, Karaskov AM, Marchenko AV, Mikova NV. Preoperative modelling of an optimal left ventricle volume for surgical treatment of ventricular aneurysm. Eur J Cardiothorac Surg 2001;21:777—82.

[23] Coltharp WH, Hoff SJ, Stoney WS, Alford Jr WC, Burrus GR, Glassford Jr DM, Lea 4th JW, Petracek MR, Starkey TD, Shuman TA. Ventricular aneurysmectomy: a 25- year experience. Ann Surg 1994;219:707—14.

[24] Couper GS, Bunton RW, Birjiniuk V, DiSesa VJ, Fallon MP, Collins Jr JJ, Cohn LH. Relative risks of left ventricular aneurysmectomy on patients with akinetic scars versus true dyskinetic aneurysms. Circulation 1990;82(Suppl. IV):IV248—56.

[25] Crosby IK, Wellons HA, Martin RP, Schuch D, Muller Jr WH. Employability. A new indication for aneurysmectomy and coronary revascularization. Circulation 1980;62(Suppl. I):I79—83.

[26] Di Donato M, Toso A, Maioli M, Sabatier M, Stanely Jr AW, Dor V, RESTORE Group. Intermediate survival and predictors of death after surgical ventricular restoration. Semin Thorac Cardiovasc Surg 2001;13:468—75.

[27] Di Mattia DG, Di Biasi P, Salati M, Mangini A, Fundaro` P, Santoli C. Surgical treatment of left ventricular post-infarction aneurysm with endoventriculoplasty: late clinical and functional results. Eur J Cardiothorac Surg 1999;15:413—8.

[28] Dor V. The endoventricular circular patch plasty (''Dor procedure'') in ischemic akinetic dilated ventricles. Heart Fail Rev 2001;6:187—93.

[29] Fundaro P, Pocar M, Marchetto G, Moneta A, Mattioli R, Donatelli F, Grossi A. Early surgical anteroseptal ventricular endocardial restoration after acute myocardial infarction. Pathophysiology and surgical considerations. Ital Heart J 2003;4:252—6.

[30] Grossi EA, Chinitz LA, Galloway AC, Delianides J, Schwartz DS, McLoughlin DE, Keller N, Kronzon I, Spencer FC, Colvin SB. Endoventricular remodeling of left ventricular aneurysm: functional, clinical and electrophysiological results. Circulation 1995;92(Suppl. I):II98—100.

[31] Isomura T, Suma H, Yamaguchi A, Kobashi T, Yuda A. Left ventricular restoration for ischemic cardiomyopathy — comparison of presence and absence of mitral valve procedure. Eur J Cardiothorac Surg 2003;23:614—9.

[32] Jais JM, Marchand M, de Riberolles C, Dubuis C, Neveux JY, Hazan E. Surgery of post-myocardial infarction scar: early and late results in 70 patients. Br Heart J 1980;43:436.

[33] Kokaji K, Shin H, Hotoda K, Mori M, Kumamaru H, Yozu R. Changes in left ventricular volume and predictors of cardiac events after endoventricular circular patch plasty. Jpn J Thorac Cardiovasc Surg 2004;52:551—9.

[34] Komeda M, David TE, Malik A, Ivanov J, Sun Z. Operative risks and longterm results of operation for left ventricular aneurysm. Ann Thorac Surg 1992;53:22—8.

[35] Lee GT, Newton MC, Crosby IK, Burwell LR, Wellons HA. Evaluating candidates for ventricular aneurysmectomy. South Med J 1980;73. p. 611—4, 617.

[36] Louagie Y, Alouini T, Lesperance J, Pelletier LC. Left ventricular aneurysm complicated by congestive heart failure: an analysis of long term results and risk factors of surgical treatment. J Cardiovasc Surg (Torino) 1989;30: 648—55.

[37] Magovern GJ, Sakert T, Simpson K, Laub GW, Park SB, Liebler G, Burkholder J, Maher T, Benckart D, Magovern Jr GJ. Surgical therapy for left ventricular aneurysm: a ten years' experience. Circulation 1989;79(Suppl.): I102—7.

[38] Maxey TS, Reece TB, Ellman PI, Butler PD, Kern JA, Bosch X, Lesperance J, Pelletier LC, Kron IL. Coronary artery bypass with ventricular restoration is superior to coronary artery bypass alone in patients with ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2004;127:428—34.

[39] Menicanti L, Di Donato M, Frigiola A, Buckberg G, Santambrogio C, Ranucci M, Santo D, RESTORE Group. Ischemic mitral regurgitation: intraventricular papillary muscle imbrication without mitral ring during left ventricular restoration. J Thorac Cardiovasc Surg 2002;123:1041—50.

[40] Mickleborough LL, Merchant N, Ivanov J, Rao V, Carson S. Left ventricular reconstruction: early and late results. J Thorac Cardiovasc Surg 2004;128: 127—37.

[41] Novick RJ, Stefaniszyn HJ, Morin JE, Symes JF, Sniderman AD, Dobell AR. Surgery for postinfarction left ventricular aneurysm. Prognosis and longterm follow-up. Can J Surg 1984;27:161—7.

[42] Olearchyk AS, Lemole GM, Spagna PM. Left ventricular aneurysm: ten years' experience in surgical treatment of 244 cases. Improved clinical status, hemodynamics, and long-term longevity. J Thorac Cardiovasc Surg 1983;88:544—53.

[43] Pasini S, Gagliardotto P, Punta G, Del Ponte S, Serra M, Parisi F, Ottino G, Di Summa M. Early and late results after surgical therapy of postinfarction left ventricular aneurysm. J Cardiovasc Surg 1998;39:209—15.

[44] Ratcliffe PJ, Kay P, Oldershaw PJ, Dawkins K, Cotter L, Lennox SC, Paneth M. Long- term survival following left ventricular aneurysmectomy. J Cardiovasc Surg 1983;24:461—6.

[45] Reddy SB, Cooley DA, Duncan JM, Norman JC. Left ventricular aneurysm: twenty-year surgical experience with 1572 patients at the Texas Heart Institute. Cardiovasc Dis Bull Tex Heart Inst 1981;8:165.

[46] Salati M, Di Biasi P, Paje A, Santoli C. Left ventricular geometry after endoventriculoplasty. Eur J Cardiothorac Surg 1993;7:574—9.

[47] Sosa E, Scanavacca M, d'Avila A, Fukushima J, Jatene A. Long-term results of visually guided left ventricular reconstruction as single therapy to treat ventricular tachycardia associated with postinfarction anteroseptal aneurysm. J Cardiovasc Electrophysiol 1998;9:1133—43.

[48] Suzer K, Yorgancioglu C, Gunaydin S, Tokmakoglu H, Tezcaner T. Surgical management of left ventricular aneurysms by endoventricular pericardial patch plasty. Cardiovasc Surg 2002;10:216—21.

[49] Ural E, Yuksel H, Pehlivanoglu S, Bakay C, Olga R. Short and long term survival of surgical treatment of left ventricular aneurysms. Ten years experience. Jpn Heart J 2002;43:379—87.

[50] Vauthey JN, Berry DW, Snyder DW, Gilmore JC, Sundgaard-Riise K, Mills NL, Ochsner JL. Left ventricular aneurysm repair with myocardial revascularization: an analysis of 246 consecutive patients over 15 years. Ann Thorac Surg 1988;46:29—35.

[51] Vicol C, Rupp G, Fischer S, Summer C, Dietrich Bolte H, Struck E. Linear repair versus ventricular reconstruction for the treatment of left ventricular aneurysm: a 10-year experience. J Cardiovasc Surg 1998;39:461—8.

[52] Wright JS, Stacey RB, Albrecht H, Murton MM. Left ventricular aneurysm surgery: determinants of results. J Thorac Cardiovasc Surg 1987;28:85—8.

[53] Yamaguchi A, Adachi H, Kawahito K, Murata S, Ino T. Left ventricular reconstruction benefits patients with dilated ischemic cardiomyopathy. Ann Thorac Surg 2005;79:456—61.

[54] Bolooki H, DeMarchena E, Mallon SM, Katariya K, Barron M, Bolooki HM, Thurer RJ, Novak S, Duncan RC. Factors affecting late survival after surgical remodeling of left ventricular aneurysms. J Thorac Cardiovasc Surg 2003;126:374—83.

[55] Castiglioni A, Quarti A, Schreuder J, Blasio A, Benussi S, Torracca L, Maisano F, Alfieri O. Surgical restoration of the left ventricle for postinfarction aneurysm. Ital Heart J 2002;3:370—4.

[56] Cooley DA, Frazier OH, Duncan JM, Reul GJ, Krajcer Z. Intracavitary repair of ventricular aneurysm and regional dyskinesia. Ann Surg 1992;215:417—23.

[57] Cosgrove DM, Lytle BW, Taylor PC, Stewart RW, Golding LA, Mahfood S, Goormastic M, Loop FD. Ventricular aneurysm resection: trends in surgical risk. Circulation 1989;79(Suppl. I):I-97—101.

[58] Cotrufo M, Romano GP, De Santo LS, Della Corte A, Amarelli C, Cafarella G, Maiello C, Scardone M. Treatment of extensive ischemic cardiomyopathy: quality of life following two different surgical strategies. Eur J Cardiothorac Surg 2005;27:481—7.

[59] Gonzalez-Santos JM, Ennabli K, Galinanes M, Bosch X, Lesperance J, Pelletier LC. Surgical treatment of the post infarction left ventricular aneurysm. Factors influencing early and late results. J Thorac Cardiovasc Surg 1985;33:86—93.

[60] Jatene AD. Left ventricular aneurysmectomy: resection or reconstruction. J Thorac Cardiovasc Surg 1985;89:321—31.

[61] Jones EI, Craver JM, Hurst JW, Bradford JA, Bone DK, Robinson PH, Cobbs BW, Thompkins TR, Hatcher Jr CR. Influence of left ventricular aneurysm on survival following coronary bypass operations. Ann Surg 1981;193: 733—41.

[62] Kaza AK, Patel MR, Fiser SM, Long SM, Kern JA, Tribble CG, Kron IL. Ventricular reconstruction results in improved left ventricular function and amelioration of mitral insufficiency. Ann Surg 2002;235:828—32.

[63] Mangschau A, Simonsen S, Abdelnoor M, Laake B, Geiran O. Evaluation of left ventricular aneurysm resection: a prospective study of clinical and hemodynamic characteristics. Eur J Cardiothorac Surg 1989;3:58—64.

[64] Marchenko AV, Cherniavsky AM, Volokitina TL, Alsov SA, Karaskov AM. Left ventricular dimension and shape after postinfarction aneurysm repair. Eur J Cardiothorac Surg 2005;27:475—80.

[65] Parrino PE, Kron IL, RESTORE Group. The role of left ventricular reconstruction for cardiogenic shock. Semin Thorac Cardiovasc Surg 2001;13: 476—9.

[66] Prates PR, Homsi Neto A, Lovato LM, Teiseira GF, Sant'Anna JR, Yordi LM, Kalil RA, Nesralla IA. Late results of endoventricular patch plasty repair in akinetic and dyskinetic areas after acute myocardial infarction. Arq Bras Cardiol 2002;79:107—16.

[67] Raman J, Dixit A, Storer M, Hare D, Buxton BF. Geometric endo-ventricular patch repair of inferior left ventricular scars improves mitral regurgitation and clinical outcome. Ann Thorac Surg 2001;72:S1055—8.

[68] Roscitano A, Capuano F, Simon C, Filippelli S, Mazzesi G, Tonelli E, Sinatra R. Left ventricular aneurysm repair: early survival. Ital Heart J 2005;6: 143—9.

[69] Sartipy U, Alba°ge A, Lindblom D. The Dor procedure for left ventricular reconstruction. Ten-year clinical experience. Eur J Cardiothorac Surg 2005;27:1005—10.

[70] Silveira WL, Leite AF, Soares EC, Nery MW, Carneiro AF, Oliveira VG. Shortterm follow-up of patients after aneurysmectomy of the left ventricle. Arq ras Cardiol 2000;75:401—4.

[71] Kawata T, Kitamura S, Kawachi K, Morita R, Yoshida Y, Hasegawa J. Systolic and diastolic function after patch reconstruction of left ventricular aneurysms. Ann Thorac Surg 1995;59:403—7.

[72] Qin JX, Shiota T, McCarthy PM, Asher CR, Hail M, Agler DA, Popovic´ ZB, Greenberg NL, Smedira NG, Starling RC, Young JB, Thomas JD. Importance of mitral valve repair associated with left ventricular reconstruction for patients with ischemic cardiomyopathy: a real-time threedimensional echocardiographic study. Circulation 2003;108(Suppl. 1): II241—6.

[73] Salati M, Di Biasi P, Paje A, Cialfi A, Bozzi G, Santoli CL. Functional results of left ventricular reconstruction. Ann Thorac Surg 1993;53:316—22.

[74] Faxon DP, Myers WO, McGabe CH, Davis KB, Schaff HV, Wilson JW, Ryan TJ. The influence of surgery on the natural history of angiographically documented left ventricular aneurysm: the Coronary Artery Study. Circulation 1986;74(Suppl.):I110—8.

[75] Shapira OM, Davidoff R, Hilkert RJ, Aldea GS, Fitzgerald CA, Shemin RJ. Repair of left ventricular aneurysm: long-term results of linear repair versus endoaneurysmorrhaphy. Ann Thorac Surg 1997;63:701—5.

[76] Schlicter J, Hellerstein HK, Katz LN. Aneurysm of the heart: a correlative study of 102 proven cases. Medicine 1954;33:43.

[77] Grondin P, Kretz JG, Bical O, Donzeau-Gouge P, Petitclerc R, Campeau L. Natural history of saccular aneurysms of the left ventricle. J Thorac Cardiovasc Surg 1979;77:57—64.

[78] Dor V, Sabatier M, Di Donato M, Maioli M, Toso A, Montiglio F. Late hemodynamic results after left ventricular patch repair associated with coronary grafting in patients with postinfarction akinetic or dyskinetic aneurysm of the left ventricle. J Thorac Cardiovasc Surg 1995;110: 1291—301.

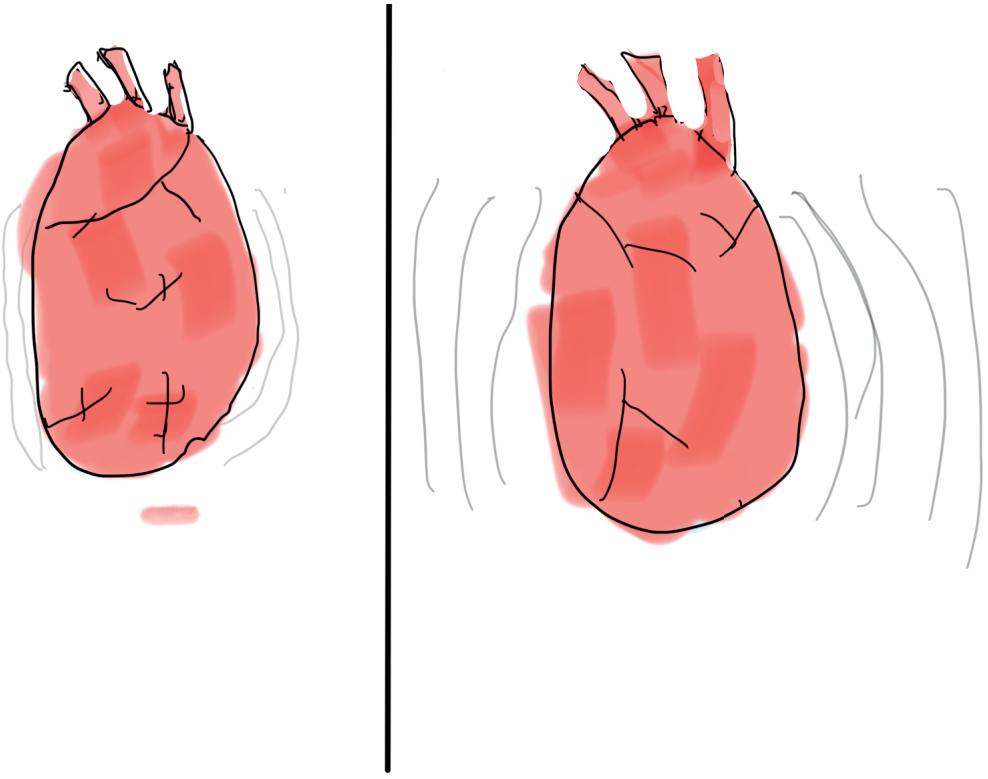
[79] Dor V, Sabatier M, Di Donato M, Montiglio F, Toso A, Maioli M. Efficacy of endoventricular patch plasty repair in large postinfarction akinetic scar and severe left ventricular dysfunction: comparison with a series of large dyskinetic scar. J Thorac Cardiovasc Surg 1998;116:50—9.

[80] Menicanti L, Di Donato M. The Dor procedure: What has changed after fifteen years of clinical practice? Editorial. J Thorac Cardiovasc Surg 2002;124:886—90.
[81] Mills NL, Everson CT, Hockmuth DR. Technical advances in the treatment of left ventricular aneurysm. Ann Thorac Surg 1993;55:792—800.
[82] Buckberg GD. Questions and answers about the STICH trial: a different perspective. J Thorac Cardiovasc Surg 2005;130:245—9.
[83] White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76: 44—51.
[84] Dor V. Left ventricular reconstruction: the aim and the reality after twenty years. J Thorac Cardiovasc Surg 2004;128:17—20.
[85] Menicanti L, Di Donato M, Castelvecchio S, Santambrogio C, Montericcio V, Frigiola A, Buckberg G, RESTORE group. Functional ischemic mitral regurgitation in anterior ventricular remodeling: results of surgical ventricular restoration with and without mitral repair. Heart Fail Rev 2004;9:317—27.
[86] Enriquez-Sarano M, Schaff HV, Frye RL. Mitral regurgitation: what causes the leakage is fundamental to the outcome of valve repair. Circulation 2003;108:253—6.
[87] Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation : long term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759—64.
[88] Stanley Jr AW, Athanasuleas CL, Buckberg GD. Heart failure following anterior myocardial infarction: an indication for ventricular restoration, a surgical method to reverse post-infarction remodeling. Heart Fail Rev 2004;9:241—54.
[89] Buckberg GD. Overview: ventricular restoration — a surgical approach to reverse ventricular remodeling. Heart Fail Rev 2004;9:233—9.
[90] Parolari A, Naliato M, Loardi C, Denti P, Trezzi M, Zanobini M, Porqueddu M, Roberto M, Kassem S, Alamanni F, Tremoli E, Biglioli P. Surgery of left ventricular aneurysm: a meta-analysis of early outcomes following different reconstruction techniques. Ann Thorac Surg 2007;83:2009—16.
[91] Romano SA, Bolling SF. Update on mitral repair in dilated cardiomyopathy. J Card Surg 2004;19:396—400.
[92] Ueno T, Sakata R, Igura Y, Yamamoto H, Ueno M, Ueno T, Matsumoto K. Mid-term changes of left ventricular geometry and function after Dor, SAVE, and overlapping procedures. Eur J Cardiothorac Surg 2007;32: 52—7.
[93] Cirillo M, Amaduci A, Quaini E, Villa E, Tomba MD, Mhagna Z, Brunelli F, Messina A, Troise G. Patch size, shape and orientation affect geometrical outcomes of surgical anterior ventricular restoration. J Cardiovasc Med (Hagerstown) 2008;9:389—95.
[94] Raman J, Dixit A, Bolotin G, Jeevanandam V. Failure modes of left ventricular reconstruction or the Dor procedure: a multiple-institutional perspective. Eur J Cardiothorac Surg 2006;30:347—52.
[95] Hernandez AF, Velazquez EJ, Dullum MK, O'Brien S, Ferguson TB, Peterson ED. Contemporary performance of surgical ventricular restoration procedures: data from the Society of Thoracic Surgeons' National Cardiac Database. Am Heart J 2006;152:494—9.
[96] Di Donato, Sabatier M, Menicanti L, Dor V. Incidence of ventricular arrhythmias after left ventricular reconstructive surgery. J Thorac Cardiovasc Surg 2007;133:289—91.

[97] Buckberg GD. Congestive heart failure: treat the disease, not the symptom — return to normalcy. J Thorac Cardiovasc Surg 2001;121:628—37.

[98] O'Neill J, Starling RC, Khaykin Y, McCarthy PM, Young JB, Hail M, Albert N, Smedira N, Chung MK. Residual high incidence of ventricular arrhythmias after left ventricular reconstruction surgery. J Thorac Cardiovasc Surg 2005;130:1250—6.

[99] Mukaddirov M, Frapier JM, Demaria RG, Albat B. Surgical treatment of postinfarction anterior left ventricular aneurysms: linear vs patch plasty repair. Interact Cardiovasc Thorac Surg 2008;7:256—61.



Chapter 3

Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure

Patrick Klein [a], Eduard R. Holman [b], Michel I.M. Versteegh [a], Eric Boersma [c], Harriette F. Verwey [b], Jeroen J. Bax [b], Robert A.E. Dion [a], Robert J.M. Klautz [a]

[a] Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
[c] Department of Biostatistics and Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

Presented at the 22nd Annual Meeting of the European Association for Cardio-thoracic Surgery, Lisbon, Portugal, September 14—17, 2008.

European Journal of Cardio-thoracic Surgery 35 (2009) 847—853

ABSTRACT

Objective: Advanced ischemic heart failure can be treated with surgical ventricular restoration (SVR). While numerous risk factors for mortality and recurrent heart failure have been identified, no plain predictor for identifying SVR patients with left ventricular damage beyond recovery is yet available. We tested echocardiographic wall motion score index (WMSI) as a predictor for mortality or poor functional result.

Methods: One hundred and one patients electively operated between April 2002 and April 2007 were included for analysis. All patients had advanced ischemic heart failure (NYHA-class ≥ III and LVEF ≤ 35%). Mean logistic EuroSCORE was 10 ± 8. All patients were evaluated at 1-year follow-up. Risk factors for poor outcome, defined as mortality or poor functional result (NYHA class ≥ III) at 1-year follow-up were identified by univariable logistic regression analysis. Preoperatively, a 16-segment echocardiographic WMSI was calculated and receiver operating characteristic curve analysis was used to identify cut-off values for WMSI in predicting poor outcome.

Results: Early mortality was 9.9%, late mortality 6.6%. NYHA class improved from 3.2 ± 0.4 to 1.5 ± 0.7. At 1-year follow-up, 10 patients (12%) were in NYHA class III and the remaining patients were in NYHA class I or II (75 patients, 88%). WMSI was found to be the only statistically significant predictor for poor outcome (odds ratio 139, 95% confidence interval (CI) 17—1116, $p < 0.0001$). The optimal cut-off value for WMSI in predicting mortality or poor functional result was 2.19 with a sensitivity and specificity of 82% (95% CI 81.5—82.5% and 81.4—82.6%). The area under the curve was 0.94 (95% CI 0.90—0.99). Positive and negative predictive values were 67% and 92% respectively (95% CI 66.4—67.6% and 91.4—92.6%).

Conclusions: Sufficient residual remote myocardium is necessary to recover from a SVR procedure and to translate the surgically induced morphological changes into a functional improvement. Preoperative WMSI is a surrogate measure of residual remote myocardial function and is a promising tool for better patient selection to improve results after SVR procedures for advanced ischemic heart failure.

Keywords: Surgical ventricular restoration (SVR); Left ventricular reconstruction surgery; Dor procedure; Ischemic heart disease; Heart failure; Wall motion score index (WMSI); Risk stratification; Risk factors

1. INTRODUCTION

Surgical ventricular restoration (SVR) has established its position in the treatment of patients with post-infarction ventricular dilatation and a wide range of symptoms [1—3]. This procedure is also increasingly performed in patients with severely depressed left ventricular function and heart failure [5,6]. SVR encompasses ventricular remodeling surgery combined with complete coronary revascularization and mitral valve plasty or replacement when moderate or severe mitral regurgitation is present. The ventricular remodeling as described by Dor et al. excludes asynergetic areas, restores the normally elliptical left ventricular shape and reduces the left ventricular volume within the normal range. This results in reduced left ventricular wall stress with decreased oxygen consumption and reorients the myocardial fibers to a more efficient orientation to improve systolic performance [4].

While numerous studies have identified risk factors for mortality and limited survival after SVR in patients with heart failure, including renal insufficiency, severe mitral regurgitation, concomitant mitral valve surgery, and progressive left ventricular dilatation, no plain risk variable is yet available to identify patients who have a poor outcome [10,11,16]. Better patient selection and preoperative risk stratification will reduce mortality and improve outcome after SVR procedures. In this study, the echocardiographic wall motion score index (WMSI) was evaluated as a predictor for mortality or poor functional result in patients with advanced ischemic heart failure undergoing SVR.

2. MATERIALS AND METHODS

2.1. Patient characteristics

Between April 2002 and April 2007, 101 patients were electively operated and included for analysis. There were 80 men and the mean age was 61 ± 10 years. All patients had advanced ischemic heart failure (NYHA class ≥ III and LVEF ≤ 35%), 81 patients were in NYHA class III and 20 patients in NYHA class IV. Patients were considered eligible for surgery, whenever at least three of the four segments of the remote myocardium, i.e. the basal pyramid of the left ventricle (septum, anterior, lateral and inferior regions) showed systolic thickening. If only two segments showed thickening, the potential for functional recovery of at least one additional basal segment was actively sought for. For this purpose, viability studies including dobutamine-stress echocardiography, and/or contrast-enhanced MRI were used. Severe renal insufficiency (serum creatinine ≥ 200 µmol/l) was present in five patients.

Table 1
Preoperative patient characteristics (n = 101).

Age (years) (mean ± SD)	61 ± 10
Gender, male/female (*n*)	81/20
Median interval after infarction (months, range)	48 (0—360)
<3 months (*n*, %)	7 (6.9%)
>3 months (*n*, %)	94 (93.1%)
Previous cardiac surgery (*n*, %)	8 (7.9%)
Renal insufficiency (*n*, %)	5 (5.0%)
Severe pulmonary hypertension (*n*, %)	13 (12.9%)
Logistic EuroSCORE (mean ± SD)	10 ± 8
NYHA class (mean ± SD)	3.2 ± 0.4
III (*n*, %)	81 (80.2%)
IV (*n*, %)	20 (19.8%)
Concomitant angina (*n*, %)	18 (17.81%)
CCS class (mean ± SD)	2.7 ± 0.6
VO2max (mean ± SD)	17 ± 5
Spontaneous VT (*n*, %)	21 (20.8%)
Preoperative ICD implantation (*n*, %)	23 (22.8%)

NYHA: New York Heart Association; VT: ventricular tachyarrhythmia; ICD, implantable cardioverter-defibrillator.

Thirteen patients had severe pulmonary hypertension (systolic pulmonary artery pressure ≥ 60 mmHg). Logistic EuroSCORE averaged 10 ± 8. Concomitant angina was present in 18 patients. The median time interval after myocardial infarction was 48 months (range 0— 360) and seven patients were operated within 3 months after infarction. Eight patients had previous cardiac surgery. Patients with coexisting aortic valve disease necessitating aortic valve replacement or previous aortic valve surgery were excluded. A summary of the patient characteristics is provided in Table 1.

Table 2
Transthoracic echocardiographic data.

	Baseline	Early postop.	*p* value early vs baseline	1-year FU	*p* value 1-year FU vs early postop.
EF (%)	25 ± 7	36 ± 9	<.01	36 ± 11	.76
LVESVI (ml/m^2 BSA)	87 ± 42	48 ± 18	<.01	53 ± 25	.50
LVEDVI (mL/m^2 BSA)	116 ± 46	73 ± 21	<.01	79 ± 26	.33
LVESD (cm)	5.1 ± 1.1	4.8 ± 1.0	0.06	4.8 ± 1.0	.75
LVEDD (cm)	6.5 ± 1.0	6.0 ± 1.0	<.01	6.1 ± 0.8	.39

EF: left ventricular ejection fraction; LVEDVI: left ventricular end-diastolic volume index; LVESVI: left ventricular end-systolic volume index; BSA: body surface area; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; postop.: postoperative; FU: follow-up; SD: standard deviation.

The mean LVEF was 25 ± 7%, mean left ventricular enddiastolic volume index (LVEDVI) and left ventricular endsystolic volume index (LVESVI) were 116 ± 46 ml/m^2 BSA and 87 ± 42 ml/m^2 BSA respectively. Moderate to severe mitral regurgitation was present in 49 patients. The preoperative echocardiographic data are shown in Table 2.

Table 3
Surgical data (n = 101).

SVR with patch (*n*, %)	98 (97.0%)
Patch size (cm^2) (mean ± SD)	13 ± 8
Inferior wall plication (*n*, %)	13 (12.9%)
Balloon/shaper size (ml) (mean ± SD)	109 ± 12
Mitral valve annuloplasty (*n*, %)	53 (52.5%)
median ring size (range)	26 (24—30)
Tricuspid valve annuloplasty (*n*, %)	19 (18.8%)
median ring size (range)	30 (26—34)
CABG (*n*, %)	60 (59.4%)
No. of distal anastomosis/patient (mean ± SD)	2.3 ± 1.2
Cryo-ablation (*n*, %)	11 (10.9%)
Epicardial LV-lead (*n*, %)	26 (25.7%)
IABP (*n*, %)	20 (19.8%)

SVR: surgical ventricular restoration; IABP: intra-aortic balloon pump.

2.2. Operative technique

All operations were performed using normothermic cardiopulmonary bypass, aortic cross-clamping and intermittent antegrade warm-blood cardioplegia. SVR was carried out according to Dor using a shaping Fontan stitch at the transitional zone between viable and scarred myocardium and sizing the residual ventricle using a saline-filled balloon or commercially available shaper (TRISVR, Chase Medical, Richardson, TX, USA) at 55 ml/m^2 BSA. An endoventricular oval Dacron patch was used to close the residual opening left after tightening the Fontan stitch around the balloon. To facilitate the creation of a neo-apex in 13 patients, one or two U stitches where placed in the inferior wall [24]. Concomitant myocardial revascularization was performed in 60 patients. The mean number of distal anastomoses was 2.3 ± 1.2. Restrictive mitral annuloplasty (RMA) with stringent down-sizing (two sizes) using a semi-rigid ring (Carpentier Edwards Physioring, Edwards Lifesciences, Irvine, CA, USA) was performed in 53 patients in whom pre- or intra-operative echocardiography demonstrated at least moderate mitral regurgitation. In 19 patients a concomitant tricuspid annuloplasty was performed using the MC3-ring (Edwards Lifesciences, Irvine, CA, USA) because the tricuspid annular diameter exceeded 40

mm (our threshold for tricuspid annuloplasty). If patients had spontaneous ventricular arrhythmias preoperatively, a cryo-ablation at the border zone between scar tissue and viable myocardium was performed; this procedure was performed in 11 patients. Since 2006 implantation of an epicardial LV-lead formed a routine part of the procedure. A summary of the surgical data is provided in Table 3.

2.3. Pre- and postoperative echocardiography

A transthoracic echocardiogram (TTE) was performed within 3 days before surgery. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer at a depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). The left ventricular dimensions (end-systolic and enddiastolic) were determined from parasternal M-mode acquisitions. The left ventricular volumes and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique. Serial TTEs were performed after surgery as part of a structured heart failure program, with the first postoperative TTE performed before hospital discharge. From the TTEs performed at discharge and at 1-year follow-up, LVEF, left ventricular dimensions, left ventricular volumes and left ventricular shape were derived. Two cardiologists, blinded from the clinical data and the timing of the echocardiogram, analyzed all TTEs in random order.

2.4. Echocardiographic wall motion score index

Preoperative regional left ventricular function was evaluated by the echocardiographic derived WMSI. As recommended by the American Society for Echocardiography a 16-segment model was used for left ventricular segmentation [23]. This model consists of six segments at both the basal and mid-ventricular levels and four segments at the apex. The attachment of the right ventricular wall to the left ventricle defines the septum, which is divided at basal and mid-left ventricular levels into anteroseptum and inferoseptum. Continuing counterclockwise, the remaining segments at both basal and mid-ventricular levels are labeled as inferior, inferolateral, anterolateral and anterior. The apex includes septal, inferior, lateral and anterior segments. Each segment was analyzed individually and scored on the basis of its motion and systolic thickening. Each segment's function was confirmed in multiple views. Segments were scored are as: normal or hyperkinesis = 1, hypokinesis = 2, akinesis = 3 and dyskinesis (or aneurysmatic) = 4. WMSI was derived as the sum of all scores divided by the number of segments visualized.

2.5. Clinical follow-up

Patients were maintained on optimal medical treatment for heart failure after surgery, i.e. whenever possible ACEinhibitors, spironolactone, diuretics and b-blockers were prescribed. Functional status was assessed using the NYHA classification for heart failure symptoms. The symptoms were evaluated within 1 week before surgery and at serial followup visits at the outpatient clinic as part of the structured heart failure program. For all surviving patients, NYHA class at 1 year was assessed.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 16.0 statistical software (SPSS Inc, Chicago, IL, USA). Categorical variables are described as frequencies and percentages and compared using the chi-square test with Yates' correction. Continuous data are expressed as mean ± standard deviation (SD) or median with ranges and compared using Student's *t*-test for paired data. Risk factors for poor outcome, defined as mortality or poor functional result (NYHA-class ≥ III) at 1- year follow-up, were identified by logistic regression analysis. The optimal cut-off value for WMSI to predict poor outcome was determined by receiver operating characteristics (ROC) curve analysis. The optimal cut-off value was defined as that providing maximal accuracy to distinguish between patients with a good outcome (NYHA class I or II) and patients with a poor outcome. A p value <0.05 was considered significant.

Table 4
Causes of early and late mortality .

Cause of early mortality	No. of patients	Cause of late mortality	No. of patients
Cardiac early mortality	7	Cardiac late mortality	3
HF/LCO	6	HF/LCO	2
AMI	1	SCD	1
Non-cardiac early mortality	3	Unknown	3
Sepsis	2		
Pump lung	1		
Total early mortality	10	Total late mortality	6

HF/LCO: heart failure or low cardiac output; AMI: acute myocardial infarction; SCD: sudden cardiac death.

3. RESULTS

3.1. Clinical results

Early mortality (in-hospital or <30 days mortality) was 9.9% (10 patients). Causes of early mortality are shown in Table 4. Mean postoperative stay in the intensive care unit was 7 ± 9 days. Mean postoperative stay in the hospital was 19 ± 15 days. In 36 patients (39.6%) an internal cardioverterdefibrillator (ICD) was implanted postopera-

tively for primary or secondary prevention (an additional 23 patients already had an ICD preoperatively).

All patients were evaluated at 1-year follow-up. Late mortality was 6.6% (six patients). Causes of late mortality are shown in Table 4. At follow-up, a significant functional improvement was observed: mean NYHA class improved from 3.2 ± 0.4 preoperatively to 1.5 ± 0.7 ($p < 0.001$) at 1-year follow-up. Of the surviving patients, 88.2% (75 patients) were in NYHA class I or II and 11.8% (10 patients) had recurrent heart failure (NYHA class ≥ III). No patients needed reoperation during the follow-up period. Endocarditis or thromboembolic events were not observed.

Table 5
Logistic regression analysis.

Preoperative variables	Univariable analysis		
	OR	95% CI	*p*
Age	1.004	0.961—1.049	0.866
Renal dysfunction	2.116	0.333—13.451	0.427
Pulmonary hypertension	2.125	0.625—7.223	0.227
Moderate—severe mitral regurgitation	1.853	0.739—4.645	0.188
EF	0.99	0.926—1.059	0.771
LVESVI	0.995	0.983—1.007	0.42
LVEDVI	0.997	0.986—1.007	0.529
WMSI	139	17—1116	<0.0001

EF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index; LVEDVI: left ventricular end-diastolic volume index; WMSI: wall motion score index; CI: confidence interval.

3.2. Risk factors for mortality or poor functional result

Preoperative WMSI was found to be a highly significant predictor at univariable analysis for poor outcome at 1 year (odds ratio (OR) 139, 95% confidence interval (CI) 17—1116, $p < 0.0001$) (Table 5). Other preoperative risk factors, including age, renal insufficiency (serum creatinine ≥ 200 μmol/l), severe pulmonary hypertension (systolic pulmonary artery pressure ≥ 60 mmHg), moderate to severe mitral regurgitation, LVEF, LVESVI, and LVEDVI were not statistically significant (Table 5). Since only one statistically significant predictor was found at univariable analysis, a multivariable analysis would be redundant.

3.3. Echocardiography and WMSI

LVEF, left ventricular dimensions and volumes (indexed) as measured by TTE preoperatively, early postoperatively (at discharge) and at 1-year follow-up are provided in Table 2. A significant improvement in LVEF occurred early postoperatively, with

a reduction in left ventricular volumes. At 1-year follow-up these changes were maintained.

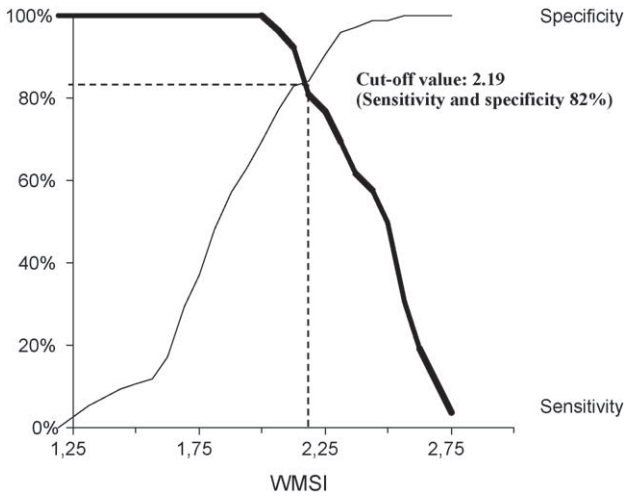


Fig. 1. ROC curve analysis shows an optimal cut-off value for WMSI in predicting mortality or poor functional result of 2.19 (sensitivity and specificity 82%). WMSI: wall motion score index.

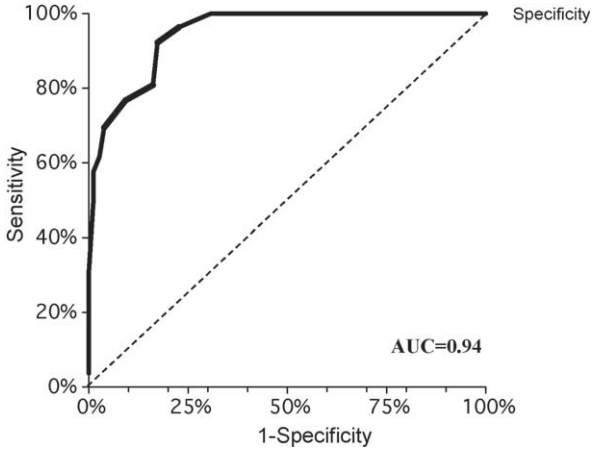


Fig. 2. ROC curve analysis shows an area under the curve (AUC) of 0.94 (95% CI 0.90—0.99).

The preoperative WMSI could range from 1 to 4. ROC curve analysis revealed that the optimal cut-off value for WMSI to predict mortality or poor functional result was 2.19; application of this cut-off value yielded a sensitivity and specificity of 82% (95% CI 81.5—82.5% and 81.4—82.6%). The ROC curve is shown in Fig. 1. The area under the curve for this cut-off value was 0.94 (95% CI 0.90—0.99) (Fig. 2). Positive and negative predictive values were 67% and 92% respectively (95% CI 66.4—67.6%

and 91.4—92.6%). Calculating 95% sensitivity and specificity yielded a WMSI of 2.3 and 2.1 respectively. The scatter-plot of WMSI versus outcome is shown in Fig. 3. It is noteworthy that below a WMSI of 2.0 no mortality or poor outcome was observed. Conversely, above a WMSI of 2.5, outcome was always poor.

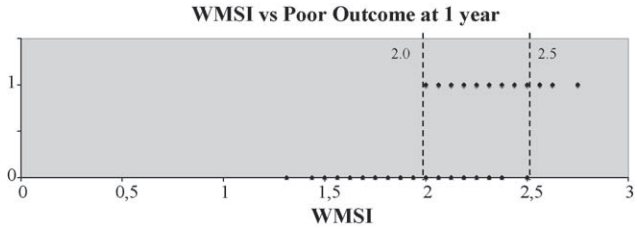


Fig. 3. Scatter-plot. The dotted lines indicate a WMSI of 2.0, below which the outcome was always favorable and a WMSI of 2.5, above which the outcome was consistently poor. WMSI: wall motion score index.

4. DISCUSSION

We found that the echocardiographically derived WMSI has a good ability to predict outcome after SVR surgery. This was the single statistically significant predictor for poor outcome at 1-year follow-up. Other preoperative variables including age, renal insufficiency, severe pulmonary hypertension, and moderate to severe mitral regurgitation proved not to be significant predictors of outcome. While numerous studies did identify renal insufficiency, posterior infarction, concomitant mitral valve surgery, age and diabetes as risk factors for mortality and limited survival after SVR in patients with heart failure, they are not useful as a screening tool for SVR [10,11]. Besides comorbidity and concomitant procedures a depressed LVEF has been reported to be a predictor of increased early and late mortality [12—14]. However, White et al. described that left ventricular dilatation after myocardial infarction was more closely related to outcome then a decreased LVEF [15]. Di Donato and Dor confirmed that in ventricular restoration procedures, relatively irrespective of LVEF, the mortality increased in parallel to preoperative left ventricular volumes [16]. However, heterogeneity in the capacity for functional recovery of the residual remote myocardium might influence operative risk in patients with equally increased left ventricular volumes. Indeed, the postinfarction remodeled left ventricle consists of heterogeneous tissue: scar (with varying degrees of transmurality), and residual myocardium with varying contractility. Volume derived indices, such as LVEDV or LVEF are incapable of predicting outcome since these parameters depend on global ventricular measurements. It was indeed observed that preoperative LVEF, LVESVI and LVEDVI were not statistically significant in predicting for poor outcome after SVR surgery. A potential screening tool needs to take into account the variability in

function of various areas of the ventricle and WMSI appears to reflect this information.

Why is screening for SVR so important? SVR is increasingly performed in patients with heart failure and severely depressed left ventricular function [5,6]. Although improved outcome have been reported, its widespread use is still hampered by a considerable early mortality and uncertainty about late outcome [8]. We recently performed a structured literature review (including 14 studies with 4135 patients) and noted an early mortality of 11.0% with a late mortality at 3 years of 15.2% in patients operated for heart failure [7]. However, the results need to be interpreted with caution, since significant heterogeneity of the underlying type and extent of dysfunction (localized dyskinesis or true aneurysms vs global hypokinesis). Menicanti et al. reported an early mortality of 6.6% in a homogenous series of patients that underwent SVR for ischemic cardiomyopathy [8]. In these patients a global increase of systolic function with a sustained reduction in left ventricular volumes was demonstrated. It is of interest that the 'real-world' application of SVR, is associated with higher operative risks as reported by Hernandez et al. as compared to the results reported by experienced tertiary referral centers [9].

In the current series of patients with advanced ischemic heart failure (NYHA class ≥ III and LVEF ≤ 35%) we observed an early mortality of 9.9% with a late mortality of 6.6% at 1- year follow-up. In addition, a significant improvement in systolic function with a reduction in left ventricular volumes was noted, which was maintained at 1-year follow-up. Given this significant improvement in both ventricular function and functional status, it therefore appears that patient selection forms the dominant problem evaluated at 1 year after the operation. Although continuous improvement in early surgical outcome has been demonstrated by various groups around the world, patient selection remains a difficult issue. Apparently, the systolic function of the remote myocardium is important for residual left ventricular systolic function after SVR and subsequent long-term outcome. In an attempt to quantify systolic left ventricular function, WMSI has been used since this parameter reflects a summation of the entire systolic function of the left ventricle. Our initial strategy to use the function of the basal pyramid to select patients eligible for SVR surgery, proved to be insufficient: about onequarter of the patients did not benefit from the procedure (26 out of 101 patients: mortality 15 patients, NYHA class ≥ III 10 patients). Indeed using the function of the basal pyramid takes into account only part of the left ventricle and does not differentiate between normo- and hypokinesia. WMSI considers the entire left ventricle and uses quantitative segmental function.

Indeed, application of WMSI to select patients appeared useful since this parameter could predict outcome with 95% sensitivity and specificity if the WMSI was above 2.3 or below 2.1 respectively. Moreover, if WMSI was below 2.0, outcome was always favorable and if WMSI was above 2.5 a poor outcome was obtained. Accordingly, patients with a WMSI <2.0 have a high likelihood of good outcome after SVR, whereas patients with a WMSI >2.5 have a high likelihood of poor outcome and should not be referred for SVR. Patients with a WMSI between 2.0 and 2.5, results may vary in outcome, and in these patients additional information may be needed to decide on SVR or not. Apparently, some patients with this score do well and others do not. This might be caused by reserve contractile properties of the left ventricle, related to ischemia (hibernation) or remodeling. The potential to reverse those factors will most likely determine the final outcome. The capability of the remaining left ventricle to improve its function after a SVR procedure is difficult to predict. Obviously, when large areas of (reversible) ischemia are present, even patients with very bad contractility will recover.

Future studies are needed in this patient category to further define additional parameters to optimize prediction of outcome after SVR. Possibly, more information on the presence and the extent of scar tissue and viable myocardium is needed, and for this, more sophisticated imaging techniques are needed such as metabolic imaging with positron emission tomography or contrast-enhanced MRI [17,18]. Hibernating myocardial segments or myocardial segments with partial scar tissue and high wall stress could improve contractility after coronary revascularization and SVR respectively [19]. Echocardiography and WMSI have the disadvantage of not being able to distinguish viable or hibernating myocardium from scar tissue among segments of not contracting myocardium compared to, for example contrast-enhanced MRI [20]. On the other hand, echocardiography can be performed in all patients, irrespective of the presence of devices like (biventricular) pacemakers or ICDs. Progressive use of device-therapy in patients with heart failure in forthcoming years renders an imaging technique with few contraindications of particular use [21,22]. Moreover, echocardiography is widely available and easy to perform. These are important advantages over MRI if used as a screening tool.

5. LIMITATIONS

Although a fairly large sample size is included, more patients need to be studied to confirm the current results. Also, longer follow-up data are needed. Finally, future studies need to focus on patients with WMSI between 2.0 and 2.5 to evaluate what

additional information (provided by which techniques) is needed to further optimize prediction of outcome after SVR.

6. CONCLUSIONS

In conclusion, sufficient residual remote myocardium is necessary to recover from a SVR procedure and to translate the surgically induced morphological changes into a functional improvement. Preoperative WMSI is a surrogate measure of residual remote myocardial function and is a promising tool for improved patient selection. Implementation of echocardiographic WMSI will help to improve results after SVR procedures for advanced ischemic heart failure.

REFERENCES

[1] Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donato M, Menicanti L, Almeida de Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy PM, Oz MC, Fontan F, Scott ML, Accola KA, RESTORE group. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilatation. J Am Coll Cardiol 2004;44:1439—45.

[2] Di Donato M, Sabatier M, Dor V, Toso A, Maioli M, Fantini F. Akinetic versus dyskinetic postinfarction scar: relation to surgical outcome in patients undergoing endoventricular patch plasty repair. J Am Coll Cardiol 1997;29:1569—75.

[3] Mickleborough LL, Merchant N, Ivanov J, Rao V, Carson S. Left ventricular reconstruction: early and late results. J Thorac Cardiovasc Surg 2004;128:127—37.

[4] Dor V, Saab M, Coste P, Kornazewska M, Montiglio F. Left ventricular aneurysm: new surgical approach. J Thorac Cardiovasc Surg 1989;37:11— 9.

[5] Maxey TS, Reece TB, Ellman PI, Butler PD, Kern JA, Bosch X, Lesperance J, Pelletier LC, Kron IL. Coronary artery bypass with ventricular restoration is superior to coronary artery bypass alone in patients with ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2004;127:428—34.

[6] Williams JA, Weiss ES, Patel ND, Nwakanma LU, Conte JV. Outcomes following surgical ventricular restoration for patients with clinically advanced congestive heart failure (New York Heart Association class IV). J Card Fail 2007;13:431—6.

[7] Klein P, Bax JJ, Shaw LJ, Feringa HH, Versteegh MI, Dion RA, Klautz RJ. Early and late outcome of left ventricular reconstruction surgery in ischemic heart disease: a systematic review of the literature. Eur J Cardiothorac Surg 2008;34:1149—57.

[8] Menicanti L, Castelvecchio S, Ranucci M, Frigiola A, Santambrogio C, de Vincentiis C, Brankovic J, Di Donato M. Surgical therapy for ischemic heart failure: single-center experience with surgical anterior ventricular restoration. J Thorac Cardiovasc Surg 2007;134:433—41.

[9] Hernandez AF, Velazquez EJ, Dullum MK, O'Brien S, Ferguson TB, Peterson ED. Contemporary performance of surgical ventricular restoration procedures: data from the Society of Thoracic Surgeons' National Cardiac Database. Am Heart J 2006;152:494—9.

[10] Cirillo M, Amaduci A, Brunelli F, Tomba MD, Parrella MD, Tascqa G, Troise T, Quanini E. Determinant of postinfarction ventricular remodelling affect outcome and left ventricular geometry after surgical treatment of ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2004;127:1648— 56.

[11] Patel ND, Williams JA, Nwakanma LU, Waldron MW, Bluemke DA, Conte JV. Surgical ventricular restoration for advanced congestive heart failure: should pulmonary hypertension be a contraindication? Ann Thorac Surg 2006;82:879—88.

[12] Sartipy U, Alba°ge A, LindblomD. Risk factors for mortality and hospital readmission after surgical ventricular restoration. Eur J Cardiothorac Surg 2006;30:762—9.

[13] Ural E, Yuksel H, Pehlivanoglu S, Bakay C, Olga R. Short and long term survival of surgical treatment of left ventricular aneurysms. Ten years experience. Jpn Heart J 2002;43:379—87.

[14] Vicol C, Rupp G, Fischer S, Summer C, Dietrich Bolte H, Struck E. Linear repair versus ventricular reconstruction for the treatment of left ventricular aneurysm: a 10-year experience. J Cardiovasc Surg 1998;39:461— 8.

[15] White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44—51.

[16] Buckberg GD. Questions and answers about the STICH trial: a different perspective. J Thorac Cardiovasc Surg 2005;130:245—9.

[17] Beanlands RS, Ruddy TD, deKemp RA, Iwanochko RM, Coates G, Freeman M, Nahmias C, Hendry P, Burns RJ, Lamy A, Mickleborough L, Kostuk W, Fallen E, Nichol G, PARR Investigators. Positron emission tomography and recovery following revascularization (PARR-1): the importance of scar and the development of a prediction rule for the degree of recovery of left ventricular function. J Am Coll Cardiol 2002;40:1734—43.

[18] Bourque JM, Velazquez EJ, Borges-Neto S, Shaw LK, Whellan DJ, O'Connor CM. Radionuclide viability testing: should it affect treatment strategy in patients with cardiomyopathy and significant coronary artery disease? Am Heart J 2003;145:758—67.

[19] Mahrholdt H, Wagner A, Parker M, Regenfus M, Fieno DS, Bonow RO, Kim RJ, Judd RM. Relationship of contractile function in transmural extent of infarction in patients with chronic coronary artery disease. J Am Coll Cardiol 2003;42:505—12.

[20] Natori S, Conte JV, Lima JA, Bluemke DA. Magnetic resonance imaging evaluation of surgical ventricular reconstruction. Ann Thorac Surg 2005;80:743.

[21] Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, Tu JV, Alter DA. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol 2003;41:1573—82.

[22] Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ,Winters SL, Gibbons RI, Antman EM, Alpert JS, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith Jr SC. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J Cardiovasc Electrophysiol 2002;13:1183—99.

[23] Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, St John Sutton M, Stewart WJ, and Members of the Chamber Quantification Writing Group. Recommendations for Chamber Quantification: a Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber QuantificationWriting Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440—63.

[24] Buckberg G, Menicanti L, De Oliveira S, Athanasuleas C, The Restore Team. Restoring an elliptical chamber during rebuilding a wrap around anterior infarction. Eur J Cardiothorac Surg 2005 Nov;28(5):772—4.

APPENDIX A. CONFERENCE DISCUSSION

Dr H. Suma *(Tokyo, Japan):* I thank you for showing us a good way to select the patient in the surgical treatment for ischemic heart failure by using echo study, which is routinely available in our practice. In fact, we still don't have a reliable method to predict an outcome following surgical ventricular restoration, particularly in case of dilated left ventricle. As we know, there are heterogeneous extents of myocardial viability, and it is hard to detect its reversibility by using ordinary examination in those groups of patients. I have two questions.

Number one, as you said, all of those patients who have a wallmotion score index more than 2.5 went bad after surgery. Was it because the remaining myocardium was too bad or you made the ventricle too small, because those bad ventricles often have low compliance and high stiffness. The second question is, because wall motion score index between 2.0 and 2.5 is a gray zone, do you think dobutamine echo or some other method is valuable to find a good candidate for surgery?

Dr Klein: We recognize your vast experience in left ventricular restoration procedures for both ischemic and non-ischemic cardiomyopathy. To answer your first question about diastolic failure in some patients: we size the residual left ventricular volume using an intracavitary balloon or a commercially available shaper device to 50 to 60 ml/m^2 of body surface area. This avoids creating a residual ventricle that is too small, which would lead to diastolic failure. All of these patients were sized according to this technique. So the failure outcome, predominantly heart failure or recurrent heart failure, which constitutes the majority of the mortality, about two thirds, can be ascribed to systolic failure and not to diastolic failure.

To answer your second question about the intermediate group, we used advanced imaging techniques like dobutamine-stress echocardiography, late enhancement MRI, and viability testing by nuclear imaging to find evidence of contractility or viability in these patients. A further study is being conducted to analyze this subgroup between a wall motion score index of 2.0 and 2.5 to find what tests may predict contractility or viability.

Dr P. Pinho *(Porto, Portugal):* I have a couple of questions. If I well remember, we focused initially on when you do the Doppler series, mostly on the extension and the type of infarcted area. I don't know if your numbers include mostly patients with akinetic or dyskinetic areas. Do you think with this score, the score is valid for both types of dysfunctional myocardium that you are supposed to reconstruct?

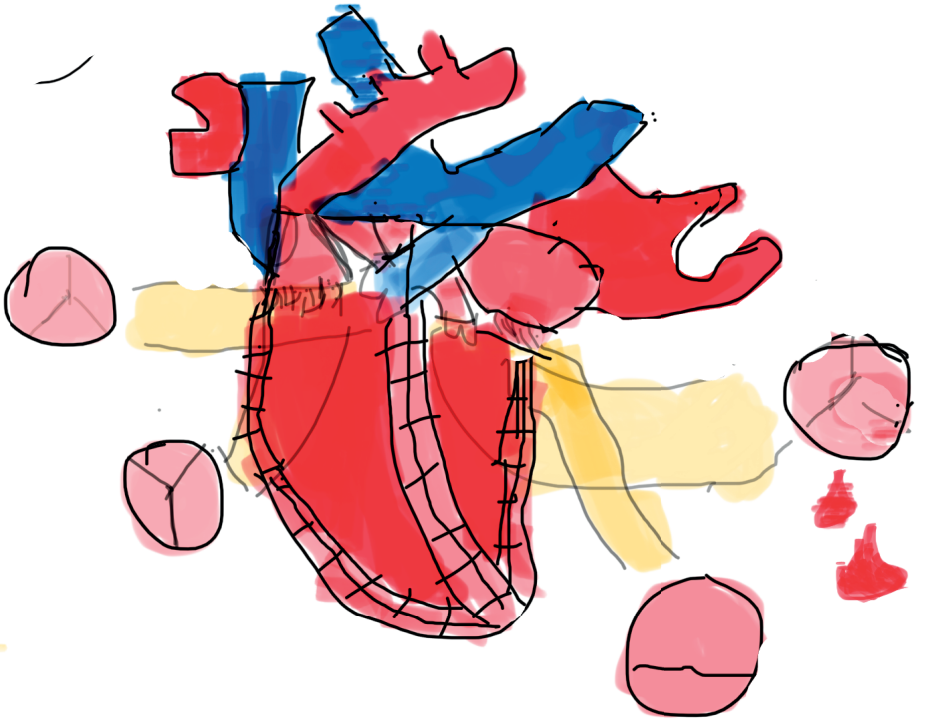
Dr Klein: The patients in our study have mainly akinetic segments; only 20% have clear dyskinesia. So 80% have extended akinesia. Wall motion score actually assigns a 3 for akinetic segments and a 4 for dyskinetic segments, which would make dyskinesia more severe than akinesia. Maybe this is correct, because in akinetic segments, part of the infarction may be not completely transmural, let's say less than 50 or 40%, and has the potential to increase contractility if wall stress is less, if there is revascularization. So contractility might improve in these segments. I think wall motion index adequately assigns a lower score to akinesia.

Dr M. Zembala *(Zabrze, Poland):* My question is, can you share just this experience from wall motion score to something more practical, like Di Donato classification, which for us is very practical and covered the echo findings, angio and magnetic resonance together, and including one territory versus multi-territory as well? That is one question.

The comments. Again, thank you for inspiration for this very important issue, but let's wait for the published outcomes of STICH data which will allow us to get to know better this significant and difficult problem.

Dr Klein: Of course, the STICH trial is also eagerly awaited in our center, which will render very interesting results for this group of patients. We are still studying the combination of wall motion score index and other risk stratifying and predictors of outcome in this patient group. So we will correlate different predictors and different imaging techniques to wall motion score index in order to come up with the best predictors and the best risk stratifying sequence.

Dr Zembala: Especially when it is practically quite easy.



Chapter 4

Management of mitral regurgitation during left ventricular reconstruction for ischemic heart failure

Patrick Klein[a], Jerry Braun[a], Eduard R. Holman[b], Michel I.M. Versteegh[a], Harriette F. Verwey[b], Robert A.E. Dion[a], Jeroen J. Bax[b] and Robert J.M. Klautz[a]

[a] Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands
Presented at the 24th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Geneva, Switzerland, September 11–15, 2010.

European Journal of Cardio-Thoracic Surgery 41 (2012) 74–81

ABSTRACT

Objective: Remodeling of the left ventricle (LV) in ischemic cardiomyopathy frequently leads to functional mitral regurgitation (MR). The indication for correcting MR in patients undergoing LV reconstruction (LVR) is unclear. In this study, we evaluated our strategy of correcting MR ≥ grade 2+ by restrictive mitral annuloplasty (RMA) during LVR.

Methods: We studied 92 consecutive patients (76 men, mean age 61 ± 10 years) who underwent LVR for ischemic heart failure (IHF). RMA was performed in all patients with MR ≥ grade 2+ on preoperative echocardiography and in patients who showed increased MR to ≥grade 2+ immediately after LVR. Patients were attributed to a RMA and no-RMA group, depending on whether or not concomitant RMA had been performed. Mean clinical and structured echocardiographic follow-up was 47 ± 20 months and was 100% complete.

Results: In 38 out of 40 patients (95%) with preoperative MR ≥ grade 2+, concomitant RMA was planned and performed. In 17 out of 52 patients (33%) with MR < grade 2+ preoperatively, MR increased after LVR to ≥grade 2+ leading to additional RMA during a second period of aortic cross-clamping. Early mortality in the RMA group (n = 55) was 12.7% and survival at 36 months 78.2 ± 11.2%. Early mortality in the no-RMA group (n = 37) was 5.4% and survival at 36 months 81.1 ± 12.8%. Patients in the RMA group had significantly more reduced LV function with greater LV dimensions and volumes preoperatively. Echocardiography demonstrated sustained improvement in LVEF with reduction of LV volumes in both patient groups. Recurrence of MR at late follow-up was observed in 2 patients (1 patient per group).

Conclusions: Patients with IHF eligible for LV reconstruction have MR ≥ grade 2+ in 44% of cases. In one-third of IHF patients with MR < grade 2+ preoperatively, MR increases to ≥grade 2+ after LVR. Concomitant mitral valve repair for MR ≥ grade 2+, on either preoperative echocardiography or immediately after LVR, results in favorable late clinical and echocardiographic outcome that proved to be similar to patients without concomitant mitral valve repair, despite more advanced disease.

Keywords: Left ventricular reconstruction (LVR) • Dor procedure • Mitral regurgitation • Restrictive mitral annuloplasty (RMA) • Ischemic heart failure (IHF)

INTRODUCTION

Remodeling of the left ventricle (LV) in ischemic cardiomyopathy leads to systolic and diastolic dysfunction, and frequently to functional mitral regurgitation (MR) as a secondary phenomenon [1–5]. Surgical ventricular restoration or left ventricular reconstruction (LVR) restores LV shape, reduces LV volume, and improves pump function in patients with ischemic cardiomyopathy [6,7]. The impact of LVR on MR – both early and late – is unclear, as is the indication for concomitant correction of the MR during LVR. Our management of MR in patients undergoing LVR encompasses performing a restrictive mitral annuloplasty (RMA) when MR ≥ grade 2+, established either preoperatively or immediately post-LVR. In this study, we evaluated the results of this strategy in patients with ischemic heart failure (IHF), who underwent LVR, with or without concomitant RMA, with a focus on late clinical and echocardiographic outcome.

MATERIALS AND METHODS

Ninety-two consecutive patients with ischemic cardiomyopathy and heart failure (NYHA class III or IV and LV ejection fraction ≤ 35%) underwent LVR between April 2002 and April 2007. Patients were considered eligible for LV reconstructive surgery when they had LV dilatation following an antero-septal myocardial infarction with an echocardiographically derived Wall Motion Score Index (WMSI) ≤ 2.5, or with evidence of contractile reserve when WMSI exceeded 2.5, as described earlier [8]. Patients were attributed to an RMA and no-RMA group, depending on whether or not concomitant RMA had been performed.

Patient characteristics

There were 76 men and mean age was 61 ± 10 years. All patients presented with IHF, 76 patients (83%) were in NYHA class III. Mean LVEF was 25 ± 7% (range 12–35%). Median interval after myocardial infarction was 36 months (range 1–360). Logistic EuroSCORE averaged 10 (range 3–42). All patients underwent elective surgery. Preoperative moderate to severe (≥grade 2+) MR was present in 40 patients (43.7%) on transthoracic echocardiography (TTE). Patient characteristics are summarized in Table 1.

Preoperative echocardiography

A transthoracic echocardiogram was performed within 5 days prior to surgery. When significant mitral and/or tricuspid regurgitation was demonstrated on TTE, transesophageal echocardiography (TEE) was additionally performed to further evaluate the severity and mechanism of the regurgitation. The severity of mitral

and/or tricuspid regurgitation was graded semiquantitatively from color-flow Doppler acquisitions in the conventional parasternal long-axis and apical four-chamber images. Mitral and tricuspid regurgitation was characterized as: mild, 1+ (jet area/ left or right atrial area <10%); moderate, 2+ (jet area/ left or right atrial area 10–20%); moderately severe, 3+ (jet area/ left or right atrial area 20–45%); and severe, 4+ (jet area/left or right atrial area >45%). LV volumes and LV ejection fraction were calculated from conventional apical two- and four-chamber images, using the biplane Simpson's technique. LV dimensions (end-systolic and end-diastolic) were determined from parasternal M-mode acquisitions. Echocardiographically derived WMSI was used to evaluate LV function. As recommended by the American Society for Echocardiography, a 16-segment model was used for left ventricular segmentation [11]. WMSI was derived as the sum of all wall motion scores divided by the number of segments visualized.

Table 1: Preoperative patient characteristics (n = 92)

	RMA group (*n* = 55)	No-RMA group (*n* = 37)
Age (years) (mean ± SD)	60 ± 9	62 ± 11
Gender, male/female (*n*)	44/11	32/5
Median interval after infarction (months, range)	48 (1–228)	84 (2–360)
≤3months (*n*, %)	4 (7.3%)	1 (2.7%)
>3 months (*n*, %)	51 (92.7%)	36 (97.3%)
No. of coronary vessels with stenosis of >70% (*n*, %)		
One	28 (50.9%)	14 (37.8%)
Two	18 (32.7%)	13 (35.1%)
Three	9 (16.4%)	10 (27.0%)
Previous cardiac surgery (*n*, %)	2 (3.6%)	4 (10.8%)
Renal insufficiency (*n*, %)	1 (1.8%)	2 (5.4%)
Severe pulmonary hypertension (*n*, %)	10 (18.2%)	0
Logistic EuroSCORE (mean ± SD)	10 ± 10	9 ± 9
NYHA class (mean ± SD)	3.2 ± 0.4	3.1 ± 0.3
III (*n*, %)	44 (80%)	32 (86.5%)
IV (*n*, %)	11 (20%)	5 (13.5%)
$V0_2max$ (ml kg^{-1} min^{-1}, mean ± SD)	16 ± 4	19 ± 6
Clinical ventricular tachyarrhythmia (VT) (*n*, %)	9 (16.4%)	4 (10.8%)
Preoperative (biventricular) ICD implantation (*n*, %)	14 (25.5%)	7 (18.9%)

NYHA: New York Heart Association; VT: ventricular tachyarrhythmia; ICD, implantable cardioverter defibrillator.

Surgical technique

The surgical technique was described earlier [8]. In summary, all operations were performed using normothermic cardiopulmonary bypass, aortic cross-clamping, and intermittent antegrade warm-blood cardioplegia. LVR was carried out according to Dor using a shaping Fontan-stitch at the transitional zone between viable and scarred myocardium. Sizing of the residual ventricle was done using a saline-filled balloon or commercially available shaper (TRISVR, Chase Medical, Richardson, TX, USA) using a reference LV size of 55 ml m^{-2} body surface area as described by Menicanti et al. [9]. An endoventricular oval Dacron patch was used to close the residual opening after tightening the Fontan stitch around the balloon. To facilitate the creation of a neo-apex, one or two u-shaped stitches were placed in the inferior wall in patients with a 'wrap-around' left anterior descending coronary artery (11–15% of patients) [10]. Concomitant myocardial revascularization was performed whenever indicated, preferentially using all arterial grafts (single or bilateral mammary arteries) in patients ≤70 years of age. A concomitant tricuspid annuloplasty was performed using an MC3-ring (Edwards Lifesciences, Irvine, CA, USA) in patients with significant tricuspid regurgitation (>grade 2+) or when the tricuspid annular diameter exceeded 40 mm on TTE. In patients with documented preoperative ventricular arrhythmias, a cryo-ablation at the border zone between scar tissue and viable myocardium was performed. Since 2006 implantation of an epicardial LV lead for resynchronisation therapy formed a routine part of the procedure. After termination of extracorporeal circulation, TEE was repeated to assess LV shape and function. Mitral and tricuspid valve competency were assessed; transmitral diastolic gradient and length of coaptation of the mitral valve leaflets were measured. A summary of the surgical data is provided in Table 2.

Management of MR

Our management of MR during LVR encompassed performing RMA in all patients with MR ≥ grade 2+ on preoperative echocardiography and in patients who showed increase of MR to ≥grade 2+ on intraoperative TEE, as routinely performed immediately after LVR after discontinuation of extracorporeal circulation. In these latter patients, additional RMA was performed during a second period of aortic cross-clamping. RMA was performed by transseptal approach with downsizing using a semirigid ring (Carpentier Edwards Physio Ring, Edwards Lifesciences, Irvine, CA, USA). For further analysis, patients were attributed to either the RMA group or the no-RMA group based on the procedure performed. A flowchart demonstrating MR management in all patients is shown in Fig. 1.

Table 2: Surgical data (*n* = 92)

	RMA group (*n* = 55)	No-RMA group (*n* = 37)
LVR with patch (*n*, %)	53 (96.4%)	36 (97.3%)
Patch size (cm^2) (mean ±SD)	13 ±7	12 ±8
Inferior wall plication (*n*, %)	8 (14.5%)	4 (10.8%)
Balloon/shaper size (ml) (mean ±SD)	109 ±13	110 ±11
Mitral valve annuloplasty (*n*, %)	55 (100%)	0
Median ring size (range)	26 (24–32)	–
Tricuspid valve annuloplasty (*n*, %)	20 (36.4%)	0
Median ring size (range)	28 (26–38)	–
CABG (*n*, %)	32 (58.2%)	26 (70.3%)
No. of distal anastomoses/patient (mean ±SD)	2 ±1	3 ±1
Use of bypass grafts		
LIMA only (*n*, %)	13 (40.6%)	4 (15.4%)
RIMA only (*n*, %)	0	2 (7.7%)
BIMA (*n*, %)	7 (21.9%)	7 (26.9%)
LIMA + vein (*n*, %)	8 (25%)	7 (26.9%)
Vein only (*n*, %)	4 (12.5%)	6 (23.1%)
Cryo-ablation (*n*, %)	5 (9.1%)	7 (18.9%)
Epicardial LV-lead (*n*, %)	15 (27.3%)	9 (24.3%)
ECC time (min.) (mean ±SD)	220 ±57	174 ±56
Aortic cross-clamping time (min) (mean ±SD)	150 ±48	122 ±31
IABP (*n*, %)	18 (32.7%)	2 (5.4%)

LVR: left ventricular restoration; CABG: coronary artery bypass grafting; LIMA: left internal mammary artery; RIMA: right internal mammary artery; BIMA: bilateral internal mammary artery; LV: left ventricle; ECC: extra corporeal circulation; IABP: intra aortic balloon pump.

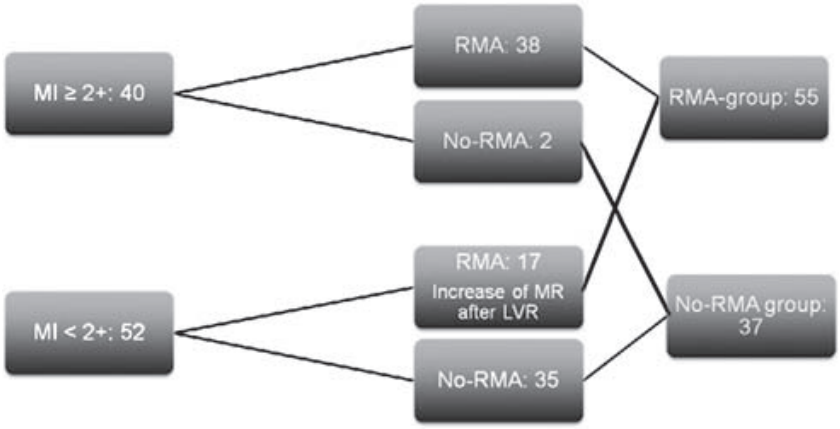


Figure 1: Management chart of MR during LVR. MR: mitral regurgitation; RMA: restrictive mitral annuloplasty; no-RMA: no restrictive mitral annuloplasty; LVR: left ventricular restoration.

Clinical and echocardiographic follow-up

Patients were maintained on optimal medical treatment for heart failure after surgery. Functional status was assessed using the NYHA classification for symptoms of heart failure. An independent physician at the outpatient clinic evaluated the symptoms before surgery and at annual follow-up. Serial transthoracic echocardiograms were performed after surgery, starting just prior to hospital discharge and followed by annual examinations at the outpatient clinic. From these examinations, LV ejection fraction, LV dimensions and volumes, presence of MR, and transmitral diastolic gradient were assessed.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical variables are described as frequencies and percentages and compared using the chi-square test with Yates' correction. Continuous data are expressed as mean ± standard deviation (SD) or median with ranges and compared using the Student's t-test for paired data. The Kaplan–Meier method was used to model survival. Survival between two groups was compared by the Mantel–Cox log rank test. A *P*-value <0.05 was considered significant.

RESULTS

Intraoperative management of MR

Preoperative TTE demonstrated MR ≥ grade 2+ in 40 patients. In 38 patients (95%), concomitant RMA was performed. RMA was not performed in two patients, because of a completely calcified posterior mitral annulus in one patient and a complicated procedure in another patient, making additional mitral surgery inappropriate. Fifty-two patients had preoperative MR < grade 2+.

Eight patients had no MR preoperatively; in these patients MR did not appear after LVR. A total of 17 patients with MR grade 1+ on preoperative examination showed increasing MR to ≥grade 2+ immediately after LVR and underwent subsequent RMA. In the remaining 35 patients, MR stayed < grade 2+ immediately after LVR. The flowchart of MR management is shown in Fig. 1.

None of the patients had primary organic valvular disease; in all patients the mechanism underlying MR was systolic restriction of both leaflets with annular dilatation. Median RMA ring size was 26 (range 24–32). Apart from the patient with the accepted MR grade 2+, intraoperative TEE demonstrated absent or mild MR in all

patients. In patients who had undergone concomitant RMA, mean length of leaflet coaptation after mitral valve repair was 8 ± 2 mm and mean transmitral diastolic gradient was 2.9 ± 1.7 mmHg.

Comparison of baseline echocardiographic characteristics between RMA and no-RMA group

Based on above-mentioned criteria for mitral valve repair, 55 patients were attributed to the RMA group and 37 to the no-RMA group. Comparing preoperative TTE data, WMSI in the RMA group proved to be significantly higher than in the no-RMA-group (2.6 ± 0.5 vs 2.3 ± 0.5, $P < 0.01$), indicating more and/or more severe regional LV wall-motion abnormalities and hence an overall greater deterioration of LV function. In addition, LV volumes and dimensions were significantly larger in the RMA group ($P < 0.01$ for left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic diameter (LVEDD)). These data are summarized in Table 3.

Early outcome

In-hospital mortality in the RMA group and no-RMA group was 12.7% (seven patients) and 5.4% (two patients), respectively. Causes of death in the RMA group were refractory heart failure in four patients (one following postoperative myocardial infarction), sepsis in two patients and acute respiratory distress syndrome (ARDS) in one patient. Patients in the RMA group who had MR < grade 2+ preoperatively (but who showed an increase of MR directly after LVR), early mortality was 5.8% (one patient). In this patient, the cause of death (sepsis) was unrelated to the concomitant mitral valve procedure. Postoperative inotropic support (inotropic support continued for ≥12 h postoperatively) was required in all patients – 18 patients (32.7%) also required intraaortic balloon counterpulsation (IABP) support. Four patients in this group required temporary postoperative hemodialysis. One patient developed an ischemic cerebral infarction. Mean postoperative stay in the intensive-care unit was 8 ± 9 days. Mean postoperative hospital stay was 18 ± 14 days.

Both patients in the no-RMA group died of heart failure. Postoperative inotropic support was also required in all patients in the no-RMA group – two patients (5.4%) required support by additional IABP. Mean postoperative stay in the intensive-care unit was 5 ± 7 days. Mean postoperative hospital stay was 15 ± 10 days.

TTE performed just prior to hospital discharge demonstrated absent or mild MR (grade 0 or 1+) in all patients in both patient groups. Serial results of echocardiographic examination of the mitral valve are presented in Table 4. Early postopera-

Table 3: Transthoracic echocardiographic data

	Baseline		Early postop		P-value baseline versus early postop.		1-year FU		*P*-value baseline versus 1 -year FU		2-year FU		*P*-value baseline versus 2-year FU	
	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group
EF (%)	24 ± 7	27 ± 7	35 ± 8	39 ± 11	<0.01	<0.01	33 ± 12	39 ± 9	<0.01	<0.01	30 ± 10	40 ± 6	<0.01	<0.01
LVESV (ml)	190 ± 88	146 ± 61	99 ± 36	87 ± 39	<0.1	<0.01	109 ± 55	95 ± 29	<0.01	<0.01	116 ± 41	87 ± 28	<0.01	<0.01
LVEDV (ml)	249 ± 96	196 ± 72	150 ± 47	136 ± 43	<0.01	<0.01	155 ± 56	151 ± 34	<0.01	0.01	167 ± 45	144 ± 38	<0.01	<0.01
LVESD (cm)	5.3 ± 1.1	4.8 ± 1.1	5.0 ± 0.9	4.3 ± 1.0	NS	0.03	4.9 ± 1.1	4.7 ± 0.8	0.11	NS	4.9 ± 1.1	4.7 ± 0.8	0.21	NS
LVEDD (cm)	6.8 ± 0.9	6.1 ± 0.9	6.2 ± 0.9	5.7 ± 0.8	<0.01	<0.01	6.2 ± 0.9	6.0 ± 0.5	<0.01	NS	6.1 ± 1.1	6.2 ± 0.5	0.01	NS
WMSI	2.6 ± 0.5	2.3 ± 0.5												

EF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; WMSI: wall motion score index; postop.: postoperative; FU: follow-up; SD: standard deviation; NS: not significant.

tively a significant improvement in LVEF occurred in both patient groups. In the RMA group, LVEF increased from 24 ± 7% to 35 ± 8% (P < 0.01). In the no-RMA group, LVEF improved from 27 ± 7% to 39 ± 11% (*P* < 0.01). In both groups a reduction in LV volumes was observed: LVESV decreased in the RMA group from 190 ± 88 ml to 99 ± 36 ml (*P* < 0.01), whereas LVEDV decreased from 249 ± 96 ml to 150 ± 47 ml (*P* < 0.01). In the no-RMA group, LVESV decreased from 146 ± 61 ml to 87 ± 39 ml (*P* < 0.01) and LVEDV decreased from 196 ± 72 ml to 136 ± 43 ml (*P* < 0.01). Results are summarized in Table 3.

Table 4: Parameters of mitral valve function

	Baseline TTE		Intraoperative TEE		Early postoperative TTE		Late follow-up TTE	
	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group	RMA group	No-RMA group
MR (grade)	2.2 ± 1.0	0.9 ± 0.6	0.0 ± 0.1	0.6 ± 0.6	0.3 ± 0.4	0.5 ± 0.5	0.5 ± 0.6	0.8 ± 0.6
Coaptation (mm)	–	–	8 ± 2	–	–	–	–	–
Transmitral grade (mmHg)	–	–	2.9 ± 1.7	–	5.3 ± 3.3	–	3.7 ± 6.5	–
MR (*n*)								
Grade 0	1	8	54	18	35	18	19	7
Grade 1 +	16	27	1	18	13	17	17	22
Grade 2 +	17	1	0	1	0	0	1	0
Grade 3 +	15	1	0	0	0	0	0	1
Grade 4 +	6	0	0	0	0	0	0	0

RMA: restrictive mitral annuloplasty; MR: mitral regurgitation; TEE: transesophageal echocardiogram; TTE: transthoracic echocardiogram; Transmitral grade, mean diastolic transmitral gradient.

Late outcome

Follow-up extended to 94 months (mean 47 ± 20). Crude late mortality at 36 months in the RMA and no-RMA groups was 10.4% (five patients) and 14.3% (five patients), respectively. Overall Kaplan–Meier estimated survival at 36 months follow-up was 78.2% ± 11.2% in the RMA group and 81.1% ± 12.8% in the no-RMA group (Fig. 2). Comparing survival at 36 months between the RMA and no-RMA groups showed no significant difference (log rank *P* = 0.247).

Significant functional improvement was observed at late follow-up in both RMA and no-RMA groups with respectively 31 patients (83.8% of surviving patients) and 27 patients (90% of surviving patients in NYHA class I or II). Mean NYHA class decreased at late follow-up from 3.2 ± 0.4 preoperatively to 1.8 ± 0.9 (*P* < 0.01) and from 3.1 ± 0.3 preoperatively to 1.7 ± 0.8 (P < 0.01) in the RMA and no-RMA groups, respectively.

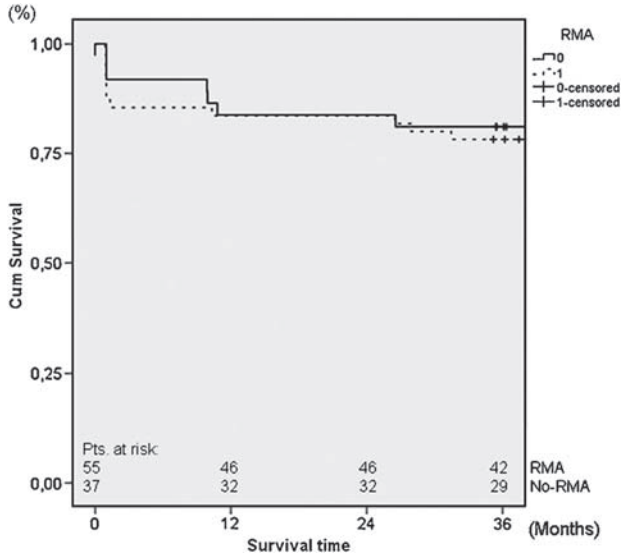


Figure 2: Thirty-six months survival in patients with and patients without concomitant RMA. RMA: restrictive mitral annuloplasty; no-RMA: no restrictive mitral annuloplasty.

Echocardiography demonstrated a sustained improvement in LVEF with reduction of LV volumes in both patient groups at 1- and 2-year follow-up (Table 3). At late follow-up, recurrence of MR (≥grade 2+) was observed only in one patient in both groups (Table 4). The patient in the RMA group was functionally in NYHA class III and showed grade 2+ recurrent MR due to systolic restriction of both leaflets with limited coaptation. The patient in the no-RMA group was in NYHA functional class II and showed grade 3+ recurrent MR (with severe pulmonary hypertension) due to progressive tethering of the mitral valve leaflets with systolic restriction on TTE. LV volumes and dimensions in this patient were still smaller than preoperatively, but showed slight progression after the initial surgically induced reduction. Preoperatively, this patient had MR grade 1+ which remained stable after LVR. At discharge MR was still grade 1+. Despite increased dosages of diuretics and ace inhibitors, MR remained stable grade 3+ at late follow-up.

Survival analysis was also performed comparing 36 months survival between patients with preoperative MR ≥ grade 2+ and patients with preoperative MR < grade 2+ and demonstrated no significant difference between the two groups. Thirty-six months survival was 75.0 ± 13.6% and 82.7 ± 10.4% in patients with preoperative MR ≥ grade 2+ and patients with preoperative MR < grade 2+, respectively (log rank P = 0.628) (Fig. 3).

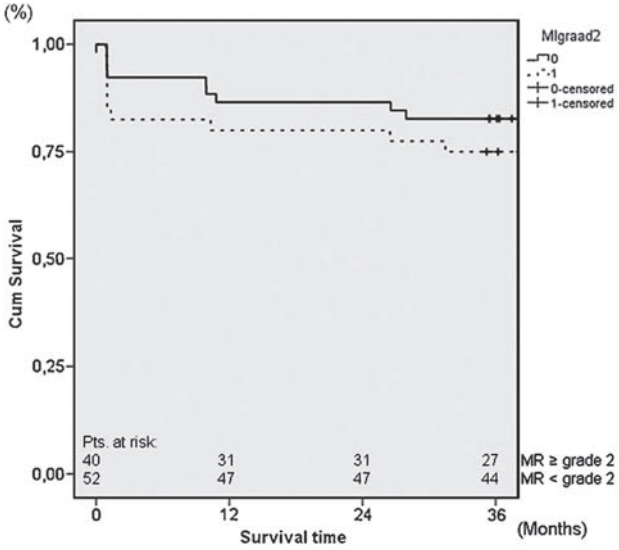


Figure 3: Thirty-six months survival in patients with and patients without preoperative MR ≥ grade 2+. MR: mitral regurgitation.

DISCUSSION

Functional MR in patients with ischemic cardiomyopathy is a secondary phenomenon caused by remodeling of the LV [1–5]. MR is related to LV dilatation and is caused by geometrical changes at the annular, subannular, and ventricular level. Annular dilatation, increased distance between annulus and papillary muscles, and increased distance between the papillary muscles alter and reduce coaptation of the mitral valve leaflets [12]. MR leads to volume overload that promotes further LV remodeling and carries an excess mortality in post-infarction patients, which is unrelated to the underlying degree of LV dysfunction [13–16]. The presence of MR has been shown to be an independent marker of excess mortality, even when the potential artificial increase in LVEF was taken into account. LVR restores LV shape, reduces LV volume, and improves pump function in patients with ischemic cardiomyopathy [6,7]. Correcting functional MR by RMA results in excellent and durable results, as we have published before [23].

The impact of LVR on MR, both immediately and during longer follow-up, remains unclear, as is the indication for concomitant correction of MR during LVR. On the one hand, immediate decrease of LV volumes and diameters, with the reduction of the distances between annulus and papillary muscle and between the papillary muscles, can lead to improved mitral valve leaflet coaptation [12,18]. Reduction of wall stress

by the decrease in LV volumes and dimensions contributes to improvement in ventricular and papillary muscle function [9]. On the other hand, it is possible that LVR leads to a distortion of the geometry of the LV and subvalvular apparatus, causing an increase in MR. Moreover, possible further LV remodeling over time with gradual increase of LV volumes and diameters might lead to the appearance or recurrence of MR at midterm follow-up if MR is left untreated [9].

There is little debate to treat functional MR when it is moderate– severe or severe (MR grade 3+ or 4+). However, there is no consensus on how to treat mild or moderate MR (MR grade 1+ and 2+). Di Donato et al. propose to leave MR grade 2+ untreated. They demonstrated an excellent survival; however, a substantial percentage of patients (29%) was found to have at least a moderate degree of MR (grade 2+) at follow-up [18]. Prucz et al. demonstrated an overall reduction in MR grade with good functional results and excellent survival in a group of patients who underwent LVR with untreated moderate MR. However, 76% of the patients still had MR > grade 2+ at follow-up [12]. As such, a conservative approach to functional MR grade 2+ will leave a significant proportion of patients at risk for the potentially deleterious effects of MR, which are further LV remodeling and increased mortality. As has been demonstrated, a moderate degree of MR proves to be of hemodynamic importance in patients with reduced LV function and imposes significant clinical implications in post-infarction patients, even in those with minimal symptoms [15,25]. In the setting of ischemic MR, even a regurgitant volume as little as 30 ml is associated with a limited 5-year survival of 47%.

A conservative approach to functional MR grade 2+ might be related to the idea of an increased perioperative mortality caused by the additional intervention on the valve. In our study, perioperative mortality and morbidity were indeed higher in the RMA group, but it should be noted that patients in that group had more advanced disease, as demonstrated by the higher preoperative WMSI (more wall-motion abnormalities) and larger LV volumes and dimensions. MR should be regarded as the result of ongoing LV remodeling, and the increased perioperative risk should be interpreted against that background and, in addition, be weighed against the increased complication rate at longer follow-up associated with untreated MR. It has also been shown by others that concomitant mitral annuloplasty does not add by itself to the risk of the operation [9,20].

Aggressive correction of MR ≥ grade 2+ by RMA during LVR results in excellent functional improvement, favorable 36 months survival, and very low recurrence of MR. Moreover, elimination of MR leads to a similar functional improvement and

equal survival comparing patients with and without preoperative MR ≥ grade 2+ (mean NYHA class at late follow-up 1.8 ± 0.9 and 1.7 ± 0.8 in the RMA and no-RMA groups, respectively, *P* = NS; 3-year survival 78.2% vs 80.7%, *P* = NS). This comparable outcome occurs despite the fact that patients with MR ≥ grade 2 + undergoing LVR have a more severely damaged LV, as also reflected by the higher early mortality and more frequent need of IABP support. Similar results were found by Athanasuleas and the RESTORE group, who demonstrated an increased 30-day mortality by two-fold from 4% to 8.7%, but the 5-year survival after LVR was not influenced [7,21]. In our previously published meta-analysis, we found however that concomitant mitral valve surgery was associated with both an increased risk for early (RR = 1.57, *P* = 0.001) and late mortality (RR = 4.28, *P* < 0.001) [22]. The discrepancy in late outcome may be explained by the fact that concomitant mitral valve surgery – in the studies that were entered into the meta-analysis – comprises both mitral valve repairs and replacements. Mitral valve repair is associated with a better survival than mitral valve replacement (especially without preservation of the subvalvular apparatus) because of better preservation of ventricular contraction and fewer complications related to prosthetic deterioration, malfunction, or hypocoagulation [24]. Moreover, patient selection, surgical techniques (myocardial protection), and peri-operative management have improved over time.

LV reverse remodeling in IHF is also influenced by myocardial revascularization. Revascularization of viable but dysfunctional myocardium because of ischemia may resolve functional MR; however, this has proved to be very unpredictable [19]. The recently published STICH-trial, reporting over 1000 patients, randomized for either coronary artery bypass grafting (CABG, *n* = 501) and CABG and LVR (*n* = 499), did not demonstrate any benefit of LVR over CABG [17]. Since patients with severe postinfarction heart failure were not included in this trial (only 49% of patients were in NYHA class III or IV), and patients who would clearly benefit from LVR were not randomized, we do not consider that study representative for the patients evaluated in the current study. Moreover, both the reduction in LV volume (19% in the STICH-trial vs 60–69% (LVEDV) in our study) and the type of LV reconstruction (in 59% of the LVR patients in the STICH-trial, an endoventricular patch was used compared to 96–97% of the patients in this study) were different. Finally, it should be noted that in our study 42% of the patients in RMA group did not have coronary vessels suitable for revascularization and thus could not benefit from revascularization alone.

As published by our group recently, the recurrence rate of MR in patients who underwent RMA for MR ≥ grade 2+ in ischemic and non-ischemic cardiomyopathy and heart failure was 19% at a mean follow-up of 2.6 year [16]. These patients had

similarly dilated LVs and reduced LVEF as the patients in the current study. The combination of reduction in LV volumes and reduction in wall stress by LVR with RMA probably contributed to the low recurrence rate of MR in these patients.

The long-term clinical and echocardiographic results of this study support our strategy of managing MR in patients undergoing LVR: when MR is absent preoperatively, neither appearance of MR directly after LVR or at late follow-up is observed. Rightfully, no concomitant RMA is performed in these patients. In patients with preoperatively MR ≥ grade 2+ and in patients showing increase of MR ≥ grade 2+ immediately after LVR, concomitant RMA is performed with excellent functional improvement, favorable 36 months survival, and very low recurrence of MR. In patients with MR < 2+ after LVR, concomitant RMA is not performed, which is justified by the low occurrence rate of MR at late follow-up.

CONCLUSIONS

Patients with IHF eligible for LV reconstruction have MR ≥ grade 2+ in 44% of cases. In one-third of IHF patients with MR < grade 2+ preoperatively, MR increases to ≥grade 2+ after LVR. Concomitant mitral valve repair for MR ≥ grade 2+, on either preoperative echocardiography or immediately after LVR, results in favorable late clinical and echocardiographic outcome that proved to be similar to patients without concomitant mitral valve repair, despite more advanced disease.

LIMITATIONS

Although the present study includes a relatively large sample size, more patients need to be studied to confirm the current results. Also, longer follow-up data are needed to evaluate the long-term results. Possibly, in some patients MR would have decreased after LVR and CABG alone. Our proven strategy of treating functional or ischemic MR ≥ grade 2+ by RMA, however, precludes any comments on this potential effect.

Conflict of interest: none declared.

REFERENCES

[1] McKay RG, Pfeffer MA, Posternak RC, Markis JE, Come PC, Nakao S, Aldermen JD, Ferguson JJ, Safian RD, Grossman W. Left ventricular remodeling after myocardial infarction: a corollary to infarct expansion. Circulation 1986;74:693–702.

[2] Pfeffer M, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990;81:1161–72.

[3] Gaudron P, Eilles G, Ertl G, Kochsiek K. Compensatory and noncompensatory left ventricular dilatation after myocardial infarction: time course and hemodynamic consequences at rest and during exercise. Am Heart J 1992;123:377–85.

[4] Levine RA, Swammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. Circulation 2005; 112:745–58.

[5] Trichon BH, Felker, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538–43.

[6] Dor V, Saab M, Coste P, Kornazewska M, Montiglio F. Left ventricular aneurysm: new surgical approach. J Thorac Cardiovasc Surg 1989;37:11–9.

[7] Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donato M, Menicanti L, Almeida DE, Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy PM, Oz MC, Fontan F, Scott ML, Accola KARESTORE group. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilatation. JACC 2004;44:1439–45.

[8] Klein P, Holman ER, Versteegh MI, Boersma E, Verwey HF, Bax JJ, Dion RA, Klautz RJ. Wall motion score index predicts mortality and functional results after surgical ventricular restoration for ischemic heart failure. Eur J Cardiothorac Surg 2009;35:847–53.

[9] Menicante L, Di Donato M, Castelvecchio S, Santambrogia C, Montericcio V, Frigriola A, Buckberg G, the RESTORE group. Functional ischemic mitral regurgitation in anterior ventricular remodelling: results of surgical ventricular restoration with and without mitral repair. Heart Fail Rev 2004;9:317–27.

[10] Buckberg G, Menicanti L, De Oliveira S, Athanasuleas C. The Restore Team. Restoring an elliptical chamber during rebuilding a wrap around anterior infarction. Eur J Cardiothorac Surg 2005;28:772–4.

[11] Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RI, Antman EM, Alpert JS, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith Jr SC. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J Cardiovasc Electrophysiol 2002;13:1183–99.

[12] Prucz RB, Weiss ES, Patel ND, Nwakanma LU, Shah AS, Conte JV. The impact of surgical ventricular restoration on mitral valve regurgitation. Ann Thorac Surg 2008;86:726–34.

[13] Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103: 1759–64.

[14] Harris KM, Sundt TM 3rd, Aeppli D, Sharma R, Barzilai B. Can late survival of patients with moderate ischemic mitral regurgitation be impacted by intervention on the valve?. Ann Thorac Surg 2002;74: 1468–75.

[15] Bolling SF. Mitral valve reconstruction in the patient with heart failure. Heart Fail Rev 2001;6:177–85.

[16] Ciarka A, Braun J, Delgado V, Versteegh M, Boersma E, Klautz R, Dion R, Bax JJ, Van de Veire N. Predictors of mitral regurgitation recurrence in patients with heart failure undergoing mitral valve annuloplasty. Am J Cardiol 2010;106:395–401.

[17] Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne-Nickens P, Rouleau JL, Lee KL, STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360: 1705–17.

[18] Di Donato M, Castelvecchio S, Brankovic J, Santambrogio C, Montericcio V, Menicanti L. Effectiveness of surgical ventricular restoration in patients with dilated ischemic cardiomyopathy and unrepaired mild mitral regurgitation. J Thorac Cardiovasc Surg 2007;134:1548–53.

[19] Aklog L, Filsoufi F, Flores KQ, Chen RH, Cohn LH, Nathan NS, Byrne JGAdams DH. Does coronary artery bypass grafting alone correct moderate ischemic mitral regurgitation?. Circulation 2001;104(12 Suppl. 1):I68–75.

[20] Diodato MD, Moon MR, Pasque MK, Barner HB, Moazami N, Lawton JS, Bailey MS, Guthrie TJ, Meyers BF, Damiano Jr RJ. Repair of ischemic mitral regurgitation does not increase mortality or improve long-term survival in patients undergoing coronary artery revascularization: a propensity analysis. Ann Thorac Surg 2004;78:794–9.

[21] Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donato M, Menicanti L, Almeida DE, Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy PM, Oz MC, Fontan F, Scott ML, Accola KA, RESTORE group. Surgical ventricular restoration: the RESTORE group experience. Heart Fail Rev 2004;9:287–97.

[22] Klein P, Bax JJ, Shaw LJ, Feringa HH, Versteegh MI, Dion RA, Klautz RJ. Early and late outcome of left ventricular reconstruction surgery in ischemic heart disease: a systematic review of the literature. Eur J Cardiothorac Surg 2008;34:1149–57.

[23] Braun J, Bax JJ, Versteegh MI, Voigt PG, Holman ER, Klautz RJ, Boersma E, Dion RA. Pre-operative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischemic mitral regurgitation. Eur J Cardiothorac Surg 2005;27:847–53.

[24] Gillinov AM, Wierup PN, Blackstone EH, Bishays ES, Cosgrove DM, White J, Lytle BW, McCarthy PM. Is repair preferable to replacement for ischemic mitral regurgitation?. J Thorac Cardiovasc Surg 2001;122: 1125–41.

[25] Grigioni F, Detaint D, Avierinos J-F, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. JACC 2005;45:260–7.

APPENDIX A. CONFERENCE DISCUSSION

***Dr L. Menicanti** (Milan, Italy):* This paper deals with a very tough group of patients with mitral regurgitation after an acute myocardial infarction, low ejection fraction, and a large left ventricle, the type of patient that presents a very high mortality in all published series. The results you reported are different in some way, and you report the same survival in the two groups of patients with and without mitral regurgitation before the procedure. So it seems that with your techniques, you put a zero on the impact of the bad ventricle that is normally present with mitral regurgitation. I have two questions for you.

You have an incredibly low rate of recurrence of mitral regurgitation, around 2%, and I would like to ask if you have the same recurrence in the patients with mitral regurgitation that are treated, irrespective of the cause, ischemic or not, with the same dilatation of the ventricle?

Dr Klein: In a recently published paper in JACC in August of this year, we showed that the predictors of recurrence of MR in patients with ischemic and non-ischemic cardiomyopathy at 2.6 years is around 19%. So probably the left ventricular reconstruction combined with restrictive mitral annuloplasty, by the reduction of left ventricular volumes and reduction in wall stress, is the cause of the low recurrence rate of MR.

Dr Menicanti: And the other thing, in your manuscript you described a group of patients in whom, after the procedures, some degree of mitral regurgitation is still present, and in this group of patients you went back onto extracorporeal circulation and you corrected the mitral regurg. So I would like to ask you if this group of patients presents a more difficult postoperative period, higher mortality? How is it in the follow-up period?

Dr Klein: Mortality in this group of 17 patients is only one patient. He died of a sepsis in the ICU. So it is a low mortality of 5.4%. And both functional improvement and follow-up are essentially the same as in the other group of patients. So concomitant restrictive mitral annuloplasty in this patient group did not add to the surgical risk and did not pose a risk of reduced survival.

Dr Menicanti: Because we are always afraid to go back onto extracorporeal circulation with this type of patient, but it seems that there is no danger at all.

Dr Klein: We need a little bit more balloon pumping, of course, in these patients, but functional class improvement is the same, survival is the same, and mortality is low.

Dr M. Deja *(Katowice, Poland):* Your paper is very interesting, and I absolutely agree with the results you are presenting. I have, however, two questions to ask. Your group, and Professor Dion in particular, was always teaching that you should never assess mitral regurgitation while under anesthesia in the operating theatre. So how are you judging when it is appropriate to go back and do a repair on the patient that you actually did SVR on a minute ago? That is the first question.

And the other is less a question and more a remark. Although I agree with the results you are showing and I believe they are true, some kind of control group is missing. You are just making the assumption that if they both fail the same way, you improved something. Maybe if you did nothing they would fail the same way, too.

Dr Klein: Interesting questions. Answering your first question, we come off bypass and then we wait for a while to let the ventricle improve or resume its function and then we evaluate. In anesthesia you can underestimate but you cannot overestimate the degree of MR if the ventricle is performing well at the time. So we wait a while and then we assess the function.

Dr Deja: Do you perform any kind of loading or anything like this?

Dr Klein: Not after the reconstruction, no. And to answer your second question, you are right, of course, there is no control group, but our previous results in both ischemic and non-ischemic patients demonstrating the efficiency of restrictive mitral annuloplasty made it standard practice in our hospital. So we performed restrictive mitral annuloplasty in this group of patients. But of course you are right, I cannot draw any conclusions as to whether the MR has decreased in a certain small group of patients.

Dr S. Bolling *(Ann Arbor, MI):* I have a question for you to reflect on Dr Menicanti's comments. Clearly you thought those that needed annuloplasty and those that did not need annuloplasty were very different groups of patients, but in the 'did not need annuloplasty' group of those 52 patients, you had to go back on 17 or 33% of those. One question. Did that make you unhappy? And two, did you change your institutional policy of perhaps being more aggressive in performing an annuloplasty with lesser preoperative MR?

Dr Klein: Yes, you are right. First, we are very aggressive in performing restrictive mitral annuloplasty in these patients. We don't do restrictive mitral annuloplasty for grade 1 MR, because it is not supposed to influence the left ventricular function and outcome in the future.

And you also wanted to know —

Dr Bolling: Did it make you unhappy to have to go back on bypass one-third of the time? That would make me unhappy. That seems like a high rate.

Dr Klein: It is all about the end results. You have to give a good treatment to these patients, and we know that leaving moderate MR or more in these patients results in a suboptimal outcome. So you have to go back and repair the valve.

Dr Bolling: I agree.

Dr K. Vural *(Ankara, Turkey):* Do your Kaplan—Meier curves and the subsequent survival comparison include operative mortality? Otherwise the perception of the diagram may be misleading, and, in my opinion, the legend or footnote of the diagram should contain this information. As far as I could see from your slides, there was a considerable difference between the mortalities of the mitral intervention group and the other group.

Dr Klein: Of course, in our Kaplan—Meier curve operative mortality is included, and in the first part of the graph you see a sharp drop that shows the operative mortality. And, yes, both groups are different. The patients in the RMA group have a more severe degree of disease, they have much more enlarged ventricles, and they therefore have a higher or a different mortality rate.

Chapter 5

10-Year Outcomes After Left Ventricular Reconstruction: Rethinking the Impact of Mitral Regurgitation

Annelieke H. J. Petrus, MD, Patrick Klein, MD, Laurens F. Tops, MD, PhD, Olaf M. Dekkers, MD, PhD, Lotje A. Hoogervorst, BSc, Lotte E. Couperus, MD, PhD, Saskia L. M. A. Beeres, MD, PhD, Robert J. M. Klautz, MD, PhD, and Jerry Braun, MD, PhD

Departments of Cardiothoracic Surgery, Cardiology, and Clinical Epidemiology, Leiden University Medical Center, Leiden; and
Department of Cardiothoracic Surgery, St Antonius Hospital, Nieuwegein, The Netherlands

Ann Thorac Surg 2019;108:81–9

ABSTRACT

Background. Heart failure with reduced ejection fraction due to a post-infarction anteroseptal aneurysm carries a poor prognosis. Patients with refractory heart failure may be considered for advanced surgery, including left ventricular assist device implantation, heart transplantation and left ventricular reconstruction. The aim of this study was to evaluate outcomes after an integrated approach of left ventricular reconstruction with concomitant procedures (mitral/tricuspid valve repair, coronary revascularization), and assess risk factors for event-free survival, focusing on left ventricular geometry/ function and presence of functional mitral regurgitation (MR).

Methods. A total of 159 consecutive heart failure patients who underwent left ventricular reconstruction between 2002 and 2011 were included. Mid-term echocardiographic and long-term clinical outcomes were evaluated. Preoperative risk factors were correlated to event-free survival (freedom from mortality, left ventricular assist device implantation, and heart transplantation).

Results. Mid-term echocardiography demonstrated decreased indexed left ventricular end-systolic volumes (89 ± 42 mL/m^2 preoperatively; 51 ± 18 at mid-term, $p <$ 0.001), and absence of MR ≥ grade 2. Event-free survival was 83% ± 3% at 1-year, 68% ± 4% at 5-year, and 46% ± 4% at 10-year follow-up. Preoperative wall motion score index (WMSI; hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.7–5.8, p < 0.001) and presence of MR ≥ grade 2 (HR 1.9, 95% CI 1.1–3.1, p = 0.014) were independently associated with adverse event-free survival.

Conclusions. Event-free survival is favorable in patients with WMSI < 2.5 and significantly worse when WMSI is ≥ 2.5. In both groups, the presence of preoperative MR ≥ grade 2 negatively affects event-free survival, despite successful correction of MR. Risk stratification by preoperative WMSI and MR grade supports the Heart team in choosing the optimal surgical strategy for patients with refractory heart failure.

INTRODUCTION

Ischemic heart disease is the most common cause of death worldwide [1, 2]. Although advances in treatment and secondary prevention have resulted in decreased mortality after myocardial infarction over the past decades, this decrease is paralleled by an increase in heart failure prevalence [1–4].

Optimal guideline-directed medical and device therapy constitute the cornerstone in the treatment of patients with heart failure with reduced ejection fraction (HFrEF) in the setting of ischemic heart disease [5–7]. When heart failure symptoms persist, advanced surgical treatment options—tailored to the specific pathology involved— may be considered by a dedicated multidisciplinary Heart team. These options include left ventricular assist device (LVAD) implantation, heart transplantation (HTx) and reconstructive surgery [6–9].

In refractory HFrEF due to a postinfarction anteroseptal aneurysm, left ventricular reconstruction (LVR) with concomitant procedures (mitral and tricuspid valve reconstruction, coronary revascularization, and arrhythmia surgery) may be considered. In a previous report, we demonstrated favorable clinical and echocardiographic outcomes up to 36 months after an integrated approach of LVR surgery with concomitant procedures [10]. Beneficial results after LVR surgery have also been reported by others [11–13]. Nevertheless, not all patients benefit from such extensive surgery, and very few studies have evaluated long-term results. Better patient selection by preoperative risk stratification may potentially reduce mortality and improve long-term outcomes after LVR procedures.

The aim of the present study was to evaluate 10-year clinical outcomes after an integrated approach of LVR with concomitant procedures (based on well-defined indications by the Heart team), and to assess preoperative risk factors for long-term clinical outcomes, focusing on left ventricular (LV) geometry, LV function, and the presence of functional mitral regurgitation.

PATIENTS AND METHODS

Study Population and Study Design

Consecutive patients with refractory HFrEF (LV ejection fraction (LVEF) ≤ 35% and New York Heart Association [NYHA] class III/IV) due to a postinfarction anteroseptal

LV aneurysm, who underwent LVR between April 2002 and April 2011, were included. Patients with concomitant aortic valve disease were excluded.

Baseline and surgical characteristics, echocardiographic data—preoperatively, at discharge, and at midterm follow-up—and clinical outcomes were evaluated for all patients. The institutional medical ethics committee approved the protocol and written informed consent was obtained from all patients.

Indications for LVR and Concomitant Procedures

The surgical strategy for each patient was determined by the Heart team, consisting of heart-failure cardiologists, interventional cardiologists, and cardiothoracic surgeons. The indication for LVR was presence of a postinfarction anteroseptal LV aneurysm and refractory HFrEF. Concomitant mitral valve repair was performed in patients with mitral regurgitation (MR) ≥ grade 2 on preoperative echocardiography, and in patients with an increase of MR to ≥ grade 2 on intraoperative transesophageal echocardiography (TEE) directly after LVR. Tricuspid annuloplasty was conducted in patients with tricuspid regurgitation ≥ grade 2 or a tricuspid annular diameter > 40 mm (or > 21 mm/m^2 body surface area [BSA]). Revascularization of remote (ie, non-infarcted) myocardium was performed in presence of ≥ 70% angiographic diameter reduction of a coronary artery. Patients with preoperative ventricular arrhythmias underwent cryoablation.

Surgical Technique

All procedures were performed using cardiopulmonary bypass, aortic cross-clamping, and intermittent warm blood cardioplegia. LVR was performed following the technique described by Dor and associates [14], using a shaping Fontan-stitch at the transitional zone between macroscopically viable and scarred myocardium. Sizing and shaping of the residual ventricular cavity was done using a balloon or, from late 2006 onwards, a commercially available shaping device (TRISVR, Chase Medical, Richardson, TX) filled to a volume of 55 mL/m^2 BSA. A remaining defect was closed with an endoventricular patch. Mitral valve repair was conducted using a downsized semi-rigid annuloplasty ring (Carpentier Edwards Physio Ring, Edwards Lifesciences, Irvine, CA) and was considered successful in case of no/mild MR and a leaflet coaptation height ≥ 8 mm on intraoperative TEE. Tricuspid annuloplasty was performed using a tricuspid annuloplasty ring (MC3 ring, Edwards Lifesciences). Epicardial and endocardial cryoablation was performed at the border zone between scar and viable myocardium.

Echocardiography

Two-dimensional and Doppler transthoracic echocardiograms were performed preoperatively, before discharge, and at mid-term follow-up, using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwaukee, WI). All images were stored and analyzed by 2 independent investigators.

Severity of mitral and tricuspid regurgitation was graded semiquantitatively from color-flow Doppler in parasternal long-axis and apical 2-, 3- and 4-chamber images [15]. LV volumes were measured in apical 2- and 4-chamber images and indexed to BSA. LVEF was calculated by the modified biplane Simpson's method [16]. Systolic pulmonary artery pressure (sPAP) was assessed using the modified Bernoulli equation on the transtricuspid continuous-wave signal, adding the estimated right atrial pressure [17]. Preoperative LV systolic function was evaluated by the wall motion score index (WMSI). A 16-segment model was used for LV segmentation and each segment was analyzed in multiple views. Segments were scored as: 1 = normal or hyperkinetic, 2 = hypokinetic, 3 = akinetic, or 4 = dyskinetic. WMSI was calculated as the average score of all visualized segments; a higher WMSI indicates a more severely comprised LV function [16]. Right ventricular (RV) function was determined by calculating tricuspid annular plane systolic excursion (TAPSE) on M-mode recordings of the lateral tricuspid annulus in the RV apical view.

Study Endpoints

Information on clinical events was obtained from patients' medical records and direct patient interview. Primary endpoint was event-free survival, defined as freedom from LVAD implantation, HTx, and all-cause mortality up to 10 years after surgery. Secondary endpoints were severity of MR, LV volumes, LVEF, sPAP, and NYHA functional class at mid-term follow-up, and mitral valve reintervention and hospital readmissions for congestive heart failure (hospitalization with administration of parenteral diuretics or inotropes) up to 10 years after surgery.

Statistical Analysis

Continuous data are expressed as mean ± SD or median with interquartile range (IQR) and compared using the paired and unpaired Student's t test when appropriate. Categorical variables are described as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. The Kaplan-Meier method was used to estimate cumulative incidence. Univariable Cox proportional hazards regression analysis was performed to assess preoperative variables associated with event-free survival; variables with $p < 0.05$ were entered in a multivariable model. For all tests

a p value of < 0.05 was considered significant. Statistical analysis was performed using SPSS statistical software version 20.0 (IBM Corp, Armonk, NY).

RESULTS

Study Population

The study population consisted of 159 patients who underwent LVR surgery for refractory HFrEF due to a postinfarction anteroseptal LV aneurysm. Baseline patient characteristics are summarized in Table 1. Mean age was 62 ± 10 years and 130 patients (82%) were men. The majority of patients were in NYHA class III (67%) or IV (15%), despite optimal medical and device therapy. Preoperative echocardiography demonstrated advanced LV remodeling with mean indexed LV end-systolic volume (LVESVI) 87 ± 39 mL/m^2 and LVEF 26% ± 7%. WMSI could be determined in 156 patients. Mean WMSI was 2.3 ± 0.4 and WMSI was ≥ 2.5 in 49 patients (31%). MR ≥ grade 2 was present in 70 patients (44%).

LVR was electively performed in all patients. Concomitant mitral valve repair was performed in 68 of 70 patients with preoperative MR ≥ grade 2. Mitral valve repair was not performed in 2 patients because of a completely calcified posterior mitral annulus. Preoperative MR ≥ grade 2 was absent in 89 patients. Nonetheless, intraoperative TEE showed an increase in MR to ≥ grade 2 immediately after LVR in 24 patients. These patients underwent additional mitral valve repair during a second period of aortic cross-clamping. Intraoperative echocardiography after mitral valve repair showed no more than mild MR in any of the patients and a leaflet coaptation height of 8 ± 1 mm. Tricuspid annuloplasty was performed in 38 patients (24%). Revascularization was conducted in 100 patients (63%). Surgical data are summarized in Table 2. In-hospital mortality was 11.9% (19 patients). Echocardiography before discharge demonstrated no or mild MR in all patients.

Mid-Term Echocardiographic and Clinical Outcomes

Mid-term echocardiographic assessment (median 21 [IQR 13 to 25] months after surgery) was available in 116 of 131 surviving patients (89%) and demonstrated a decrease in LVESVI (89 ± 42 to 51 ± 18 mL/m^2, p < 0.001), with improved LVEF (26% ± 7% to 35% ± 9%, p < 0.001). Furthermore, MR grade was significantly reduced (1.6 ± 1.1 to 0.7 ± 0.5, p < 0.001), with recurrent MR grade 2 in only 5 patients (4%). Comparison of preoperative and mid-term echocardiography is shown in Table 3. NYHA functional class had significantly improved after surgery (3.0 ± 0.6 preoperatively to 1.8 ± 0.7 at mid-term followup, p < 0.001).

Table 1. Baseline Patient Characteristics

Baseline Characteristics	Total Study Population (N = 159)	Survivors (n = 78)	Deaths (n = 81)	*p* Value
Preoperative clinical data				
Age, years	62 ± 10	59 ± 10	65 ± 8	<0.001
Male	130 (82)	62 (80)	68 (84)	0.531
Interval in years of infarction to surgery (median [IQR])	7 [1–14]	3 [1–10]	10 [1–18]	0.008
No. of coronary vessels with stenosis > 70%				
1	62 (39)	33 (42)	29 (36)	
2	43 (27)	20 (26)	23 (28)	
3	46 (29)	21 (27)	25 (31)	
Previous cardiac surgery	16 (10)	2 (3)	14 (17)	0.002
Renal insufficiency	9 (6)	2 (3)	7 (9)	0.168
Severe PH (sPAP > 60 mm Hg)	16 (10)	6 (8)	10 (12)	0.330
Logistic EuroSCORE I	8 ± 10	5 ± 6	10 ± 12	0.003
NYHA class	3.0 ± 0.6	2.8 ± 0.6	3.1 ± 0.5	0.002
III	107 (67)	50 (64)	57 (70)	
IV	23 (15)	7 (9)	16 (20)	
Clinical VT	35 (22)	9 (12)	26 (32)	0.002
Preoperative ICD	40 (25)	15 (19)	25 (31)	0.091
Preoperative echocardiographic data				
MR grade	1.6 ± 1.0	1.3 ± 1.0	1.8 ± 1.1	0.003
LVEF, %	26 ± 7	27 ± 7	25 ± 6	0.050
LVEDV, mL	228 ± 86	227 ± 87	228 ± 86	0.932
LVESV, mL	171 ± 78	168 ± 81	173 ± 76	0.678
LVEDVI, mL/m^2	116 ± 43	116 ± 44	116 ± 41	0.975
LVESVI, mL/m^2	87 ± 39	86 ± 42	88 ± 37	0.768
WMSI[a]	2.3 ± 0.4	2.2 ± 0.4	2.4 ± 0.5	0.002
sPAP, mm Hg[b]	37 ± 15	34 ± 15	40 ± 15	0.060
TAPSE	18 ± 4	18 ± 3	17 ± 4	0.003

[a] Wall motion score index (WMSI) was available in 156 patients. [b] Systolic pulmonary artery pressure (sPAP) was available in 92 patients, due to absence of tricuspid regurgitation in 67 patients.
Values are mean ± SD or n (%) unless otherwise indicated.
EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter defibrillator; IQR = interquartile range; LVEDV = left ventricular end-diastolic volume; LVEDVI = LVEDV indexed to body surface area; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVI = LVESV indexed to body surface area; MR = mitral regurgitation; No. = number; NYHA = New York Heart Association; PH = pulmonary hypertension; TAPSE = tricuspid annular plane systolic excursion; VT = ventricular tachyarrhythmia.

Table 2. Surgical Data

Surgical Characteristics	Total Study Population (N = 159)	Survivors (n = 78)	Deaths (n = 81)	*p* Value
LVR with patch	153 (96)	75 (96)	78 (96)	0.962
Patch size, cm^2	13 ± 7	13 ± 7	14 ± 7	0.808
Balloon/shaper size, mL	108 ± 12	108 ± 12	109 ± 11	0.527
CABG	100 (63)	47 (60)	53 (65)	0.499
No. of distal anastomoses/patient	2.3 ± 1.2	2.3 ± 1.1	2.4 ± 1.2	0.548
Use of bypass grafts				
LIMA only	26 (26)	17 (36)	9 (17)	
RIMA only	5 (5)	1 (2)	4 (8)	
BIMA	19 (19)	13 (28)	6 (11)	
LIMA+vein	29 (29)	11 (23)	18 (34)	
Vein only	21 (21)	5 (11)	16 (30)	
Mitral valve repair	92 (58)	43 (55)	49 (61)	0.493
Median ring size [IQR]	28 [26–28]	28 [26–28]	26 [24–28]	
Tricuspid annuloplasty	38 (24)	12 (15)	26 (32)	0.013
Median ring size [IQR]	30 [28–32]	30 [28–32]	32 [28–32]	
Cryoablation	53 (33)	24 (31)	29 (36)	0.501
LV lead	76 (48)	33 (42)	43 (53)	0.174
IABP	38 (24)	11 (14)	27 (33)	0.004
ECC time, minutes	208 ± 63	196 ± 56	217 ± 68	0.100
Aortic cross-clamp time, minutes	142 ± 43	138 ± 40	145 ± 45	0.393

Values are n (%) or mean ± SD unless otherwise indicated.
BIMA = bilateral internal mammary artery; CABG = coronary artery bypass grafting; ECC = extracorporeal circulation; IABP = intraaortic balloon pump; IQR = interquartile range; LIMA = left internal mammary artery; LV = left ventricular; LVR = LV reconstruction; No. = number; RIMA = right internal mammary artery.

Long-Term Clinical Outcomes

Clinical follow-up was complete for all patients and median follow-up duration was 8.7 years (IQR, 3.9 to 10 years). During follow-up, 4 patients underwent LVAD implantation (all between 5.5 and 7.5 years after LVR surgery) and 2 patients underwent HTx (both 2.5 years after surgery), all for progressive heart failure. In addition to the 19 in-hospital deaths, 62 patients died. Cause of death was cardiac in 69% (heart failure, arrhythmias, and death from unknown causes). Overall cumulative eventfree survival rate was 83% ± 3% at 1-year, 68% ± 4% at 5-year, and 46% ± 4% at 10-year follow-up (Fig 1).

Mitral valve replacement was performed in 2 patients because of endocarditis with partial mitral ring dehiscence. Thirty-seven patients (23%) were readmitted for congestive heart failure; in total these patients experienced 105 readmissions (9.8 per 100 patient-years).

Table 3. Preoperative and Mid-Term Echocardiographic Data (n = 116)

Echocardiographic Characteristics	Preoperative	Mid-Term Follow-Up	*p* Value
MR grade	1.6 ± 1.1	0.7 ± 0.5	<0.001
Grade 0	13 (11)	44 (38)	
Grade I	54 (47)	67 (58)	
Grade II	22 (19)	5 (4)	
Grade III	18 (16)	0	
Grade IV	9 (8)	0	
LVEF, %	26 ± 7	35 ± 9	<0.001
LVEDV, mL	234 ± 94	156 ± 52	<0.001
LVESV, mL	176 ± 87	101 ± 39	<0.001
LVEDVI, mL/m^2	119 ± 46	79 ± 23	<0.001
LVESVI, mL/m^2	89 ± 42	51 ± 18	<0.001
sPAP, mm Hg[a]	35 ± 15	36 ± 16	0.903

[a] Systolic pulmonary artery pressure (sPAP) was available in 64 patients.
Values are mean ± SD or n (%) unless otherwise indicated.
LVEDV = left ventricular end-diastolic volume; LVEDVI = LVEDV indexed to body surface area; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVI = LVESV indexed to body surface area; MR = mitral regurgitation.

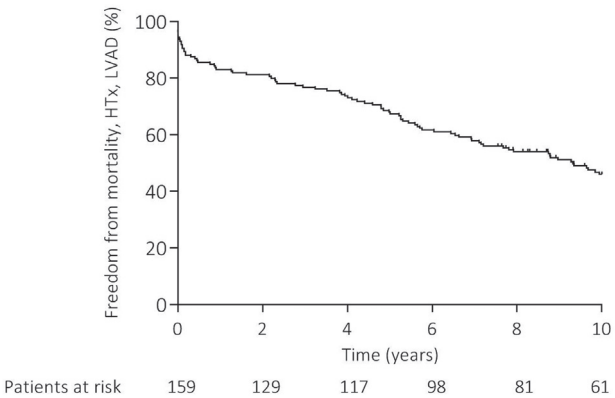


Fig 1. Overall event-free survival after surgery (n = 159). (HTx = heart transplantation; LVAD = left ventricular assist device.)

Preoperative Risk Factors for Event-Free Survival

Potential preoperative risk factors for event-free survival after surgery were assessed using univariable Cox regression analysis (Table 4). Six risk factors for adverse event-free survival were identified: increased age, preoperative renal insufficiency, higher preoperative WMSI, presence of preoperative MR (≥ grade 2), lower TAPSE, and a longer interval between myocardial infarction and surgery. Note that preoperative LV volumes were not associated with event-free survival. In a multivariable analysis, age (hazard ratio [HR] 1.03, 95% confidence interval [CI] 1.01–1.06, p = 0.016),

preoperative WMSI (HR 3.14, 95% CI 1.72–5.75, $p < 0.001$), presence of preoperative MR (HR 1.89, 95% CI 1.14–3.14, $p = 0.014$), and a longer interval between myocardial infarction and surgery (HR 1.05, 95% CI 1.02–1.08, $p = 0.001$) were independently associated with adverse event-free survival.

Table 4. Preoperative Risk Factors for Event-Free Survival

Variable	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio [95% CI]	*p* Value	Hazard Ratio [95% CI]	*p* Value
Age	1.04 [1.02–1.07]	<0.001	1.03 [1.01–1.06]	0.016
Gender	0.75 [0.42–1.35]	0.750		
Renal insufficiency	2.77 [1.27–6.03]	0.010	2.24 [0.87–5.74]	0.093
Severe PH (sPAP > 60 mm Hg)	1.40 [0.70–2.68]	0.343		
NYHA class IV	1.53 [0.88–2.50]	0.135		
Interval in years of infarction to surgery	1.04 [1.02–1.07]	0.001	1.05 [1.02–1.08]	0.001
LVEF	0.97 [0.94–1.00]	0.066		
LVEDVI	1.00 [1.00–1.01]	0.910		
LVESVI	1.00 [1.00–1.01]	0.837		
WMSI	2.86 [1.75–4.68]	<0.001	3.14 [1.72–5.75]	<0.001
MR ≥ grade 2	2.00 [1.30–3.08]	0.002	1.89 [1.14–3.14]	0.014
TAPSE	1.10 [1.04-1.18]	0.002	1.06 [0.99–1.15]	0.105

CI = confidence interval; LVEDVI = left ventricular end-diastolic volume indexed to body surface area; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume indexed to body surface area; MR = mitral regurgitation; NYHA = New York Heart Association; PH = pulmonary hypertension; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; WMSI = wall motion score index.

Combined Effect of Preoperative WMSI and Preoperative MR

The combined effect of preoperative WMSI and preoperative MR ≥ grade 2 on the primary endpoint can be appreciated in Figure 2, where patients are divided into 4 groups: (1) patients with WMSI < 2.5 without MR (n = 64), used as reference; (2) patients with WMSI < 2.5 with MR (n = 43); (3) patients with WMSI ≥ 2.5 without MR (n = 24); and (4) patients with WMSI ≥ 2.5 with MR (n = 25). In patients with WMSI < 2.5, the presence of MR negatively affected event-free survival (HR 2.33, 95% CI 1.30–4.17, $p = 0.005$). Event-free survival was even worse in patients with WMSI ≥ 2.5 without MR (HR 3.11, 95% CI 1.61–6.01, $p = 0.001$), and extremely poor for patients with WMSI ≥ 2.5 with MR (HR 4.74, 95% CI 2.54–8.85, $p < 0.001$).

Heart failure readmissions were observed in 13% of patients with WMSI < 2.5 without MR (4 readmissions per 100 patient-years), in 26% of patients withWMSI<2.5 with MR (13 readmissions per 100 patient-years), in 42% of patients withWMSI ≥

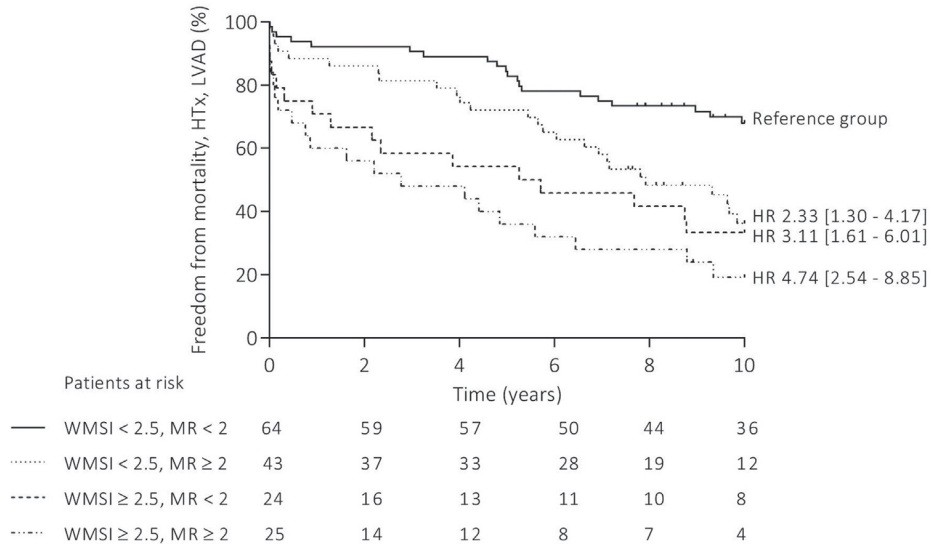


Fig 2. Event-free survival for patients with wall motion score index (WMSI) < 2.5 and ≥ 2.5, and mitral regurgitation (MR) < and ≥ grade 2. (HR = hazard ratio; HTx = heart transplantation; LVAD = left ventricular assist device.)

2.5 without MR (22 readmissions per 100 patient-years), and in 32% of patients with WMSI ≥ 2.5 with MR (14 readmissions per 100 patient-years).

COMMENT

In the present study, mid-term echocardiographic and long-term clinical outcomes were evaluated in patients who underwent an integrated surgical treatment, consisting of LVR with concomitant procedures (mitral valve repair, tricuspid valve repair, revascularization, and arrhythmia surgery) for refractory HFrEF due to a postinfarction anteroseptal LV aneurysm. This integrated approach resulted in LV reverse remodeling and absence of MR ≥ grade 2 at mid-term follow-up, and 46% event-free survival 10 years after surgery. Increased age, higher preoperative WMSI, preoperative presence of MR ≥ grade 2 and a longer time interval after myocardial infarction were associated with worse eventfree survival after surgery. Event-free survival is favorable in patients with WMSI < 2.5 and significantly worse when WMSI is ≥ 2.5. In both groups, the presence of preoperative MR grade ≥ 2 negatively affects event-free survival, despite successful correction of MR.

Surgery for Refractory HFrEF: Echocardiographic and Clinical Outcomes

Heart failure is the most common complication due to myocardial infarction and is associated with adverse clinical outcomes [3, 4, 18]. Optimal medical and device therapy improve outcomes in these patients. However, when heart failure symptoms persist, surgical treatment options—implantation of an LVAD, HTx, and reconstructive surgery (targeting the left ventricle as well as concomitant functional valve regurgitation)—should be carefully considered by a dedicated Heart team [6–9].

In the present study, all patients underwent a personalized surgical approach with LVR as the mainstay, combined with concomitant procedures based on welldefined indications. Structured outpatient follow-up and optimal medical therapy were continued after surgery in all patients. This integrated medicosurgical approach resulted in LV reverse remodeling (LVESVI –36%), improved LVEF (+46%), and absence of MR ≥ grade 2 at mid-term follow-up. Others have reported similar echocardiographic results after LVR surgery [11–13]. To the best of our knowledge, the current study is the first to extend clinical follow-up to 10 years after surgery. Eventfree survival in this study (83% ± 3% at 1-year, 68% ± 4% at 5-year, and 46% ± 4% at 10-year follow-up) is better than the overall 5-year survival of patients with heart failure after myocardial infarction (approximately 50%) [4], and comparable to the 5-year survival after LVR surgery reported by others [11, 12].

Risk Factors for Event-Free Survival

Risk stratification and careful preoperative patient selection are crucial to optimize outcomes after LVR surgery. In the present study, 4 preoperative risk factors for adverse event-free survival were identified: increased age, higher WMSI, presence of MR ≥ grade 2 and a longer interval between myocardial infarction and surgery.

WMSI is an echocardiographic measure of LV systolic function. In a previous study, we demonstrated that WMSI at a cutoff value of ≥ 2.5 is associated with poor outcomes 1 year after LVR surgery (a combined endpoint of mortality and NYHA class ≥ III) [19]. In the present study, WMSI ≥ 2.5 proved to be an independent risk factor for event-free survival up to 10 years after surgery as well. This finding indicates that the extent and function of the remote myocardium plays a key role in translating surgically induced LV changes into beneficial long-term outcomes.

Functional MR is a common phenomenon in patients with ischemic heart failure, resulting from a combination of papillary muscle displacement, systolic leaflet tethering, annular dilatation, and reduced closing forces due to LV remodeling [20].

Functional MR is associated with poor survival [21, 22], but its management at the time of LVR surgery remains controversial [13]. In the present study, mitral valve repair was performed in all patients with MR ≥ grade 2. The presence of preoperative MR negatively affected event-free survival in both patients with WMSI < 2.5 and WMSI ≥ 2.5 despite successful mitral valve repair. Consequently, the presence of preoperative MR could be interpreted as a marker of LV remodeling. Advanced LV systolic dysfunction and presence of functional MR provide a fatal combination.

Finally, a longer interval between myocardial infarction and LVR surgery was independently associated with adverse event-free survival. The compensatory LV volume increase seen in remodeling after myocardial infarction results in increased LV wall pressure with hypoperfusion of the remote myocardium [23]. Because LV remodeling is a progressive process, myocardial fibrosis will be more severe in patients with a longer interval between myocardial infarction and surgery, which might explain its association with adverse clinical outcomes.

Interestingly, preoperative LV volumes were not associated with adverse outcomes in the present study, in contrast to previous reports [11, 12, 24]. However, the extent and function of the remote myocardium—and consequently the ability to recover after LVR surgery— may differ between patients with equally increased LV volumes. This heterogeneity in remote myocardium may explain why global ventricular measures such as LV volumes may not accurately predict event-free survival after LVR surgery.

Although RV function, as determined by TAPSE, was not independently associated with event-free survival, this does not imply that RV function should be disregarded. Other studies have shown reduced 30-day and long-term survival after LVR in patients with RV dysfunction, but these studies did not take into account the degree of LV systolic dysfunction or MR severity [25, 26]. The interaction between LV and RV dysfunction remains complex; in the current study LV dysfunction as reflected by WMSI and MR grade proved to be the strongest predictor of long-term event-free survival.

Clinical Implications

The optimal treatment strategy for patients with refractory HFrEF due to a postinfarction anteroseptal LV aneurysm remains a subject of debate. LVAD implantation and HTx may be considered for these patients [5]. Although survival after LVAD implantation as destination therapy has improved (1-year survival of approximately 50%), LVADs still have their limitations—namely, thromboembolic events,

anticoagulation-related hemorrhage, and infection [27]. Heart transplantation is limited by donor shortage and strict selection criteria, and has a 5-year survival rate of approximately 70%. An integrated approach consisting of LVR with concomitant procedures, as described in this study, is a viable alternative for these patients.

In the present study, we identified risk factors that can easily be determined and may help the Heart team to decide on which intervention to choose for patients with refractory HFrEF. LVR with concomitant procedures is favorable for patients with a preoperative WMSI < 2.5— both with and without functional MR, provided that the mitral valve is successfully repaired. In patients with WMSI ≥ 2.5 without MR, LVR may still be considered a viable option, however with slightly worse outcomes at longer follow-up. For patients with WMSI ≥ 2.5 and presence of MR, event-free survival is extremely poor despite durable correction of MR. For these patients, the Heart team might first consider alternatives such as LVAD implantation or HTx. LVR might still have a place in patients with contraindications for these alternatives, and in those for whom it might be warranted to defer LVAD implantation or HTx. Given that a longer interval between myocardial infarction and surgery was associated with adverse event-free survival, LVR surgery should preferably be considered in an early stage if patients develop symptoms of heart failure.

Study Limitations

The present study is a single-center observational study, with a limited study population. However, 10-year followup was complete for all patients and the study population was very homogeneous, only including patients with refractory HFrEF (LVEF ≤ 35% and NYHA class III/IV) due to a postinfarction anteroseptal aneurysm. Higher preoperative WMSI and preoperative presence of MR ≥ grade 2 were found to be independently associated with adverse event-free survival. These findings should be confirmed in other, larger studies. Because of the retrospective nature of this study and the study period (starting in 2002), data regarding preoperative viability were not available for the majority of patients and quality of echocardiographic images was insufficient for assessment of more-advanced RV function parameters (such as RV fractional area change or RV longitudinal peak systolic strain).

CONCLUSION

In the present study, an integrated approach of LVR with concomitant procedures for patients with HFrEF due to a postinfarction anteroseptal aneurysm resulted in LV reverse remodeling and absence of functional MR at midterm follow-up. Event-free

survival is favorable in patients with WMSI < 2.5 and significantly worse when WMSI is ≥ 2.5. In both groups, the presence of preoperative MR grade ≥ 2 negatively affects event-free survival, despite successful correction of MR. These findings indicate that preoperative echocardiographic assessment, specifically focused on preoperative WMSI and presence of MR, is useful for the decision-making process on which intervention to choose for patients with refractory HFrEF.

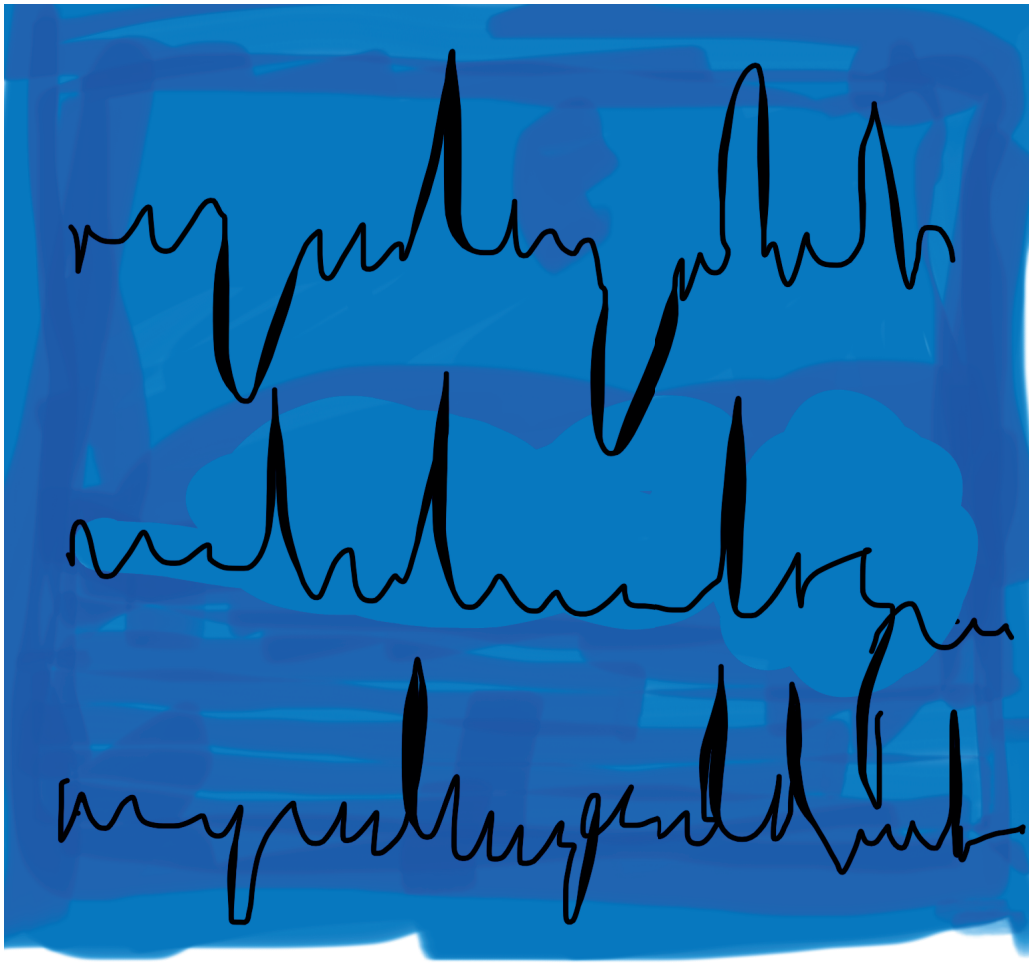
Dr Klein discloses a financial relationship with Edwards Lifesciences and BioVentrixs Inc.

REFERENCES

1. Wilkins E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels. Available at http://www.ehnheart.org/cvd-statistics.html. Accessed March 9, 2019.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146–603.
3. Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 2008;118:2057–62.
4. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30–41.
5. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. Circulation 2013;128:e240–327.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol 2017;70: 776–803.
8. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J 2014;35:2541–619.
9. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2017;00: 1–66.
10. Klein P, Braun J, Holman ER, et al. Management of mitral regurgitation during left ventricular reconstruction for ischemic heart failure. Eur J Cardiothorac Surg 2012;41:74–80.
11. Athanasuleas CL, Buckberg GD, Stanley AW, et al. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. J Am Coll Cardiol 2004;44:1439–45.
12. Menicanti L, Castelvecchio S, Ranucci M, et al. Surgical therapy for ischemic heart failure: single-center experience with surgical anterior ventricular restoration. J Thorac Cardiov Sur 2007;134:433–41.
13. Castelvecchio S, Garatti A, Gagliardotto PV, Menicanti L. Surgical ventricular reconstruction for ischaemic heart failure: State of the art. Eur Heart J Suppl 2016;18(suppl E): E8–14.
14. Dor V, Saab M, Coste P, Kornaszewska M, Montiglio F. Left ventricular aneurysm: a new surgical approach. Thorac Cardiovasc Surg 1989;37:11–9.
15. Thomas JD. How leaky is that mitral valve? Simplified Doppler methods to measure regurgitant orifice area. Circulation 1997;95:548–50.
16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16: 233–70.
17. Pepi M, Tamborini G, Galli C, et al. A new formula for echo- Doppler estimation of right ventricular systolic pressure. J Am Soc Echocardiog 1994;7:20–6.
18. Desta L, Jernberg T, Lofman I, et al. Incidence, temporal trends, and prognostic impact of heart failure complicating acute myocardial infarction. The Swedeheart registry

(Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies): a study of 199, 851 patients admitted with index acute myocardial infarctions, 1996 to 2008. JACC Heart Fail 2015;3:234–42.

19. Klein P, Holman ER, Versteegh MI, et al. Wall motion score index predicts mortality and functional result after surgical ventricular restoration for advanced ischemic heart failure. Eur J Cardiothorac Surg 2009;35:847–52; discussion 852–3.
20. Levine RA, Hung J, Otsuji Y, et al. Mechanistic insights into functional mitral regurgitation. Curr Cardiol Rep 2002;4: 125–9.
21. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–64.
22. Bursi F, Enriquez-Sarano M, Jacobsen SJ, Roger VL. Mitral regurgitation after myocardial infarction: a review. Am JMed 2006;119:103–12.
23. Talman V, Ruskoaho H. Cardiac fibrosis in myocardial infarction—from repair and remodeling to regeneration. Cell Tissue Res 2016;365:563–81.
24. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.
25. Couperus LE, Delgado V, Palmen M, et al. Right ventricular dysfunction affects survival after surgical left ventricular restoration. J Thorac Cardiovasc Surg 2017;153:845–52.
26. Garatti A, Castelvecchio S, Di Mauro M, Bandera F, Guazzi M, Menicanti L. Impact of right ventricular dysfunction on the outcome of heart failure patients undergoing surgical ventricular reconstruction. Eur J Cardiothorac Surg 2015;47:333–40.
27. de By TMMH, Mohacsi P, Gahl B, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio- Thoracic Surgery (EACTS): second report. Eur J Cardiothorac Surg 2018;53:309–16.



Chapter 6

Left Ventricular Ejection Fraction as Criterion for Implantation of an Implantable Cardioverter-Defibrillator in Heart Failure Patients Undergoing Surgical Left Ventricular Reconstruction

Sjoerd A. Mollema, M.D.,* Patrick Klein, M.D.,† Jogien Heersche, M.D.,* Martin J. Schalij, M.D., PH.D.,* Ernst E. van der Wall, M.D., PH.D.* Michel I.M. Versteegh, M.D.,† Robert J.M. Klautz, M.D., PH.D.,† Lieselot van Erven, M.D., PH.D.,* and Jeroen J. Bax, M.D., PH.D.*

*Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and †Department of Cardiothoracic Surgery, Leiden University Medical Center, Leiden, The Netherlands

Pacing Clin. Electrophysiol. 2009 Jul. 32(7):913-7

ABSTRACT

Background: Besides implantation of an implantable cardioverter-defibrillator (ICD), a proportion of patients with left ventricular (LV) dysfunction due to ischemic cardiomyopathy are potential candidates for surgical LV reconstruction (Dor procedure), which changes LV ejection fraction (LVEF) considerably. In these patients, LVEF as selection criterium for ICD implantation may be difficult. This study aimed to determine the value of LVEF as criterium for ICD implantation in heart failure patients undergoing surgical LV reconstruction.

Methods: Consecutive patients with end-stage heart failure who underwent ICD implantation and LV reconstruction were evaluated. During admission, two-dimensional (2D) echocardiography (LV volumes and LVEF) was performed before surgery and was repeated at 3 months after surgery. Over a median follow-up of 18 months, the incidence of ICD therapy was evaluated.

Results: The study population consisted of 37 patients (59 ± 11 years). At baseline, mean LVEF was 23 ± 5%. Mean left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were 175 ± 73 mL and 225 ± 88 mL, respectively. At 3-month follow-up, mean LVEF was 41 ± 9%($P < 0.0001$ vs. baseline), and mean LVESV and LVEDV were 108 ± 65 mL and 176 ± 73 mL, respectively ($P < 0.0001$ vs. baseline). During 18-month follow-up, 12 (32%) patients had ventricular arrhythmias, resulting in appropriate ICD therapy. No significant relations existed between baseline LVEF ($P = 0.77$), LVEF at 3-month follow-up ($P = 0.34$), change in LVEF from baseline to 3-month follow-up ($P = 0.28$), and the occurrence of ICD therapy during 18-month follow-up.

Conclusion: LVEF before and after surgical LV reconstruction is of limited use as criterium for ICD implantation in patients with end-stage heart failure. (PACE 2009; 32:913–917)

Keywords: implantable cardioverter-defibrillator, ischemic cardiomyopathy, left ventricular reconstruction, left ventricular ejection fraction, heart failure, echocardiography

INTRODUCTION

Randomized trials demonstrated im-proved survival with implantable cardioverter-defibrillator (ICD) therapy in high-risk patients with left ventricular (LV) dysfunction due to ischemic cardiomyopathy.[1–6] In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), a relative risk reduction in mortality of 31% was achieved by ICD implanta-tion in patients with previous infarction and LV dysfunction (LV ejection fraction [LVEF] ≤30%) without evidence of ventricular arrhythmias.2 This subsequently resulted in a class I indication for prophylactic ICD implantation in patients meeting the MADIT II criteria (AHA/ACC/NASPE Guidelines), with an exponential growth in the ICD implantation rate.[7] On the other hand, recent analysis of the MADIT II population revealed that only 35% of patients who received an ICD developed ventricular arrhythmias requiring ICD shocks over a 3-year follow-up period.[8] As a consequence, there has been considerable debate about the value of LVEF as a major selection criterium for patient selection in need of ICD implantation.[9]

A substantial number of patients with ischemic cardiomyopathy, LVEF ≤30–40%, and previous anterior myocardial infarction will present with an apical LV aneurysm.[10] These patients are candidates for ICD implantation according to the MADIT II criteria. In addition, some of these patients may eventually be referred for surgical LV reconstruction (Dor procedure), which may result in improvement of the LVEF.[11–13] Particularly in these patients, the LVEF as selection cri-terium for ICD implantation may be difficult.

In the current study, 41 consecutive patients were evaluated who underwent ICD implantation (based on the MADIT II criteria) and LV reconstruction (Dor procedure). LVEF was obtained before surgery and 3 months after surgery. Over a median follow-up of 18 months after surgery, the prevalence of ICD therapy was evaluated.

METHODS

Patients and Study Protocol

For this study, 41 consecutive patients with end-stage heart failure who underwent ICD implantation and LV reconstruction according to the Dor procedure[14,15] were evaluated. During admission (baseline), before surgery, two-dimensional (2D) echocardiography was performed in all patients and LV volumes and LVEF were assessed. All patients underwent ICD implantation based on LVEF ≤30%. A combined ICD-

cardiac resynchronization therapy (CRT) device was implanted in 16 patients. All patients underwent LV reconstruc-tion according to the Dor approach. 2D echocardiography (including assessment of LV volumes and LVEF) was repeated at 3 months after surgery in the outpatient clinic. During a median (25th and 75th percentiles) follow-up after surgery of 18 (11, 43) months, the occurrence of ICD therapy was registered. Four patients died within 1 month after surgery due to sepsis (n = 1) or progression of heart failure (n = 3) and therefore did not have a complete follow-up assessment. These patients were excluded from the study. The final study population therefore comprised 37 patients who all underwent ICD implantation, Dor procedure, and had complete follow-up assessment.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, WI, USA). Standard images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis images) and apical (two- and four-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. LV volumes (end-systolic [LVESV] and end-diastolic [LVEDV]) and LVEF were calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique.[16]

All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient. Inter- and intraobserver agreements for assessment of LV volumes were 90 and 93% for LVESV, and 92 and 93% for LVEDV, respectively.

ICD Implantation

A dual-chamber ICD device for primary prevention was subcutaneously implanted under local anesthesia.[17] Implantation of an endocardial lead system was performed in all patients. No complications occurred during ICD implantation. After implantation, a defibrillation test was performed under conscious sedation (using midazolam and fentanyl). The ICD was programmed for both ventricular tachycardia and ventricular fibrillation detection and therapy using three zones: a monitor zone, an antitachycardia pacing (ATP) zone, and a ventricular fibrillation zone. In each patient, cutoff rates were programmed according to individual needs. All ICD events were individually analyzed by experienced and blinded physicians during regular pacemaker checkups. ICD therapy was defined as appropriate ATP and/or shock therapy.

Surgical Technique

LV reconstruction was performed in all patients by means of endoventricular circular patch plasty as previously described by Dor et al.[14,15] All procedures were performed under normothermic conditions with intermittent antegrade warm blood cardioplegia. The LV was opened through the infarcted area. An endocardial encircling suture (Fontan stitch) was placed approximately at the transitional zone between scarred and normal tissue, giving preference to the resulting ellipsoidal shape of the left ventricle over the exact transitional zone. A balloon containing 55 mL/m^2 body surface area saline was introduced into the LV, and the Fontan stitch was tightened to approximate the ventricular wall to the balloon. An oval Dacron patch was tailored and used to close the residual orifice. The excluded scar tissue was closed over the patch to ensure hemostasis. Care was taken to eliminate the entire septal scar and to delineate a new LV apex with the goal to restore the normal elliptical shape.

Statistical Analysis

Summary statistics for all continuous variables are presented as means ± standard deviation. Categorical data are summarized as frequencies and percentages. Comparison of continuous data was performed using the paired and unpaired Student's *t*-test when appropriate. Categorical data were compared using ^{2} analysis.

Logistic regression analysis was applied to evaluate the relation between (change in) LVEF and the occurrence of ICD therapy during follow-up. Hazard ratios (HR) with 95% confidence intervals (CI) were provided. For all tests, a P value <0.05 was considered statistically significant.

RESULTS

Baseline Data of the Study Population

The study population consisted of 37 patients (30 men, mean age 59 ± 11 years). Clinical characteristics of the study population are summarized in Table I. All patients had a history of myocardial infarction and were in sinus rhythm.

The Dor procedure was combined with coronary artery bypass grafting in 19 patients, mitral valve repair in 26 patients, and tricuspid valve repair in 15 patients. Rethoracotomy was needed in three patients due to substantial loss of blood. The Dor procedure was uncomplicated in all other patients.

Table I.
Clinical Characteristics of the Study Population (n = 37)

Variable	Value
Age (years)	59 ± 11
Gender (M/F) (%)	30/7 (81/19)
Previous MI (%)	37 (100)
NYHA class	3.1 ± 0.6
QRS duration (ms)	124 ± 30
Risk factors for CAD	
Diabetes (%)	4 (11)
Hypertension (%)	10 (27)
Hyperlipidemia (%)	10 (27)
Smoking (%)	18 (49)
Family history of CAD (%)	12 (32)
Medication at baseline	
β-Blocker (%)	31 (84)
ACE inhibitor/ARB (%)	28 (76)
Anticoagulants (%)	33 (89)
Statin (%)	28 (76)
Antiarrhythmics (%)	15 (41)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; NYHA = New York Heart Association; MI = myocardial infarction.

Echocardiography

At baseline, all patients had a LVEF ≤30%with a mean LVEF of 23 ± 5%. Mean LVESV and LVEDV were 175 ± 73 mL and 225 ± 88 mL, respectively. Between baseline and 3-month follow-up, mean LVESV (175 ± 73 mL vs. 108 ± 65 mL; $P < 0.0001$) and LVEDV (225 ± 88 mL vs. 176 ± 73 mL; $P < 0.0001$) decreased significantly. During echocardiography at 3-month follow-up, mean LVEF of 41 ± 9% was demonstrated ($P < 0.0001$ vs. baseline).

ICD Therapy during Follow-Up

During a median follow-up of 18 (11, 43) months after surgery, registered ventricular arrhythmias resulting in appropriate ICD therapy occurred in 12 (32%) patients. Six patients had appropriate shocks delivered by the ICD. In the other six patients, episodes in which ATP was applied were demonstrated during follow-up.

As demonstrated by logistic regression analysis, no significant relation existed between baseline LVEF and the occurrence of ICD therapy during 18 months of follow-up (HR 1.02, 95%CI 0.88–1.19, $P = 0.77$). In addition, no significant relation

was demonstrated between LVEF at 3-month follow-up and the occurrence of ICD therapy during follow-up (HR 0.96, 95% CI 0.89–1.04, P = 0.34). Furthermore, there was no significant relation between the change in LVEF from baseline to 3-month follow-up and the occurrence of ICD therapy during follow-up (HR 0.99, 95% CI 0.98–1.01, P = 0.28).

DISCUSSION

The results of the present study can be summarized as follows: (1) considerable improvement in LVEF with reduction in LV volumes is demonstrated at 3-month follow-up in heart failure patients undergoing LV reconstruction (Dor procedure); (2) appropriate ICD therapy occurred in 32% of patients after ICD implantation during 18-month follow-up; (3) neither LVEF at baseline and at 3-month follow-up nor the change in LVEF during 3-month follow-up was related to the occurrence of ICD therapy during 18-months follow-up.

After the onset of symptomatic heart failure, morbidity and mortality are reported to be high.[18–24] Data from early studies (e.g., the Framingham Heart Study) demonstrated a 1-year survival of 55–70% in patients with newly diagnosed symptomatic heart failure.[19,20,23] Subsequent studies demonstrated improvement in mortality with recent developments in medical therapy. Still, mortality in heart failure patients remains high.[25,26] Jong et al. studied over 38,000 consecutive patients from Canada with a first admission for heart failure between 1994 and 1997.[25] The crude 30-day and 1-year mortality rates were 11.6 and 33.1%.

The two main causes of death in patients with heart failure are sudden death and progression of pump failure.[27,28] Several studies suggested a stable pattern with 30–50% of all cardiac deaths in patients with heart failure being categorized as sudden deaths.[24,28–32] In the MADIT II trial, 31% of the cardiac deaths occurred within 1 hour of onset of symptoms, 36% occurred more than 1 hour after symptom onset, and 33% were unwitnessed.[8] Furthermore, the MADIT II trial demonstrated a relative risk reduction in mortality of 31% by ICD implantation in patients with previous infarction and LV dysfunction (LVEF ≤30%) without evidence of ventricular arrhythmias.[2] A class I indication for prophylactic ICD implantation in patients meeting the MADIT II criteria (AHA/ACC/NASPE Guidelines) was the consequence.[7] On the other hand, recent analysis of the MADIT II population revealed that only 35% of patients who received an ICD developed ventricular arrhythmias requiring ICD shocks over a 3-year follow-up period.[8] Consequently, there has been much discussion concerning

the value of LVEF as a major selection criterium for patient selection in need of ICD implantation.[9]

In addition to optimal pharmacological treatment and potential ICD implantation, LV reconstruction may be considered in patients with heart failure and extensive akinesia or dyskinesia of the anterior wall.[11–14] In 1989, Dor and colleagues introduced a surgical approach to restore LV geometry.[14] Over the years, several studies described the advantageous effects of the Dor procedure on LV geometry and function, including substantial increase in LVEF.[11–13] In the present study, mean LVEF increased considerably from 23% before surgery to 41% at 3 months after the Dor procedure ($P < 0.0001$). The majority of patients referred for LV reconstruction may be candidates for ICD implantation as well, according to the MADIT II criteria. In these patients, the LVEF as selection criterium for ICD implantation may be even more difficult as LV reconstruction leads to increase in LVEF. This underscores the dilemma of ICD implantation based on LVEF in this specific group of patients.

In the current study, all patients had LVEF ≤30% at baseline and received an ICD, according to the MADIT II criteria. During median follow-up of 18 months after surgery, appropriate ICD therapy was noted in 32% of patients. The relatively high incidence of appropriate ICD therapy can be explained by a decreased overall clinical condition of the patient population and possibly by increased electrical heterogeneity following surgery, resulting in ventricular arrhythmias. Moreover, the current observations are in line with the MADIT II trial showing that 35% of patients received appropriate ICD shocks over a 3-year follow-up period.[2]

In the present study, LVEF at baseline was not predictive for the occurrence of ICD therapy during follow-up. In addition, a significant relation could not be demonstrated between LVEF at 3-month follow-up and the occurrence of ICD therapy during 18-month follow-up. Furthermore, no significant relation was demonstrated between the change in LVEF from baseline to 3-month follow-up and the occurrence of ICD therapy during 18 months of follow-up.

The small group of patients form an important limitation. Furthermore, it cannot be ruled out that concomitant surgical procedures (coronary artery bypass grafting, valve surgery) during the Dor procedure might have influenced the change in LVEF after the procedure. However, this study is the first to report on the relation between LVEF in the period around surgical LV reconstruction and the occurrence of ICD therapy during follow-up. Future studies should include larger numbers of

patients and should focus more on the impact of the surgical procedure on the occurrence of (inappropriate) ICD therapy during follow-up.

CONCLUSION

The findings of the present study suggest that LVEF before and after surgical LV reconstruction is of limited use as criterium for ICD implantation in patients with end-stage heart failure.

This study was supported by an unrestricted research grant from St. Jude Medical.

Dr. Bax receives research grants from GE Healthcare, BMS, Boston Scientific, Medtronic, St. Jude, and Edwards Lifesciences.

Dr. Schalij receives research grants from Boston Scientific, Medtronic, and Biotronik.

REFERENCES

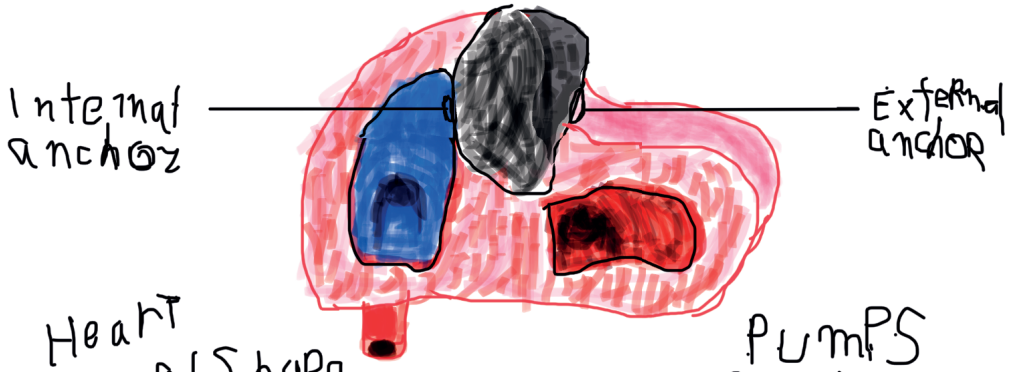
1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996; 335:1933– 1940.
2. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346:877–883.
3. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, et al. Amiodarone or an implantable cardioverterdefibrillator for congestive heart failure. N Engl J Med 2005; 352: 225–237.
4. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999; 341:1882–1890.
5. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: A systematic review of randomized, controlled trials. Ann Intern Med 2003; 138:445–452.
6. Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, Tu JV, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: A meta-analysis. J Am Coll Cardiol 2003; 41:1573–1582.
7. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: Summary article. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). J Cardiovasc Electrophysiol 2002; 13:1183–1199.
8. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004; 43:1459–1465.
9. Moss AJ. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter-defibrillator? Everyone with an ejection fraction < or = 30% should receive an implantable cardioverter-defibrillator. Circulation 2005; 111:2537–2549.
10. Mills NL, Everson CT, Hockmuth DR. Technical advances in the treatment of left ventricular aneurysm. Ann Thorac Surg 1993; 55:792–800.
11. Dor V. Left ventricular aneurysms: The endoventricular circular patch plasty. Semin Thorac Cardiovasc Surg 1997; 9:123–130.
12. Di Donato M, Sabatier M, Dor V, Gensini GF, Toso A, Maioli M, Stanley AW, et al. Effects of the Dor procedure on left ventricular dimension and shape and geometric correlates of mitral regurgitation one year after surgery. J Thorac Cardiovasc Surg 2001; 121:91–96.
13. Dor V, Saab M, Coste P, Sabatier M, Montiglio F. Endoventricular patch plasties with septal exclusion for repair of ischemic left ventricle: Technique, results and indications from a series of 781 cases. Jpn J Thorac Cardiovasc Surg 1998; 46:389–398.

14. Dor V, Saab M, Coste P, Kornaszewska M, Montiglio F. Left ventricular aneurysm: A new surgical approach. Thorac Cardiovasc Surg 1989; 37:11–19.
15. Dor V, Sabatier M, Di Donato M, Montiglio F, Toso A, Maioli M. Efficacy of endoventricular patch plasty in large postinfarction akinetic scar and severe left ventricular dysfunction: Comparison with a series of large dyskinetic scars. J Thorac Cardiovasc Surg 1998; 116:50–59.
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2:358–367.
17. van Rugge FP, Savalle LH, Schalij MJ. Subcutaneous single-incision implantation of cardioverter-defibrillators under local anesthesia by electrophysiologists in the electrophysiology laboratory. Am J Cardiol 1998; 81:302–305.
18. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole- Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: A population based study. Heart 2000; 83:505–510.
19. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993; 88:107–115.
20. Rodeheffer RJ, Jacobsen SJ, Gersh BJ, Kottke TE, McCann HA, Bailey KR, Ballard DJ. The incidence and prevalence of congestive heart failure in Rochester, Minnesota. Mayo Clin Proc 1993; 68:1143– 1150.
21. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjectswith normal versus reduced left ventricular ejection fraction: Prevalence and mortality in a populationbased cohort. J Am Coll Cardiol 1999; 33:1948–1955.
22. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Cardiol 1992; 20:301–306.
23. MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, et al. Evidence of improving prognosis in heart failure: Trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. Circulation 2000; 102:1126–1131.
24. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, Grobbee DE. The prognosis of heart failure in the general population: The Rotterdam Study. Eur Heart J 2001; 22:1318–1327.
25. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: A population-based study. Arch Intern Med 2002; 162:1689–1694.
26. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA. Longterm survival after heart failure: A contemporary population-based perspective. Arch Intern Med 2007; 167:490–496.
27. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429–1435.
28. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325:293–302.

29. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327: 685–691.
30. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in CongestiveHeart Failure (MERIT-HF). Lancet 1999; 353:2001–2007.
31. Kannel WB, Wilson PW, D'Agostino RB, Cobb J. Sudden coronary death in women. Am Heart J 1998; 136:205–212.
32. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327:669–677.

Less Invasive Treatment

Live Therapy



ankertjedoornet hart

Chapter 7

Hybrid transcatheter left ventricular reconstruction for the treatment of ischaemic cardiomyopathy

Carlo Zivelonghi, MD; Patrick Klein, MD; Martin J. Swaans, MD, PhD; Pierfrancesco Agostoni, MD, PhD

Department of Cardiology and Cardiothoracic Surgery, St Antonius Hospital, Nieuwegein, the Netherlands
C. Zivelonghi and P. Klein contributed equally to this manuscript.

EuroIntervention 2018;13:1899-1901

INTRODUCTION

Remodelling of the left ventricle (LV) after a myocardial infarction (MI) results in increased volumes and a reduced ejection fraction (EF). The transmurality of the infarction determines whether a true LV aneurysm will result. Patients with advanced ischaemic cardiomyopathy often suffer recurrent episodes of cardiac decompensation with the need for multiple hospitalisations; they have a limited prognosis. Mixed outcomes have been demonstrated after conventional surgical LV reconstruction[1,2]. We describe a novel hybrid transcatheter technique to reconstruct the remodelled LV by plication of the anteroseptal LV scar, in order to reduce the enlarged LV volume, decrease the wall stress and increase the EF.

METHODS

The procedure, called less invasive ventricular enhancement (LIVE), has the objective of reconstructing the LV by plication of fibrous scar and relies on the micro-anchoring technology of the Revivent TC™ Ventricular Enhancement System (BioVentrix Inc., San Ramon, CA, USA) (Figure 1). This system consists of a number of paired anchors connected by a poly-ether-ether-ketone (PEEK) tether that, once properly positioned, are pulled together with a controlled force by means of a specialised force gauge and finally released. The Revivent TC System represents the evolution of its previous fully surgical version. Major steps forward are represented by the avoidance of both sternotomy and extracorporeal circulation.

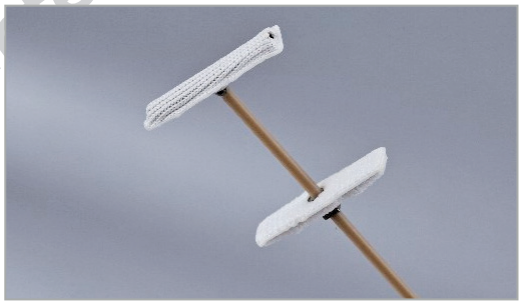


Figure 1. Internal and external anchor.

Patients eligible for the procedure present with symptomatic heart failure (NYHA Class ≥II) and ischaemic cardiomyopathy (EF <40%) after anteroseptal MI resulting in a dilated LV with an akinetic/dyskinetic scar in the anteroseptal wall and apex.

Preoperative planning requires gadolinium-enhanced magnetic resonance imaging (MRI) (or alternatively contrast computed tomography [CT]) to define the scar morphology clearly. Scarred regions must comprise at least 50% of the wall thickness to enable safe anchor implantation. The LIVE procedure is a hybrid transcatheter procedure performed by both an interventional cardiologist (IC) and a cardiothoracic surgeon (CTS) in co-operation. Additional support is provided by the presence of a cardiologist skilled in three-dimensional transoesophageal echocardiography (3D-TEE).

LV reconstruction is achieved by implantation of a series of internal and external micro-anchors and brought together over a PEEK tether to form a longitudinal line of apposition between the LV free wall and the anterior septum of the right ventricle (RV) (Figure 2). Typically, two to three pairs are used, depending on the size of the LV and the areas of akinesia/dyskinesia. These "RV-LV" anchor pairs are used in combination with a final "LV-LV" anchor pair that is placed through the LV apex. The aim is to achieve a conical reconstruction of the LV with a completely excluded endoventricular scar and an LV volume reduction of 30-40% (Figure 3).

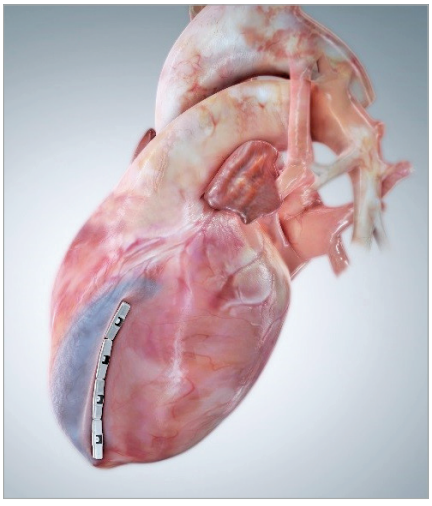


Figure 2. External anchors and plicated LV.

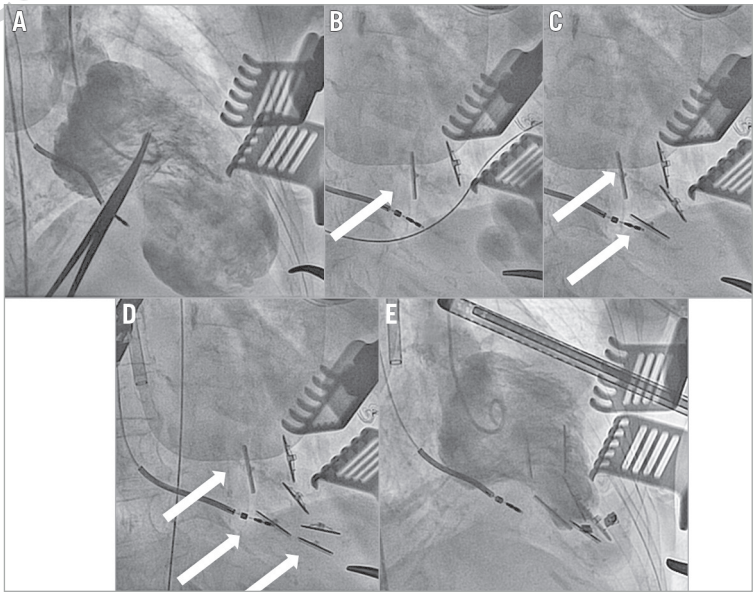


Figure 3. Intraprocedural images with basal LV angiogram (A), subsequent anchor-pair placement (B, C, D) and final result (E).

RESULTS

The CTS performs a left-sided anterolateral minithoracotomy through a 7-8 cm skin incision and accesses the left pleural cavity through the 4th or 5th intercostal space. The IC accesses the right internal jugular vein (RIJV) using the standard technique, with placement of a 14 Fr introducer reaching the right atrium (RA). A Swan-Ganz balloon-tipped catheter is then introduced and advanced to the RV outflow tract (RVOT)/pulmonary artery (PA) via the RV apex and along the free wall of the RV. A 0.025" stiff guidewire is placed into the Swan-Ganz catheter and the 14 Fr sheath is advanced into the RV. The Swan-Ganz catheter is then exchanged for an 8 Fr multipurpose catheter (MP), leaving the 0.025" wire in the RVOT. A multi-looped snare is advanced though the MP and deployed in the RVOT. This will serve to capture a 0.018" guidewire delivered by the CTS through the LV free wall and across the scarred ventricular septum. At this point, the tricuspid valve is evaluated by transoesophageal echocardiography (TEE) for competence.

Transventricular needle placement

The CTS inserts an 18 G and 10 cm long standard needle 1-2 cm under the LAD through the scarred LV free wall, guided by fluoroscopy, TEE and continuous pressure monitoring. The needle is aimed at the (also scarred) anterior to mid interven-

tricular septum and is advanced towards the RV. The septal puncture location is defined by preoperative MRI or CT. Once entry into the RV cavity is verified, a 0.032" guidewire is advanced into the RV. A 6 Fr dilator is then placed over the 0.032" wire and brought to the RV. The 0.032" wire is withdrawn and a 5 Fr Amplatz Right Mod Catheter (AR) with a right-angle tip is advanced to the RV. The AR directs the 0.018" guidewire into the RVOT and towards the multi-looped snare.

Wire snaring and retrieval

Once the 0.018" guidewire is through the loops of the snare, the 0.025" stiff guidewire is withdrawn and the snare is pulled back to grab the 0.018" guidewire. The MP is then advanced over the 0.018" guidewire and the snare. The CTS advances the AR to the tip of the MP. The snare, 0.018" guidewire, and the MP are withdrawn through the 14 Fr introducer. In a carefully coordinated manner, the CTS initially advances the AR through the LV and then into the 14 Fr introducer. The IC continues retracting the MP through the 14 Fr introducer and the CTS continues to advance the AR until wire and catheter are completely across the heart from the LV free wall through the septum and RV then out of the RIJV. The 0.018" wire is then exchanged for a 0.014" wire.

Internal anchor insertion and placement

The internal anchor assembly with the "over-the-wire" tether is advanced over the 0.014" wire by the IC from the RIJV. This wire must be kept under tension by both surgeon and cardiologist at all times to allow smooth advancement. The internal anchor assembly is advanced into the 14 Fr introducer ensuring proper orientation for seating on the septum (anchor hinge towards patient's midline). Simultaneously, the CTS pulls in synchrony with the IC on the opposite end of the anchor tether. Once the internal anchor reaches the RV septum, the 14 Fr introducer is slightly withdrawn, exposing the anchor. The thumb switch on the assembly anchor handle is activated and rotated if necessary to gain proper alignment parallel to the septum.

External anchor attachment

The CTS grasps the exposed tether protruding from the LV free wall and places the external anchor onto it. The anchor is advanced until slight resistance is felt at the epicardial surface. It is critical to maintain such tension on the anchor tether so that the internal anchor remains properly positioned on the RV septum. Once placed, the tether can be bent away from the surgical field and clamped temporarily with a mosquito clamp. The IC releases the internal anchor from the delivery system by turning the release mechanism completely. Final disengagement is performed after

checking accurate positioning on fluoroscopy. Until that point, the anchor assembly can still be retrieved and withdrawn (Moving image 1).

The procedure continues with placement of anchor pairs until complete plication of the scarred wall, using the previously implanted anchor as reference. Adjacent anchors do not need to be in direct contact to obtain full exclusion. The recommended sequence is to start with the most apical "RV-LV" anchor-pair placement and proceed towards the more basilar regions with additional anchors.

Apical anchor placement

The last anchor pair is placed at the LV apex beyond the point at which the RV extends, dictating the final conical shape of the reconstructed LV. The CTS begins by identifying the scarred regions of the LV apex and palpating the most apical "RV-LV" anchor pair. Using a strong needle holder, the needle tip of the apical anchor assembly is then directed from the right side of the LV apex towards the left. Once the needle tip is seen protruding out of the left side of the apex, it is grasped and the tether pulled through the apex and out of the incision. The needle tip is cut from the tether and, as before, an external anchor is mounted to the exposed tether.

DISCUSSION

The LIVE technique is a novel hybrid transcatheter technique to reconstruct a remodelled LV in patients with symptomatic ischaemic heart failure. By means of micro-anchoring technology, the myocardial scar is plicated, which reduces the enlarged LV volume, decreases the wall stress and increases the EF. It is a minimally invasive and "off-pump" alternative to the classic surgical ventricular reconstruction.

LIMITATIONS

At present, the main limitation of this technique is represented by its applicability only in patients with previous antero-septal-lateral infarction, while patients with infarctions in other territories are not candidates for this procedure.

CONCLUSION

This minimally invasive technique has the promise of offering an effective LV reconstruction at lower risk in a very high-risk group of patients.

IMPACT ON DAILY PRACTICE

The LIVE technique is a promising innovation with the potential to offer a new treatment option for patients with advanced ischaemic cardiomyopathy. The relatively suboptimal results currently offered by the conventional surgical interventions[1] could be overcome by this novel less invasive technique, thus adding a valuable tool for the treatment of these delicate patients.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

REFERENCES

1. Jones RH, Velazquez EJ, Michler RE, Sopko G, Oh JK, O'Connor CM, Hill JA, Menicanti L, Sadowski Z, Desvigne- Nickens P, Rouleau JL, Lee KL; STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med. 2009;360:1705-17.
2. Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg. 2011;141: 905-16.

SUPPLEMENTARY DATA

Moving image 1. Detailed animation reproducing all steps of the LIVE technique.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/131st_issue/309

Chapter 8

Transcatheter and minimally invasive surgical left ventricular reconstruction for the treatment of ischaemic cardiomyopathy: preliminary results

Patrick Klein[a], Pierfranceso Agostoni[b], Wim-Jan van Boven[c], Rob J. de Winter[d] and Martin J. Swaans[b]

[a] Department of Cardiothoracic Surgery, St Antonius Hospital, Nieuwegein, Netherlands
[b] Department of Cardiology, St Antonius Hospital, Nieuwegein, Netherlands
[c] Department of Cardiothoracic Surgery, Academic Medical Centre, Amsterdam, Netherlands
[d] Department of Cardiology, Academic Medical Centre, Amsterdam, Netherlands

Presented at the 31st Annual Meeting of the European Association for Cardio-Thoracic Surgery, Vienna, Austria, 7–11 October 2017.

Interactive CardioVascular and Thoracic Surgery 28 (2019) 441–446

ABSTRACT

Objectives: Adverse remodelling of the left ventricle (LV) after myocardial infarction (MI) results in a pathological increase in LV volume and reduction in LV ejection fraction (EF). We describe the preliminary results of a novel, multicentre, combined transcatheter and minimally invasive technique to reconstruct the remodelled LV by plication and exclusion of the scar, and to reduce the excess volume, resulting in decreased wall stress and increased EF.

Methods: A novel hybrid transcatheter technique that relies on microanchoring technology (Revivent TC™ System, BioVentrix Inc., San Ramon, CA, USA) was used. The LV is reconstructed without the use of extracorporeal circulation by plication of the fibrous scar. This is achieved by implantation of a series of internal and external microanchors brought together over a PEEK (poly-ether-ether-ketone) tether to form a longitudinal line of apposition between the LV free wall and the anterior septum. Internal anchors are deployed by a transcatheter technique on the right side of the ventricular septum through the right internal jugular vein. Paired external anchors are advanced through a left-sided minithoracotomy and deployed on the LV epicardium. A specialized force gauge is used to bring these 'right ventricle (RV)-LV' anchors together under measured compression forces. LV-LV' anchor pairs through the LV apex beyond the distal tip of the RV complete the reconstruction. Patients who were considered eligible for the procedure presented with symptomatic heart failure (New York Heart Association class >II) and ischaemic cardiomyopathy (EF <40%) after anteroseptal MI. All patients had a dilated LV with either an a- or dyskinetic scar in the anteroseptal wall and apex of ≥50% transmurality.

Results: Between October 2016 and April 2017, 9 patients (8 men, 1 woman; mean age 60 ± 8 years) were operated on in 2 Dutch centres. Procedural success was 100%. On average, 2.6 anchor pairs were used to reconstruct the LV. Comparing echocardiographic data preoperatively and directly postoperatively, LV ejection fraction increased from 28 ± 8% to 40 ± 10% (change +43%, $P < 0.001$) and LV volumes decreased LV end-systolic volume index 53 ± 8 ml/m^2 to 30 ± 11 ml/m^2 (change -43%, $P < 0.001$) and LVEDVI 75 ± 23 ml/m^2 to 45 ± 6 ml/m^2 (change -40%, $P = 0.001$). In 1 patient, an RV perforation occurred which necessitated conversion to full sternotomy. One patient underwent a postoperative revision because of RV restriction. After the removal of 1 'RV-LV' anchor pair, the patient recovered completely. Hospital mortality was 0%. The median duration of intensive care unit stay was 2 days [interquartile range (IQR) 1–46 days], and the median length of hospital stay was 9 days (IQR 3–57 days).

Conclusions: Hybrid transcatheter LV reconstruction is a promising novel treatment option for patients with symptomatic heart failure and ischaemic cardiomyopathy after anteroseptal MI. The early results demonstrate that the procedure is safe and results in a significant improvement in EF and reduction in LV volumes in the early postoperative period.

Keywords: Hybrid left ventricular reconstruction • Ischaemic heart failure • Ischaemic cardiomyopathy • Left ventricular remodelling

Key question

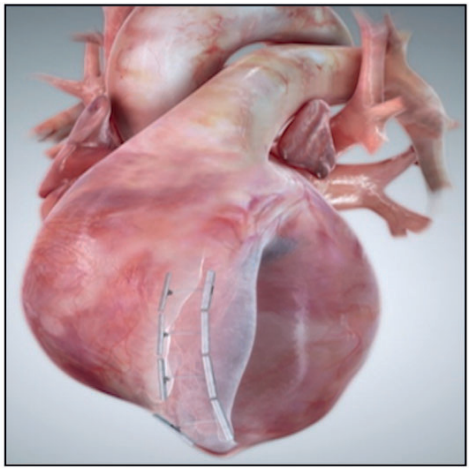
What are the preliminary results of hybrid left ventricular (LV) reconstruction in ischaemic cardiomyopathy?

Key findings

On average 2.6 anchor-pairs were needed for the reconstruction. Both LV volumes and LV ejection fraction improved significantly.

Take-home message

Hybrid transcatheter LV reconstruction is a promising novel treatment option for symptomatic heart failure and ischaemic cardiomyopathy.



INTRODUCTION

Remodelling of the left ventricle (LV) after myocardial infarction (MI) results in an increase in volume and a reduction in ejection fraction (EF). Transmurality of the infarction determines whether or not a true LV aneurysm will result. Surgical ventricular reconstruction (SVR) reduces the LV volume and reconstructs the shape of the remodelled LV leading to improvement in systolic function. Consensus from expert centres for SVR is that appropriately selected patients could benefit from a well-conducted procedure sufficiently reducing the LV end-systolic volume (LVESV) and reconstructing the elliptical shape of a normal LV [1–4]. Conventional SVR relies on full median sternotomy, the use of extracorporeal circulation, cardioplegic arrest and ventriculotomy, which inflicts a considerable physical burden on often vulnerable patients with ischaemic heart failure. A less invasive procedure able to achieve the same results as conventional SVR is appealing, and we report our preliminary results of a novel hybrid procedure which is a combination of a transcatheter intervention with a minimally invasive surgical procedure. The remodelled LV is reconstructed by plication of the anteroseptal and apical LV scar using microanchoring technology without the use of extracorporeal circulation.

METHODS

Patient characteristics

Patients considered eligible for the procedure presented with symptomatic heart failure [New York Heart Association (NYHA) class ≥II] and ischaemic cardiomyopathy (EF <40%) after anteroseptal MI. All patients had a dilated LV with either an a- or dys-kinetic scar in the anteroseptal wall and apex with ≥50% transmurality. None of the patients in this study were contraindicated to surgery, and in case of a conversion to full sternotomy, it was also an option to perform a conventional SVR as was described before [5]. The exclusion criteria were previous sternotomy and significant valvular pathology, necessitating concomitant valvular repair or replacement. The institutional medical ethics committees of both centres approved the study, and written informed consent was obtained from all participating patients.

Preoperative workup

Preoperative planning requires Gadolinium-enhanced magnetic resonance imaging (or contrast computed tomography in the presence of ICD/pacemaker) to clearly define the scar morphology. Scarred regions must comprise at least 50% of the wall thickness to enable a safe anchor implantation. Additionally, preoperative echo is

adopted to define wall motion abnormalities, identify areas of viable myocardium, measure LV volumes and determine valvular dysfunction and EF.

Hybrid transcatheter procedure

The hybrid transcatheter technique relies on microanchoring technology (Revivent TC™ System, BioVentrix Inc., San Ramon, CA, USA) and is called less invasive ventricular enhancement (LIVE). The procedure is performed under general anaesthesia and 'off-pump', e.g. without the use of extracorporeal circulation. Transvenous excess for the reconstruction is through the right internal jugular vein. The surgical approach is through a left-sided minithoracotomy in the 4th, 5th or 6th intercostal space depending on the location of the apex of the LV. For safety reasons, in these first patients, arterial and venous sheaths are inserted in the common femoral artery and vein, respectively. Through these sheaths, guidewires can be readily inserted over which cannulas can be inserted for emergent institution of extracorporeal circulation. The LV is reconstructed by plication of the fibrous scar. This is achieved by implantation of a series of internal and external microanchors (Fig. 1) brought together over a PEEK (poly-etherether- ketone) tether to form a longitudinal line of apposition between the LV free wall and the anterior septum (Figs 2 and 3). Internal anchors are deployed by a transcatheter technique on the right side of the ventricular septum through a delivery catheter inserted in the right internal jugular vein. Paired external anchors are advanced through a left-sided minithoracotomy and deployed on the LV epicardium. The surgeon punctures the anterolateral scar, and thereafter, the (anterior) septum with an 18-Gauge needle, through which a guidewire is advanced into the RV. After the introduction of a 6-F introducing sheath over this wire, an angulated catheter (8-F internal mammary artery (IMA) or multipurpose) is advanced through this introducing sheath and directed towards the pulmonary artery. A 0.018 inch guidewire is now advanced into the direction of the pulmonary artery. In the meantime, the interventional cardiologist has deployed a snare in the pulmonary artery. The guidewires can be snared, and now over the guidewires, the 8-F IMA or multipurpose catheter can be pulled into the 14-F introducing sheath, which has been inserted through the internal jugular vein. In this way, a transseptal catheter is in place from the internal jugular vein to the anterolateral surface of the LV. Through this 'delivery canal', the PEEK tether with the microanchors can be placed 'over the wire'. A specialized force gauge (Fig. 4) is used to bring these 'RV-LV' anchors together under measured compression forces (1–2 Newtons of force). 'LV-LV' anchor pairs through the LV apex beyond the distal tip of the RV to complete the reconstruction (Figs 5 and 6). A combination of LV and RV angiograms and fluoroscopy transoesophageal echocardiography guide the reconstruction. Postoperatively, the patients are maintained on coumadins or warfarin for 3 months.

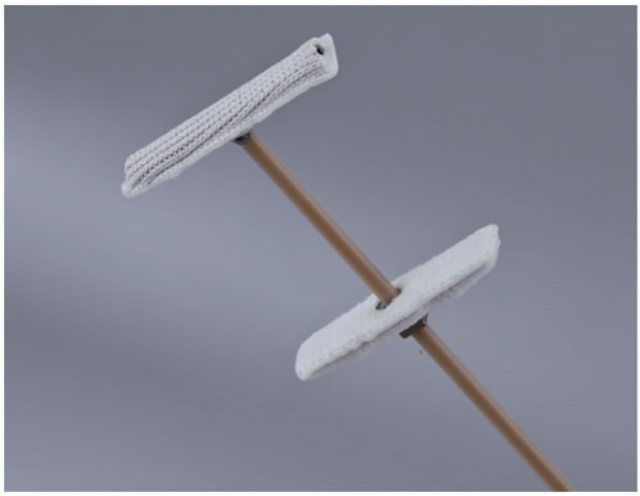


Figure 1: Internal and external anchors.

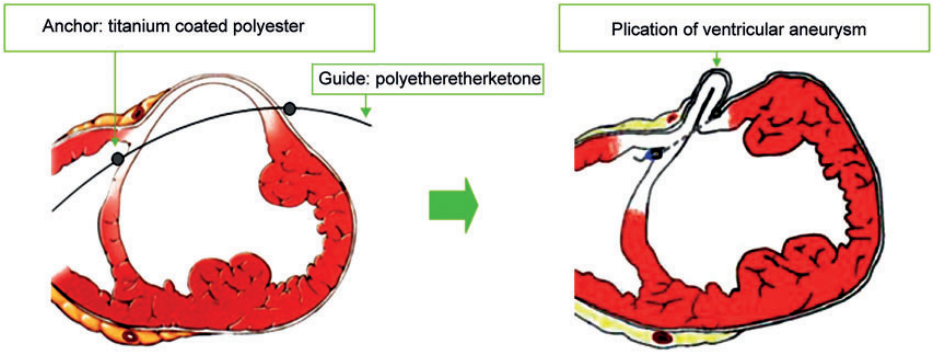


Figure 2: An illustration of a plicated anterolateral scar onto the interventricular septum.

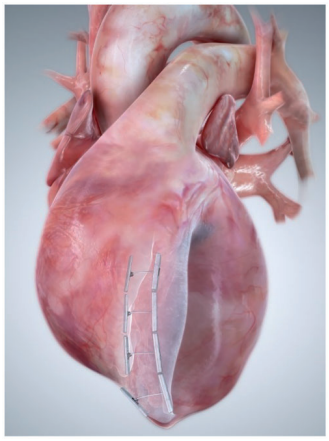


Figure 3: An illustration of the results.

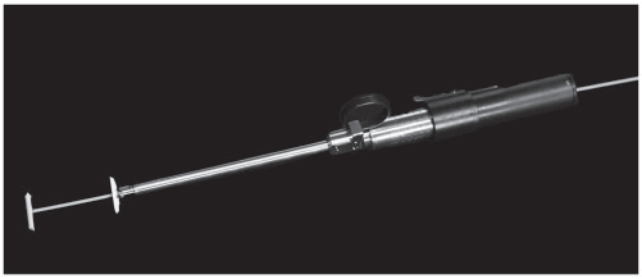


Figure 4: A specialized Forge gauge with the tether inserted and pushing on the external anchor.

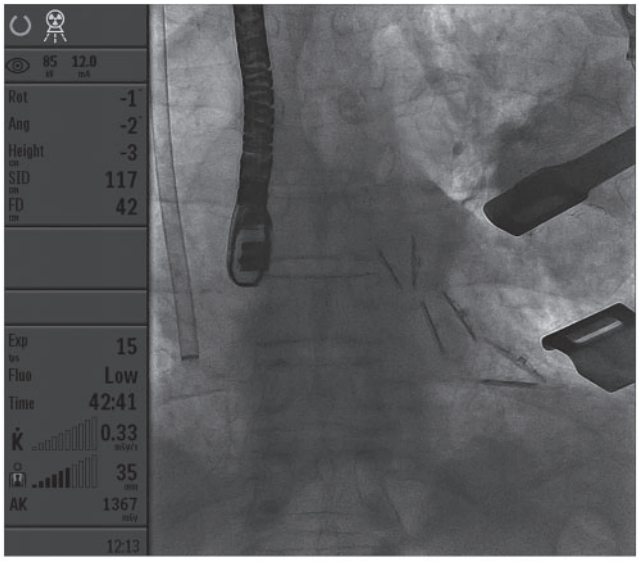


Figure 5: Intraprocedural fluoroscopy with anchor pairs in place.

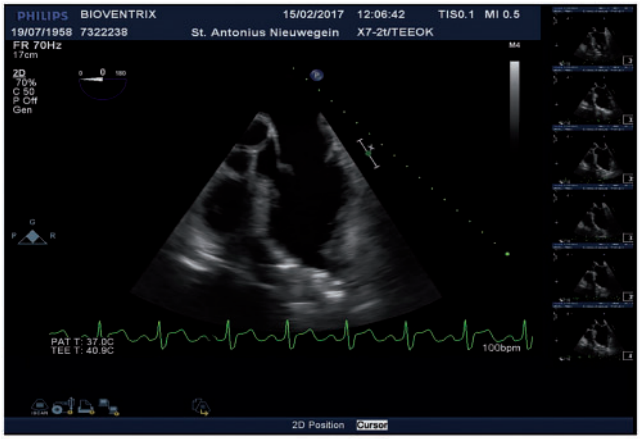


Figure 6: Intraprocedural transoesophageal echocardiography with completed reconstruction.

Clinical and echocardiographic examinations

Patients were given optimal medical treatment for heart failure after surgery. Functional status was assessed using the NYHA classification for symptoms of heart failure at discharge. Transthoracic echocardiograms were performed after surgery, just prior to hospital discharge. From these examinations, LV ejection fraction, LV dimensions and volumes and the presence of MR and TR were assessed. The sphericity index (SI) was calculated as the ratio between the greater cross-sectional diameter and the greater longitudinal diameter of the LV in end-systolic apical 4-chamber view. This index was used as an indicator of geometry change.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). Categorical variables are described as frequencies and percentages and compared using the χ^2 test with Yates's correction. Continuous data are expressed as mean ± standard deviation or median with ranges and compared using the Wilcoxon signed-rank test for paired data. A *P*-value <0.05 was considered statistically significant.

Table 1: Preoperative patient characteristics (*n*= 9)

Age (years), mean ± SD	60 ± 8
Male gender, *n* (%)	8 (89)
Height (cm), mean ± SD	177 ± 8
Weight (kg), mean ± SD	83 ± 17
BSA (m^2), mean ± SD	2.0 ± 0.3
ICD, *n* (%)	3 (33)
Diabetes, *n* (%)	2 (22)
Atrial fibrillation, *n* (%)	2 (22)
COPD > GOLD Class II, *n* (%)	1 (11)
LVEF (%), mean ± SD	28 ± 8
LVESD (mm), mean ± SD	44 ± 7
LVEDD (mm), mean ± SD	56 ± 5
LVESVI (ml/m^2 BSA), mean ± SD	53 ± 8
LVEDVI (ml/m^2 BSA), mean ± SD	75 ± 23
Mitral regurgitation ≥ Grade 2, *n* (%)	1 (11)
Tricuspid regurgitation ≥ Grade 2, *n* (%)	1 (11)
NYHA class	2.7 ± 0.4

BSA: body surface area; COPD: chronic obstructive pulmonary disease; GOLD: global initiative on obstructive lung disease; ICD: internal cardioverter defibrillator; LVEDD: left ventricular end-diastolic dimension; LVEDVI: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic dimension; LVESVI: left ventricular end-systolic volume index; NYHA: New York Heart Association; SD: standard deviation.

RESULTS

Between October 2016 and April 2017, 9 patients (8 men and 1 woman; mean age 60 ± 8 years) were operated on in 2 Dutch centres (Table 1).

Procedural success was 100%. In all patients, a reconstruction with complete exclusion of the aneurysmatic part of the LV was achieved. On average, 2.6 anchor pairs were used to reconstruct the LV. The average skin-to-skin time for the procedure was 217 ± 100 min (Table 2). Comparing echocardiographic data preoperatively and directly postoperatively, LV ejection fraction increased from 28 ± 8% to 40 ± 10% (change +43%, $P < 0.001$) and LV volumes decreased from left ventricular end-systolic volume index (LVESVI) 53 ± 8 ml/m^2 to 30 ± 11 ml/m^2 (change -43%, $P < 0.001$) and LVEDVI 75 ± 23 ml/m^2 to 45 ± 6 ml/m^2 (change -40%, $P = 0.001$). The SI remained unchanged from 0.5 ± 0.1 to 0.5 ± 0.1 ($P = 0.7$). One patient had a moderate–severe functional mitral regurgitation prior to surgery, which decreased to moderate after the reconstruction. In 2 patients, a mild increase in tricuspid regurgitation was observed after surgery (mild increase to moderate in both patients).

Table 2: Procedural data (*n*=9)

Internal anchors (*n*), mean ± SD	1.3 ± 0.5
External anchors (*n*), mean ± SD	1.2 ± 0.7
Total anchors (*n*), mean ± SD	2.6 ± 0.7
Procedural success (%)	100
Skin-to-skin (h, min), mean ± SD	21 ± 100
Fluoroscopy time (mm:s), mean ± SD	50:50 ± 31:26
Dosage (mGy/cm^2), mean ± SD	2277 ± 2379

SD: standard deviation.

In 1 patient, an RV perforation occurred which necessitated conversion to full sternotomy. After the conversion, the bleeding was controlled and the reconstruction completed. Additionally, a single venous graft to the right coronary artery was constructed on the beating heart. A percutaneous coronary intervention was also an option to treat this lesion. One patient underwent a postoperative revision because of RV restriction. Initially, 4 anchor pairs were placed. During the postoperative course, a clinical condition resembling diastolic failure with tachycardia and low output was observed. Transoesophageal echocardiography showed a small right ventricular cavity (~50% of the preoperative volume) with an improved left ventricular systolic function when compared preoperatively (left ventricular ejection fraction postoperatively 36% compared to left ventricular ejection fraction (LVEF)

25% preoperatively). The interventricular septum seemed to bulge into the right ventricular cavity due to the reconstruction. The decision was made to remove 1 'RV-LV' anchor pair during a revision surgery. Patient was reoperated through the initial left anterior thoracotomy. The RV-LV anchor pair could easily be released: the external anchor was removed, and the bleeding from the puncture site of the anchor was controlled temporally by manual compression with a gauze. The internal anchor stayed fixed with the tether in the septum. At follow-up, the position of this detached internal anchor remained unchanged. After the revision, the patient recovered completely. Hospital mortality was 0%. The median duration of intensive care unit stay was 2 days [interquartile range (IQR) 1–46 days], and the median length of hospital stay was 9 days (IQR 3–57 days). Average NYHA class at discharge was 2.3 ± 0.7 (2, 3 and 3 patients in NYHA Classes I–II, II and III, respectively), compared to 2.7 ± 0.4 preoperatively ($P = 0.58$; 1, 3 and 5 patients in NYHA Classes II, II–III and III, respectively). A detailed summary of the pre- and postoperative echocardiographic data and follow-up duration of all 9 patients is provided as Supplementary Material.

DISCUSSION

Postinfarction ventricular remodelling leading to ischaemic heart failure is an important cause for morbidity and mortality. Efforts to improve ventricular function, symptoms and survival have included medical therapy such as neurohormonal inhibition and cardiac resynchronization therapy. Although these treatments have demonstrated clinical effect, they do not address the underlying pathology: coronary artery disease and dysfunction of the remodelled myocardium [4]. Revascularization can improve contractile function in ischaemic but viable myocardial segments, but both non-ischaemic dysfunctional myocardium and areas of scar tissue will not improve. SVR procedures have demonstrated—in selected patients—that the dysfunctional myocardium can be favourably remodelled. Usually, these procedures are performed in adjunct with coronary artery bypass surgery [6]. The Hypothesis 2 arm of the multicentre, randomized controlled Surgical Treatment for Ischaemic Heart Failure (STICH) trial compared coronary artery bypass grafting (CABG) alone with a combined procedure CABG and SVR. No difference was demonstrated for the primary outcome of death from any cause or rehospitalization for heart failure [2]. Also, both procedures were evenly effective in a reduction of symptoms and an improvement of the 6-min walk test. Obviously, a greater reduction in LVESVI was achieved with the combined procedure of CABG and LV reconstruction. Michler *et al.* [7] analysed the subgroup of patients from the STICH trial who had left ventricular volumes examined at baseline and at 4 months postoperatively (555 of 1000 patients)

to determine whether any magnitude of postoperative end-systolic volume reduction affected survival. They found that a survival benefit was realized in patients after CABG and LV reconstruction compared to CABG alone when a postoperative LVESVI of 70 ml/m^2 BSA was achieved. They also found that a reduction in LVESVI of 30% could only be realized in 45% of the patients. Interestingly, in 17% of the patients after combined CABG and LV reconstruction, no change or even an increase in LVESVI at 4 months was observed.

We evaluated the preliminary results of a novel hybrid transcatheter technique also called less invasive ventricular enhancement (LIVE) to reconstruct the remodelled LV after an anteroseptal MI by plication of the anteroseptal LV scar using microanchoring technology. Compared to conventional LV reconstruction, the hybrid technique does not rely on a full median sternotomy, the use of extracorporeal circulation, cardioplegic arrest and ventriculotomy. All of which inflicts a considerable physical burden on vulnerable and sometimes frail patients. So far, only a case report of this technique has been published [8]. Our early results in a small series of patients demonstrated that the procedure is both safe and results in a significant improvement in EF and reduction in LV volumes. Di Donato *et al.* [7, 9] suggested that one of the goals of LV reconstruction is an LVESVI of less than 60 ml/m^2. The results of the subanalysis of the STICH trial confirm this idea, but the cut-off closer to 70 ml/m^2 for the benefit of the reconstruction. We found an average reduction in LVESVI of 43%, and moreover, in all patients, a postoperative LVESVI of <60 ml/m^2 body surface area was achieved. A generally accepted fact is that surgical reduction in LV volume is beneficial; however reduced wall stress and improved systolic function are counterbalanced by a reduction in the diastolic function (less distensibility) [4]. Whether this negative impact on the diastolic function is of the same magnitude with this hybrid transcatheter technique as the conventional surgical procedure has to be evaluated in future studies. Also, longer follow-up studies are needed to evaluate the clinical effect and stability over time. Concerning the reshaping of the LV, we found no change in the SI. This was also previously described in the article by Di Donato *et al.* [11] and the RESTORE group in 2006. We consider this as an indicator that the hybrid reconstruction has an effect on the global shape of the ventricle, as both LV long-axis and basal LV dimensions have to be reduced to maintain the same SI. If only the apex was amputated in this procedure, the sole reduction in LV long axis would lead to an increase in the SI. Furthermore, this procedure is a standalone LV reconstruction, so should revascularization be indicated, a percuteneous coronary intervention (PCI) procedure could be performed either preoperatively or postoperatively. Theoretically, important functional mitral regurgitation could be

reduced because of the improvement in LV systolic function and reduction in LV volumes.

Although our preliminary results are very promising, we would like to emphasize that the patients were highly selected. A sufficient transmural anteroseptal scar should be present for safe transseptal anchor placement and plication. The extent of the scar in both the interventricular septum and the anterolateral wall also dictates the amount of volume reduction that can be achieved. We also demonstrated that care has to be taken not to create a too-restrictive RV implantation of internal anchors on the RV septum far posterior and external anchors on the same time far lateral, may lead to bulging of the septum in between after plication. In a pre-existing relatively small RV, this can lead to a restriction. Fortunately, revision of the reconstruction is possible but most likely reduces the efficacy of the reconstruction.

LIMITATIONS

The present study is an observational study of the early results of a small number of patients operated on in 2 Dutch centres. However, apart from a case report and an experimental paper of the technique in an ovine model, this is the first article describing the clinical results of this novel technique. These findings should be confirmed in other, larger studies with a longer follow-up. Because this technique requires that all anchors should be placed well into the scar tissue, possibly not all the aneurysmatic tissues might be excluded for this technique. We have demonstrated, however, that this does not lead to an inferior anatomical reconstruction of the LV.

CONCLUSIONS

Hybrid transcatheter LV reconstruction is a promising novel treatment option for patients with symptomatic heart failure and ischaemic cardiomyopathy after anteroseptal MI. Early results demonstrate that the procedure is safe and results in a significant improvement in EF and reduction in LV volumes in the early postoperative period.

SUPPLEMENTARY MATERIAL

Supplementary material is available at ICVTS online.

Conflict of interest: Patrick Klein acts as a proctor and consultant for BioVentrix Inc.

REFERENCES

[1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation 2016;133:e38–360.

[2] Jones RH, Velazquez EJ, Michler RE et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360: 1705–17.

[3] Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg 2011;141:905–16.

[4] Eisen HJ. Surgical ventricular reconstruction for heart failure. N Engl J Med 2009;360:1781–4.

[5] Klein P, Holman ER, Versteegh MI, Boersma E, Verwey HF, Bax JJ et al. Wall motion score index predicts mortality and functional results after surgical ventricular restoration for ischemic heart failure. Eur J Cardiothorac Surg 2009;35:847–53.

[6] Menicanti L, Castelvecchio S, Ranucci M, Frigiola A, Santambrogio C, de Vincentiis C et al. Surgical therapy for ischemic heart failure: singlecenter experience with surgical anterior ventricular restoration. J Thorac Cardiovasc Surg 2007;134:433–41.

[7] Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM et al. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg 2013;146:1139–45.e6.

[8] Faria R, Melica B, Pires-Morais G, Rodrigues A, Ribeiro J, Guerra M et al. New less invasive ventricular reconstruction technique in the treatment of ischemic heart failure. Rev Port Cardiol 2014;33:469.e1–5.

[9] Di Donato M, Castelvecchio S, Menicanti L. End-systolic volume following surgical ventricular reconstruction impacts survival in patients with ischaemic dilated cardiomyopathy. Eur J Heart Fail 2010; 12:375–81.

[10] Di Donato M, Toso A, Maioli M, Sabatier M, Stanley AW, Dor V. Intermediate survival and predictors of death after surgical ventricular restoration. Semin Thorac Cardiovasc Surg 2001;13:468–75.

[11] Di Donato M, Dabic P, Castelvecchio S, Santambrogio C, Brankovic J, Collarini L et al. Left ventricular geometry in normal and post-anterior myocardial infarction patients: sphericity index and 0new0 conicity index comparisons. Eur J Cardiothorac Surg 2006;29:S225–30.

Chapter 9

Less invasive ventricular reconstruction for ischaemic heart failure

Patrick Klein[1*], Stefan D. Anker[2,3,4*], Andrew Wechsler[5], Ivo Skalsky[6], Petr Neuzil[7], Lon S. Annest[8], Mauro Bifi[9], Theresa McDonagh[10], Christian Frerker[11], Tobias Schmidt[11], Horst Sievert[12,13], Anthony N. Demaria[14], and Sebastian Kelle[4,15,16]

[1]Department of Cardiothoracic Surgery, St Antonius Hospital, Nieuwegein, The Netherlands; [2]BIH Center for Regenerative Therapies (BCRT), Charité, Universitätsmedizin Berlin, Berlin, Germany; [3]Division of Cardiology and Metabolism, Department of Cardiology (CVK), Charité, Berlin, Germany; [4]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Germany; [5]Department of Cardiothoracic Surgery, Drexel University College of Medicine, Philadelphia, PA, USA; [6]Department of Cardiac Surgery, Na Homolce Hospital, Prague, Czech Republic; [7]Department of Cardiology, Na Homolce Hospital, Prague, Czech Republic; [8]BioVentrix, San Ramon, CA, USA; [9]Intituto di Cardiologia, Azienda Ospedaliero, Universitaria di Bologna, Bologna, Italy; [10]Department of Cardiology, Kings College Hospital, London, UK; [11]Department of Cardiology, Asklepios Klinik St Georg, Hamburg, Germany; [12]CardioVascular Center Frankfurt, Frankfurt am Main, Germany; [13]Anglia Ruskin University, Chelmsford, UK; [14]Division of Cardiology, Department of Medicine, University of California, Sulpizio Cardiovascular Center, San Diego, CA, USA; [15]Department of Internal Medicine, Cardiology German Heart Center Berlin, Berlin, Germany; and [16]Department of Internal Medicine/Cardiology, Charité Campus Virchow Clinic, Berlin, Germany

*These authors contributed equally to this study.

European Journal of Heart Failure (2019) 21, 1638–1650

ABSTRACT

Aims

Surgical ventricular reconstruction to remodel, reshape, and reduce ventricular volume is an effective therapy in selected patients with chronic heart failure (HF) of ischaemic aetiology. The BioVentrix Revivent TC System offers efficacy comparable to conventional surgical ventricular reconstruction and is less invasive utilizing micro-anchor pairs to exclude scarred myocardium on the beating heart. Here, we present 12-months follow-up data of an international multicenter study.

Methods and results

Patients were considered eligible for the procedure when they presented with symptomatic HF [New York Heart Association (NYHA) class ≥II], left ventricular (LV) dilatation and dysfunction caused by myocardial infarction, and akinetic and/or dyskinetic transmural scarred myocardium located in the anteroseptal, anterolateral, and/or apical regions. A total of 89 patients were enrolled and 86 patients were successfully treated (97%). At 12months, a significant improvement in LV ejection fraction (29±8% vs. 34±9%, P <0.005) and a reduction of LV volumes was observed (LV end-systolic and end-diastolic volume index both decreased: 74±28 mL/m^2 vs. 54±23 mL/m^2, P <0.001; and 106±33 mL/m^2 vs. 80±26 mL/m^2, respectively, P <0.0001). Four patients (4.5%) died in hospital and survival at 12 months was 90.6%. At baseline, 59% of HF patients were in NYHA class III compared with 22% at 12-month follow-up. Improvements in quality of life measures (Minnesota Living with Heart Failure Questionnaire 39 vs. 26 points, P <0.001) and 6-min walking test distance (363 m vs. 416 m, P = <0.001) were also significant.

Conclusions

Treatment with the Revivent TC System in patients with symptomatic HF results in significant and sustained reduction of LV volumes and improvement of LV function, symptoms, and quality of life.

KEYWORDS

Volume reduction • Heart failure • Ventricular remodelling • Myocardial infarction • Device intervention

INTRODUCTION

Heart failure (HF) is an important global public health problem due to the associated high morbidity, mortality, and cost. It is estimated that 26 million people are living with chronic HF worldwide, and only half of these patients will live beyond 5 years.[1] Ischaemic heart disease is a major cause of HF, and current therapies do not address directly the scar tissue of the adversely remodelled ventricle after myocardial infarction (MI).[2]

Myocardial infarction from occlusion of a coronary artery often results in areas of dyskinetic or akinetic myocardium, causing increased wall stress and subsequent left ventricular (LV) dilatation. Following anterior MI, increased LV volume and symptomatic systolic dysfunction occur in approximately 30% of patients despite revascularization.[3] The dilated and scarred area of the LV wall causes chamber geometry to change from elliptical to spherical, which increases myocardial wall stress further, inducing ischaemia, resulting in afterload mismatch and activation of neurohormonal compensation.[4] The degree of LV dilatation has a major impact on the severity of HF symptoms and mortality rates.[5,6] Exclusion of the non-viable or scarred myocardium with a reduction in LV size and conical reshaping of the chamber decreases LV end-systolic and end-diastolic wall stress and myocardial oxygen consumption, with subsequent improvement in LV function and HF symptoms.[7,8]

Surgical ventricular reconstruction (SVR) has shown to be an effective therapy in selected patients with chronic HF of ischaemic aetiology.[3,9–11] However, SVR is a highly invasive surgical procedure that necessitates median sternotomy, cardiopulmonary bypass with cardioplegic myocardial arrest, and ventriculotomy. The BioVentrix Revivent TC System offers potential efficacy comparable to conventional SVR, aiming to exclude non-functioning scarred myocardium, reshape ventricular geometry, and reduce ventricular volume, but is a less invasive procedure performed on the beating heart with the use of titanium anchor pairs. The implantation procedure for the first-generation system requires median sternotomy, but it is performed on the beating heart without cardiopulmonary bypass.[12] The second-generation system utilizes the same implanted anchor pairs but these are deployed through a hybrid approach: on the beating heart, with access to the heart achieved through a combination of a left-lateral mini-thoracotomy in the 4th or 5th intercostal space and via the right internal jugular vein.

This prospective, multicentre, international single-arm study was designed to evaluate the functional effectiveness and safety of the Revivent TC System, offering a less invasive option for volume reduction and reshaping of the remodelled left ventricle after MI.

MATERIAL AND METHODS

Study design

Prospective, multicentre, single-arm study designed to evaluate the efficacy and safety of the Revivent TC System for myocardial scar exclusion, reduction of volume and reshaping of the left ventricle in selected patients with ischaemic cardiomyopathy. The delivery system was modified during the study *(Figure 1)*. The study was initiated using a delivery system that required implantation through a median sternotomy. Subsequently, the implantation was performed through a hybrid transcatheter and mini-thoracotomy technique. The study protocols were approved by applicable governmental regulatory agencies (registered under ClinicaltTrials.org NCT01568164 and NCT01568138) and the ethics committees of each participating institution. All enrolled subjects were required to give informed consent. The study was conducted according to the principles of the Declaration of Helsinki.

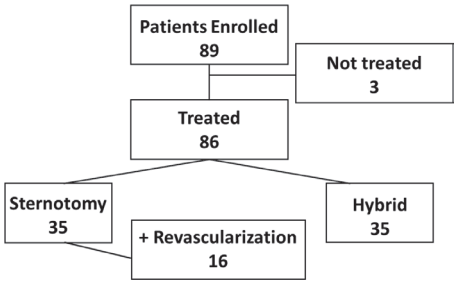


Figure 1 Schematic design of the study. The study was conducted using identical micro-anchor pairs implanted via a sternotomy or hybrid approach. A subgroup of patients implanted via sternotomy were also treated with a planned concomitant coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention).

The primary efficacy endpoint for the Revivent TC System was a combination of the reduction of LV volume assessed by echocardiographic changes in LV end-systolic (LVESVI) and end-diastolic volume index (LVEDVI) and improvement in LV ejection fraction (LVEF). All echocardiographic measurements were obtained according to a standardized protocol and analysed at an independent core laboratory at the Ohio State University, Columbus, Ohio. Secondary efficacy endpoints were the reduction of HF symptoms and improvement in the patient's clinical status, assessed by New York Heart Association (NYHA) functional class, 6-min walk test (6MWT) distance, and quality of life score measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Additional data included severity and changes of functional mitral regurgitation (MR) and length of hospital and intensive care unit stay. Safety was assessed by the overall rate of serious adverse events. The specified follow-up times were 6 months and 1 year. Data from this study were used to obtain CE Mark certification.

An analysis to identify functional responders and non-responders to the less invasive ventricular reconstruction was additionally performed. Conditional of qualifying as

a responder is survival up to 12months of follow-up. A responder is defined as a patient demonstrating an increase in 6MWT distance >32m between baseline and 12-month follow-up, or (when 6MWT distance was not >32 m) an improvement in quality of life of >14 points between baseline and 12-month follow-up, but only if there was also an improvement in 6MWT distance.[13,14] Additionally (should the aforementioned criteria have not been met), an improvement in NYHA class between baseline and 12-month follow-up of at least one class would also classify a patient as a responder. When the criteria were not met, a patient will be classified as a non-responder.

Patients

Eligible HF patients were ≥18 and ≤80 years old with LV dilatation and dysfunction, caused by MI that occurred at least 90 days prior to study enrolment, and akinetic and/or dyskinetic wall motion located in the anteroseptal, anterolateral, and/or apical regions. Additional criteria include a LVEF >15% and ≤45%, NYHA functional class II–IV, and LVESVI ≥60 mL/m^2 and ≤120 mL/m^2. Imaging studies verified that candidates had sufficient functional remote myocardium (non-infarcted myocardial wall segments), In general three-quarters (or 75%) of remote myocardial segments should be at worst hypokinetic in motion, but preferably exhibit normokinesis. Moreover, the septal scar should be sufficient transmural and suitable for anchor placement. Patients with moderate to severe MR (grade 4) were excluded from this clinical study. A complete listing of the inclusion and exclusion criteria is provided in online supplementary *Table S1*).

Device description and implantation

The implantable components of the Revivent TC System are a series of titanium anchor pairs (23 mm × 4 mm; one internal hinged anchor and one external locking anchor) covered by polyester coating *(Figure 2A)*. The anchor pairs are connected to each other by a tether (1.7 mm × 1.0 mm) made of poly-ether-ether-ketone. The distance between anchors is adjustable and is determined by the location of the sliding locking anchor relative to the fixed hinged anchor. The hinged anchor pivots to facilitate placement through a low-profile introducer, with subsequent rotation to a perpendicular orientation. The sliding locking anchor houses a cam with a reversible locking mechanism, allowing apposition of the two anchors at a continuum of positions. The delivery system comprises of needles, snares, introducers, catheters, and a gauge to control the force at which the anchors are pulled together.

Anteroseptal scarred myocardium is excluded by drawing the locking (epicardial) and hinged (from the right side of septum) anchors together. The fundamental

technical manoeuvres for implantation are to place the hinged anchor in the right ventricle, against the septum, and place the locking anchor on the LV epicardium. Then both anchors are drawn toward each other until contact between the two walls is established and apposed along the anchor lengths. The action is repeated along the long axis of the left ventricle until a linear portion of the anterolateral wall is in contact with a corresponding portion of the septum, thus excluding the entire intervening wall segment from the circumference of the chamber. When properly deployed, a discrete portion of the circumference of the LV wall is excluded and the size of the chamber is reduced primarily due to decreased circumference and radius.

The first-generation delivery system required a median sternotomy for direct placement of an internal hinged anchor on the right side of the interventricular septum and a paired locking external locking anchor on the LV epicardium; a tether connected both anchors. Under fluoroscopic guidance, a needle is passed through the LV free wall and across the septum, a guide wire is inserted and the needle removed, and the septal anchor is introduced over the guide wire. A second, locking external locking anchor is fitted onto the tether to allow apposition of the LV free wall at the scar perimeter to the septum. The anchors are fixed in position using a force gauge to limit compression pressure on the anchors and surrounding tissue.

The second-generation hybrid delivery system allows less invasive implantation on the beating heart, utilizing identical anchors, tethers, and implant locations. An outline of the hybrid delivery system is seen in *Figure 2B.* A snare catheter is positioned into the right ventricle via jugular access to capture a wire passed through a needle that is introduced through the anterior wall of the left ventricle and the septum through a small thoracotomy. The snared wire is withdrawn from the jugular vein, and the internal hinged anchor is placed over the wire and advanced to the right side of the interventricular septum. The device is designed to allow removal of the internal hinged anchor at any stage of positioning prior to final deployment. The external locking anchor is positioned on the LV anterior wall and the two anchors are connected by the tether. Plication of the affected left ventricle is accomplished by cinching the anchors together through the mini-thoracotomy. Two to three pairs of anchors are usually implanted to achieve sufficient area of scar exclusion and volume reduction *(Figure 2C* and *2D)*. The length of the septal scar from the base to apex determines the number of anchors implanted.

It is of utmost importance to ensure that the internal hinged anchor is placed in scar with at least 50% transmurality. Because it is difficult to visualize septal scar directly during the procedure, the implanting team must have precise and accurate knowl-

edge of the individual scar morphology from preoperative imaging. Furthermore, tactile feedback when passing the needle and, subsequently, catheters through the scar together with information from intraoperative transoesophageal echocardiography will ensure proper internal hinged anchor placement. An animation of the procedure is provided in the online supplementary *Video S1*.

Warfarin anticoagulation with a target international normalized ratio of 2.0 to 2.5 for 3 months, starting 2 days after the procedure, was recommended for all patients. Thereafter, anticoagulation therapy was at the discretion of the investigator.

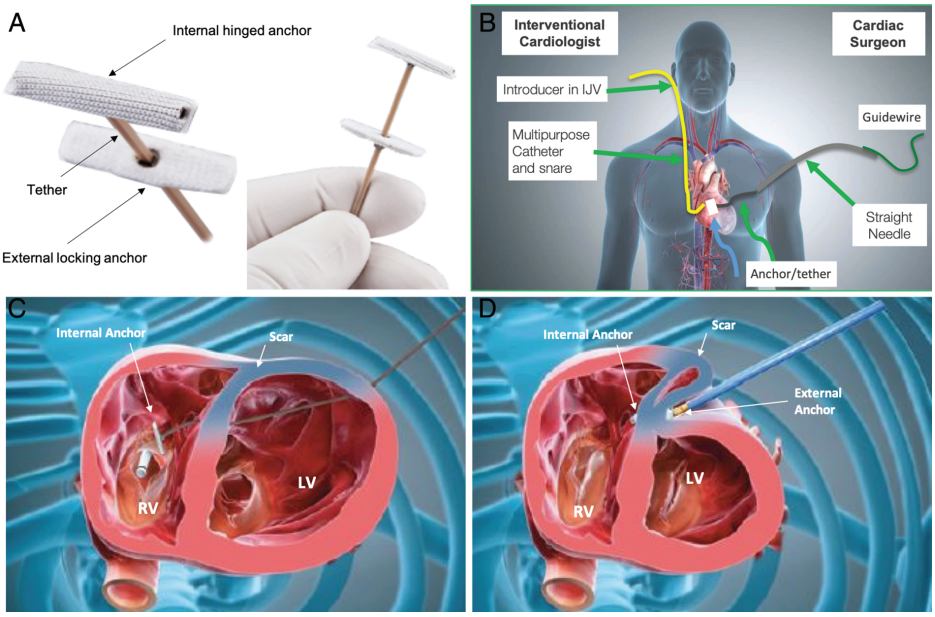


Figure 2 Schematic views of the Revivent TC System anchor with internal hinged and external locking anchor (*A*) and visualization of the hybrid approach (*B*). Further explanation and corresponding movie can be found in the online supplementary *Video S1*. In the example of left ventricular volume reduction shown in (*C*) and (*D*), the external locking anchor is pushed toward the internal hinged anchor to draw the anterior and the septal walls close, resulting in a significant volume reduction. IJV, internal jugular vein; LV, left ventricle; RV, right ventricle.

Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are given as mean ± standard deviation. Pre- and postoperative continuous data of the same patients were compared using the Wilcoxon signed-rank test. Pre- and postoperative categorical data of the same patients were analysed by Pearson's chi-squared test for count data. Adverse event data are presented as the number of patients with the event and the percentage of patients with events. Survival was

evaluated using the Kaplan–Meier method and comparisons were made using the log-rank test. Cox proportional hazards regression analysis was performed to identify predictors for survival. Logistic binary regression was used to identify predictors for patients being a responder (or non-responder) to the treatment. Variables with P <0.1 were included in multivariable analysis. For all tests, a P-value of <0.05 was considered statistically significant. Statistics were performed using the R software package (R Core Team 2018, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 89 HF patients were enrolled in the study at 22 medical centres in 12 European countries between August 2010 and March 2016. All patients were being treated according to guideline-directed medical therapy at the time of admission to the hospital.[14] Patient demographics, medical history, preoperative medication, and baseline functional status are provided in *Table 1.* All patients had NYHA class II or III symptoms. Baseline 6MWT distance was 345 ± 108 m. Prior percutaneous coronary intervention had been performed in 74% of patients. Successful device implantation was accomplished in 86 of 89 patients (97%). The three patients with unsuccessful implants were considered as not treated and were removed from the study after 30 days (online supplementary *Appendix S1*). Of the 86 patients with a successful device implantation, 51 were treated via sternotomy and 35 were treated using the hybrid approach. Sixteen patients that underwent implantation via sternotomy also had a planned concomitant coronary revascularization procedure (either coronary artery bypass grafting or percutaneous coronary intervention) *(Figure 1).*

In-hospital mortality and safety data

There were four in-hospital deaths (4.5%), three of which were procedure-related: LV injury (n=1), subendocardial necrosis (n=1), and pulmonary artery injury (n=1). One other death was attributed to bowel perforation. Four late deaths were due to sudden cardiac death (n=2), lung cancer (n=1), and stroke (n=1). Median hospital stay was 14 days (range 5–51 days), and median stay on intensive care unit was 92 h (range 0–1104 h). Patients operated via hybrid approach had a shorter hospital stay (median 12days, range 5–51 days; P = 0.01) than patients who were treated with the sternotomy approach only (median 14days, range 5–43 days). Major and minor adverse events during hospital stay are listed according to implant technique (sternotomy vs. hybrid) and the total number of patients who experienced events for the 'per protocol' population *(Table 2).* Over the 12-month follow-up period, the most

frequent observed adverse events were ventricular arrhythmia (14.0%) and bleeding (8.1%). No significant differences were observed regarding both major and minor adverse events between sternotomy and hybrid approach.

Table 1 Preoperative patient characteristics, medications, and clinical and haemodynamic data of all enrolled patients (*n* = 89)

Age, years, mean ± SD	60.4 ± 9.9
Female sex, *n* (%)	17 (20)
BMI, kg/m^2, mean ± SD	28.9 ± 5.7
Diabetes mellitus, *n* (%)	16 (19)
Arterial hypertension, *n* (%)	56 (65)
Hyperlipidaemia, *n* (%)	58 (67)
Creatinine, mg/dL, mean ± SD	1.04 ± 0.32
Ischaemic cardiomyopathy, *n* (%)	86 (100)
Age of infarct, years, mean ± SD	5.5 ± 6.5
Previous PCI, *n* (%)	63 (73)
Previous CVA, *n* (%)	10 (12)
PM, *n* (%)	3 (4)
ICD, *n* (%)	27 (31)
Medication, *n* (%)	
Statin	69 (80)
Beta-blocker	69 (80)
ACE-inhibitor	62 (72)
ARB	10 (12)
Diuretic	60 (70)
Platelet inhibitor(s)	59 (69)
Aldosterone antagonist	60 (70)
Coumadin	17 (20)
Long/short-acting nitrate	16 (19)
Anti-arrhythmic	14 (16)
Clinical data	
NYHA class, *n* (%)	
I	0 (0)
II	35 (41)
III	51 (59)
IV	0 (0)
6-min walk test, m, mean ± SD	345 ± 108
MLHFQ quality of life score (mean)	42

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; SD, standard deviation.

Table 2 Serious adverse event rates at 12 months grouped by treatment approach

	Sternotomy approach (*n* =51)	Hybrid approach (*n* =35)	All (*n* =86)	*P*-value (difference sternotomy – hybrid approach)
Major adverse events				
Tricuspid valve insufficiency increase	1 (2.0)	4 (11.4)	5 (5.8)	0.0734
Mitral valve insufficiency increase	1 (2.0)	1 (2.9)	1 (1.2)	0.79
Pulmonary valve insufficiency increase	3 (5.9)	0 (0.0)	3 (3.5)	0.15
Ventricular septal defect	1 (2.0)	1 (2.9)	2 (2.3)	0.79
Bleeding	3 (5.9)	4 (11.4)	7 (8.1)	0.36
Renal dysfunction	3 (5.9)	1 (2.9)	4 (4.7)	0.52
Respiratory failure	1 (2.0)	1 (2.9)	2 (2.3)	0.79
Stroke	3 (5.9)	1 (2.9)	4 (4.7)	0.52
Late cardiac arrest	0 (0.0)	2 (5.9)	2 (2.3)	0.09
Minor adverse events				
Atrial fibrillation	1 (1.9)	2 (5.9)	3 (3.5)	0.72
Pleural effusion	3 (5.9)	2 (5.9)	5 (5.8)	0.97
Ventricular arrhythmias	8 (15.7)	4 (11.4)	12 (14.0)	0.58
Low cardiac output	4 (7.8)	1 (2.9)	5 (5.8)	0.34
Pulmonary infection	2 (3.8)	3 (8.6)	5 (5.8)	0.37
Sepsis	4 (7.8)	1 (2.9)	5 (5.8)	0.34

Values are presented as *n* (%).

Anatomic and functional data

Echocardiographic matched data from all patients treated demonstrated significant LV volume reduction and functional improvement comparing baseline and 12-month follow-up *(Table 3)*. Compared with baseline values, mean LVESVI significantly decreased by 27% at 12months (P <0.001) *(Figure 3A)*, and LVEDVI decreased by 24% at 12months *(Figure 3B)*. Mean LVEF was significantly increased by 16% at 12months (P <0.005) (*Figure 3C*). Evaluating individual changes in LVESVI, all patients demonstrated a significant and sustained reduction in LV volumes (online supplementary *Figure S1)*.

Clinical data

Clinical outcomes significantly improved from baseline to 12-month follow-up (*Table 3*). Mean NYHA class improved from 2.6 ± 0.5 to 1.9 ± 0.8 at 12-month follow-up (P <0.001). At baseline, 59% of patients were in NYHA class III compared with 22% at 12months (*Figure 4A*). Mean 6MWT distance improved by 21% (or 53 m) to 416 m at 12-month follow-up (P <0.001) (*Figure 4B*). Mean MLHFQ score was improved,

compared with baseline, by 34% at 12-month follow-up (P <0.001) (*Figure 4C*). Mean N-terminal pro-B-type natriuretic peptide levels of matched data showed a decrease of 22% at 12-month follow-up, which was statistically non-significant (P = 0.37) (*Table 4*). We observed eight hospital readmissions due to recurrent HF symptoms. One patient was readmitted four times, so out of the 82 surviving patients, five patients experienced one or more readmissions for HF during the 12-month follow-up.

Table 3 Haemodynamic data and clinical status at baseline and 12 months for the as treated population with matched data

	Baseline	12 months	% Change	*P*-value
LVEF (%) (n = 64)	29 ± 8	34 ± 9	16	<0.005
LVESVI (mL/m^2) (n = 67)	74 ± 28	54 ± 23	27	<0.001
LVEDVI (mL/m^2) (n = 67)	106 ± 33	80 ± 26	24	<0.0001
NYHA class (n = 77)	2.6 ± 0.5	1.9 ± 0.8	26	<0.001
6-min walk distance (m) (n = 46)	363 ± 92	416 ± 106	21	<0.001
MLHF score (n = 46)	39 ± 21	26 ± 22	34	<0.001

Values are presented as mean ± standard deviation.
LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; MLHF, Minnesota Living with Heart Failure; NYHA, New York Heart Association.

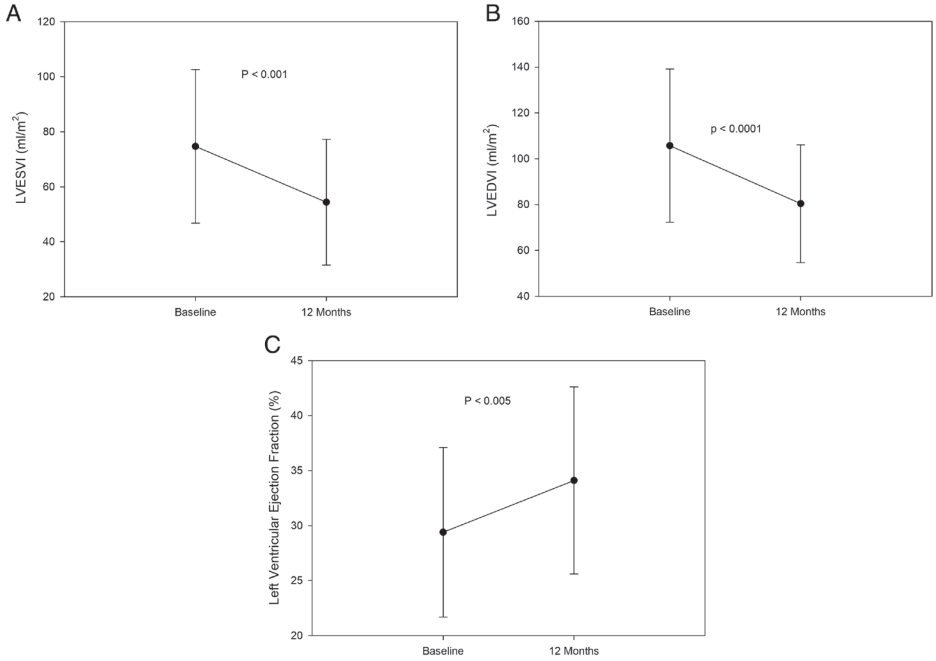


Figure 3 Data plots at baseline and 12-month follow-up for left ventricular end-systolic volume index (LVESVI) (*A*), left ventricular end-diastolic volume index (LVEDVI) (*B*) and left ventricular ejection fraction (*C*).

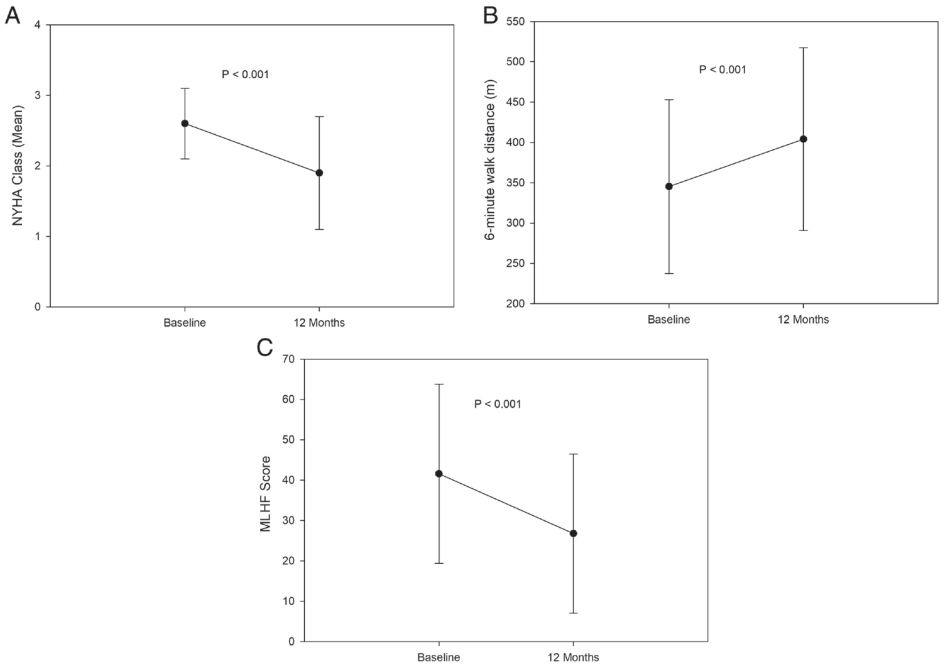


Figure 4 Clinical data for all patients and 12-month follow-up showing results from New York Heart Association (NYHA) class (*A*), 6-min walk test (*B*), and Minnesota Living with Heart Failure Questionnaire (MLHF) (*C*).

Table 4 N-terminal pro-B-type natriuretic peptide levels (pg/mL) at baseline and 12-month follow-up of matched pairs

	Baseline	Follow-up
n	39	39
Mean ± SD	1175.1 ± 1655.2	913.9 ± 1090.4
Min–max	31.5–9042.4	12.8–5291
% Change		22.2%
P-value		0.36577

SD, standard deviation.

Twelve months after treatment, NYHA class improved regardless of delivery method (sternotomy or hybrid) or adding revascularization. At baseline, 63% (sternotomy), 63% (hybrid), and 44% (adding revascularization) were in NYHA class III–IV compared to 24%, 20% and 20% at 12-month follow-up, respectively.

At baseline, 68 of the 86 patients treated in this study had measurable MR of at least grade 1+, while 19 of the 86 patients enrolled in this study had MR grade 2+ or 3+. Of the 68 patients who entered the study with measurable FMR, the average MR grade was reduced from a mean of 1.12 at baseline to a mean of 0.57 at 6 months and 0.86 at 12months (*Table* 5).

Table 5 Functional mitral regurgitation data at baseline, 6-month and 12-month follow-up as measured by transthoracic echocardiography

	Baseline	6 months	12 months
n	82	47	63
Mean ± SD	1.12 ± 0.73	0.57 ± 0.58	0.86 ± 0.64
Min–max	0–3	0–2	0–3
% Change		48.9%	23.7%
t-test		0.0005	0.03
Median	1	1	1
Grade 1	49	23	39
Grade 2	15	2	6
Grade 3	4	0	1
Grade 4	0	0	0

Survival data

The Kaplan–Meier estimated survival rate was 90.6% at 12 months (*Figure 5*). Univariable Cox proportional hazards regression analysis identified age [hazard ratio 1.11, 95% confidence interval (CI) 1.02–1.21; $P = 0.017$] and smoking (hazard ratio 0.19, 95% CI 0.04–0.78; $P = 0.022$) as significant variables associated with survival. Of note, no haemodynamic variables (i.e. LVEF or LVESVI/LVEDVI) were found significantly associated with survival after the procedure (*Table 6*).

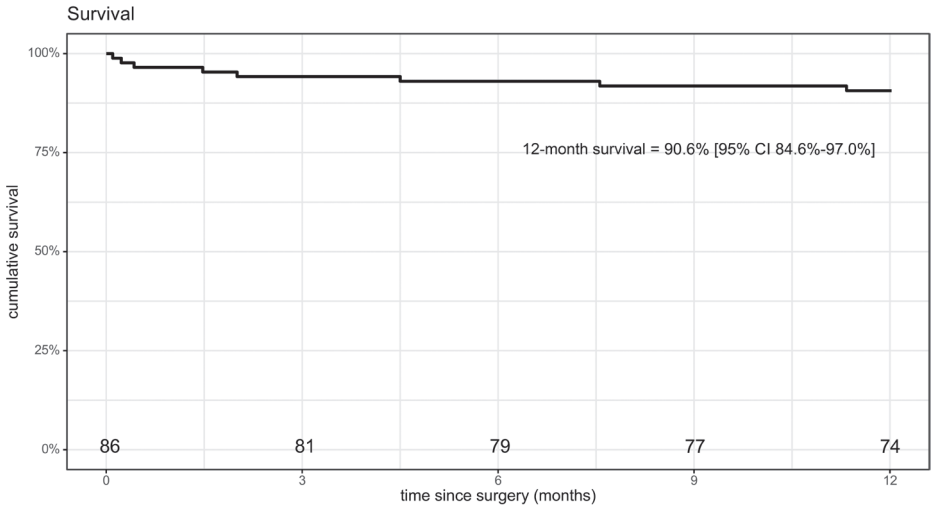


Figure 5 General survival analysis using the Kaplan–Meier survival curve at 12months ($n = 86$). CI, confidence interval.

Table 6 Univariable Cox proportional hazards regression analysis for predictors of survival

Variable	All (n = 86)	No event (n = 78)	Event (n = 8)	HR (95% CI)	P-value ratio	P-value overall	n
Approach							86
EC (full median sternotomy)	51 (59.3%)	50 (64.1%)	1 (12.5%)	Ref.	Ref.		
TC (hybrid transcatheter)	35 (40.7%)	28 (35.9%)	7 (87.5%)	11.2 [1.38–91.1]	0.024		
Demographic parameters							
Gender							86
Female	17 (19.8%)	15 (19.2%)	2 (25.0%)	Ref.	Ref.		
Male	69 (80.2%)	63 (80.8%)	6 (75.0%)	0.74 [0.15–3.68]	0.716		
Age, years	60.3± ±9.84	59.5±9.66	68.6±7.92	1.11 [1.02–1.21]	0.017	0.017	86
BSA, m^2	2.00±0.23	2.01±0.24	1.90±0.14	0.14 [0.01–3.38]	0.227	0.227	86
BMI, kg/m^2	28.9±5.70	28.9±5.72	28.8±5.79	0.99 [0.88–1.13]	0.918	0.918	86
Diabetes							
No	69 (81.2%)	62 (80.5%)	7 (87.5%)	Ref.	Ref.		
Yes	16 (18.8%)	15 (19.5%)	1 (12.5%)	0.62 [0.08–5.05]	0.656		
Smoking							85
No	22 (25.9%)	17 (22.1%)	5 (62.5%)	Ref.	Ref.		
Yes	63 (74.1%)	60 (77.9%)	3 (37.5%)	0.19 [0.04–0.78]	0.022		
Hypertension							85
No	29 (34.1%)	25 (32.5%)	4 (50.0%)	Ref.	Ref.		
Yes	56 (65.9%)	52 (67.5%)	4 (50.0%)	0.52 [0.13–2.09]	0.359		
Hyperlipidaemia							85
No	27 (31.8%)	25 (32.5%)	2 (25.0%)	Ref.	Ref.		
Yes	58 (68.2%)	52 (67.5%)	6 (75.0%)	1.38 [0.28–6.85]	0.692		
CVA/TIA							85
No	75 (88.2%)	69 (89.6%)	6 (75.0%)	Ref.	Ref.		

Table 6 Univariable Cox proportional hazards regression analysis for predictors of survival (*continued*)

Variable	All (*n* = 86)	No event (*n* = 78)	Event (*n* = 8)	HR (95% CI)	*P*-value ratio	*P*-value overall	*n*
Yes	10 (11.8%)	8 (10.4%)	2 (25.0%)	2.55 [0.51–12.6]	0.252		
Arrhythmia							85
No	53 (62.4%)	50 (64.9%)	3 (37.5%)	Ref.	Ref.		
Yes	32 (37.6%)	27 (35.1%)	5 (62.5%)	2.78 [0.66–11.6]	0.162		
Prior PCI							85
No	22 (25.9%)	20 (26.0%)	2 (25.0%)	Ref.	Ref.		
Yes	63 (74.1%)	57 (74.0%)	6 (75.0%)	1.08 [0.22–5.35]	0.926		
Prior ICD							85
No	58 (68.2%)	54 (70.1%)	4 (50.0%)	Ref.	Ref.		
Yes	27 (31.8%)	23 (29.9%)	4 (50.0%)	2.27 [0.57–9.08]	0.246		
Prior PM							68
No	65 (95.6%)	59 (96.7%)	6 (85.7%)	Ref.	Ref.		
Yes	3 (4.41%)	2 (3.28%)	1 (14.3%)	4.85 [0.58–40.4]	0.144		
Functional parameters							
NYHA class							86
II	35 (40.7%)	33 (42.3%)	2 (25.0%)	Ref.	Ref.		
III	51 (59.3%)	45 (57.7%)	6 (75.0%)	2.06 [0.42–10.2]	0.375		
Quality of life (MLHFQ)	41.6±22.2	41.4±21.9	43.1±27.4	1.00 [0.97–1.04]	0.809	0.809	83
6 min walking test distance (m)	345±108	347±106	329±136	1.00 [0.99–1.01]	0.687	0.687	83
NT-proBNP	737 [274–1621]	716 [272–1603]	2156 [2156–2156]	1.00 [1.00–1.00]	0.560	0.560	46
Echocardiographic parameters							
LVEF (%)	61.6±7.77	61.5±7.69	63.2±8.96	1.03 [0.94–1.13]	0.537	0.537	79
LVEDD (mm)	50.0±8.85	49.6±8.71	53.7±10.1	1.05 [0.97–1.13]	0.220	0.220	78

Table 6 Univariable Cox proportional hazards regression analysis for predictors of survival (*continued*)

Variable	All (*n* = 86)	No event (*n* = 78)	Event (*n* = 8)	HR (95% CI)	*P*-value ratio	*P*-value overall	*n*
LVESD (mm)	74.7±27.9	73.5±27.0	87.3±35.4	1.02 [0.99–1.04]	0.157	0.157	86
LVESVI (mL/m^2 BSA)	106±33.4	104±32.2	119±43.6	1.01 [0.99–1.03]	0.197	0.197	86
LVEDVI (mL/m^2 BSA)	29.4±7.66	29.6±7.78	27.5±6.60	0.97 [0.88–1.06]	0.476	0.476	86
Functional mitral regurgitation							80
Grade 0	13 (16.2%)	11 (15.1%)	2 (28.6%)	Ref.	Ref.		
Grade 1	49 (61.3%)	46 (63.0%)	3 (42.9%)	0.39 [0.07–2.36]	0.307		
Grade 2	14 (17.5%)	13 (17.8%)	1 (14.3%)	0.47 [0.04–5.20]	0.540		
Grade 3	4 (5.00%)	3 (4.11%)	1 (14.3%)	1.82 [0.16–20.1]	0.626		

BMI, body mass index; BSA, body surface area; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESVI, left ventricular end-systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; TIA, transient ischaemic attack.

Predictors for responders and non-responders

Univariate logistic binary regression identified hypertension (odds ratio 4.37, 95% CI 1.57–12.9; $P = 0.005$) as significant variable associated with survival. LVESVI showed a tendency towards significance (odds ratio 0.98, 95% CI 0.97–1,00; $P = 0.051$) (*Table 7*). At multivariable logistic regression, no other variable reached statistical significance when hypertension was in the model.

DISCUSSION

Left ventricular remodelling after MI is a complex process that leads to ventricular dilatation, shape alteration, increase in wall stress and a reduction in contractile force of the remote myocardium. This reduction in contractile force is partly based on a decrease in LV torsion, in which the base of the left ventricle rotates in an overall clockwise direction and the apex rotates in a counter-clockwise direction when viewed from apex to base. LV torsion is a critical mechanism of ventricular ejection and filling. The concept of ventricular reconstruction is based on exclusion of scar tissue, volume reduction, reshaping of the distorted chamber and improvement in cardiac function. This improvement is based on a combination of a decrease in wall stress, more optimal myofiber orientation, and recovery of torsional dynamics. The results of this study demonstrate that the Revivent TC System (*Figure 6*) can be used for ventricular reconstruction with acceptable safety using less invasive techniques and that the majority of patients experienced improvement in HF symptoms. The 12-month follow-up data indicate that patients experience sustained improvement in LVEF, 6MWT distance and quality of life. The LVESVI and LVEDVI data before and after device implantation demonstrate that a significant and sufficient LV volume reduction is achieved with this device (*Figure 7*). Patients in this study had an improvement in LVEF of 16%, and a reduction in LVESVI of 27%.

Surgical ventricular reconstruction has been applied clinically in a large number of patients during the past two decades.[10,15–18] SVR improves HF symptoms and long-term survival for patients with ischaemic cardiomyopathy.[19] The majority of cases in these studies underwent standard open-heart surgery via sternotomy with cardiopulmonary bypass, cardioplegic myocardial arrest, and ventriculotomy. Concomitant coronary revascularization was performed in most cases, sometimes also in combination with an intervention to the mitral valve for functional or secondary MR. Implantation of the Revivent TC System device does not require cardiopulmonary bypass, cardioplegic arrest, or a ventriculotomy. Implantation was initially performed with sternotomy, followed by the hybrid approach. Both approaches are less invasive compared to standard SVR procedures.

Table 7 Logistic binary regression (univariable) for predictors for patients being a responder (or non-responder) to the treatment

Variable	Non-responder (n = 28)	Responder (n = 46)	OR (95% CI)	P-value ratio	P-value overall	n
Approach						74
EC (full median sternotomy)	17 (60.7%)	33 (71.7%)	Ref.	Ref.		
TC (hybrid transcatheter)	11 (39.3%)	13 (28.3%)	0.61 [0.22–1.69]	0.341		
Demographic parameters						
Gender						74
Female	4 (14.3%)	11 (23.9%)	Ref.	Ref.		
Male	24 (85.7%)	35 (76.1%)	0.55 [0.13–1.84]	0.340		
Age, years	60.5±9.68	58.6±9.91	0.98 [0.93–1.03]		0.422	74
BSA, m^2	1.96±0.21	2.04±0.24	4.93 [0.58–42.0]		0.130	74
BMI, kg/m^2	27.8±5.27	29.6±5.72	1.06 [0.97–1.17]		0.168	74
Diabetes						73
No	24 (88.9%)	35 (76.1%)	Ref.	Ref.		
Yes	3 (11.1%)	11 (23.9%)	2.41 [0.65–12.1]	0.196		
Smoking						73
No	7 (25.9%)	9 (19.6%)	Ref.	Ref.		
Yes	20 (74.1%)	37 (80.4%)	1.44 [0.44–4.52]	0.538		
Hypertension						73
No	15 (55.6%)	10 (21.7%)	Ref.	Ref.		
Yes	12 (44.4%)	36 (78.3%)	4.37 [1.57–12.9]	0.005		
Hyperlipidaemia						73
No	12 (44.4%)	11 (23.9%)	Ref.	Ref.		
Yes	15 (55.6%)	35 (76.1%)	2.50 [0.90–7.14]	0.079		
CVA/TIA						73
No	24 (88.9%)	42 (91.3%)	Ref.	Ref.		

Table 7 Logistic binary regression (univariable) for predictors for patients being a responder (or non-responder) to the treatment (*continued*)

Variable	Non-responder (*n* = 28)	Responder (*n* = 46)	OR (95% CI)	*P*-value ratio	*P*-value overall	*n*
Yes	3 (11.1%)	4 (8.70%)	0.76 [0.15–4.41]	0.740		
Arrhythmia						73
No	16 (59.3%)	32 (69.6%)	Ref.	Ref.		
Yes	11 (40.7%)	14 (30.4%)	0.64 [0.23–1.76]	0.385		
Prior PCI						73
No	4 (14.8%)	16 (34.8%)	Ref.	Ref.		
Yes	23 (85.2%)	30 (65.2%)	0.34 [0.08–1.09]	0.069		
Prior ICD						73
No	16 (59.3%)	37 (80.4%)	Ref.	Ref.		
Yes	11 (40.7%)	9 (19.6%)	0.36 [0.12–1.05]	0.061		
Prior PM						57
No	20 (90.9%)	35 (100%)	Ref.	Ref.		
Yes	2 (9.09%)	0 (0.00%) .[&$$$–]	0.145			
Functional parameters						
NYHA class						74
II	10 (35.7%)	20 (43.5%)	Ref.	Ref.		
III	18 (64.3%)	26 (56.5%)	0.73 [0.27–1.92]	0.524		
Quality of life (MLHFQ)	39.9±22.5	43.0±22.1	1.01 [0.98–1.03]		0.570	72
6 min walking test distance (m)	365±106	332±108	1.00 [0.99–1.00]		0.216	72
NT-proBNP	1318 [366–1753]	601 [251–1442]	1.00 [1.00–1.00]		0.271	45
Echocardiographic parameters						
LVEF (%)	28.3±6.66	30.0±8.55	1.03 [0.97–1.09]		0.345	74
LVEDD (mm)	62.8±7.39	60.2±7.61	0.95 [0.89–1.02]		0.164	69

Table 7 Logistic binary regression (univariable) for predictors for patients being a responder (or non-responder) to the treatment (*continued*)

Variable	Non-responder (n = 28)	Responder (n = 46)	OR (95% CI)	P-value ratio	P-value overall	n
LVESD (mm)	51.5±7.07	48.1±9.34	0.95 [0.90–1.01]		0.095	68
LVESVI (mL/m^2 BSA)	81.3±27.0	68.4±26.8	0.98 [0.97–1.00]		0.051	74
LVEDVI (mL/m^2 BSA)	112±29.6	99.0±33.8	0.99 [0.97–1.00]		0.089	74
Functional mitral regurgitation					0.914	70
Grade 0	3 (11.1%)	7 (16.3%)	Ref.	Ref.		
Grade 1	19 (70.4%)	26 (60.5%)	0.61 [0.11–2.57]	0.509		
Grade 2	4 (14.8%)	8 (18.6%)	0.87 [0.12–5.68]	0.884		
Grade 3	1 (3.70%)	2 (4.65%)	0.84 [0.05–33.3]	0.909		

BMI, body mass index; BSA, body surface area; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESVI, left ventricular end-systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; TIA, transient ischaemic attack.

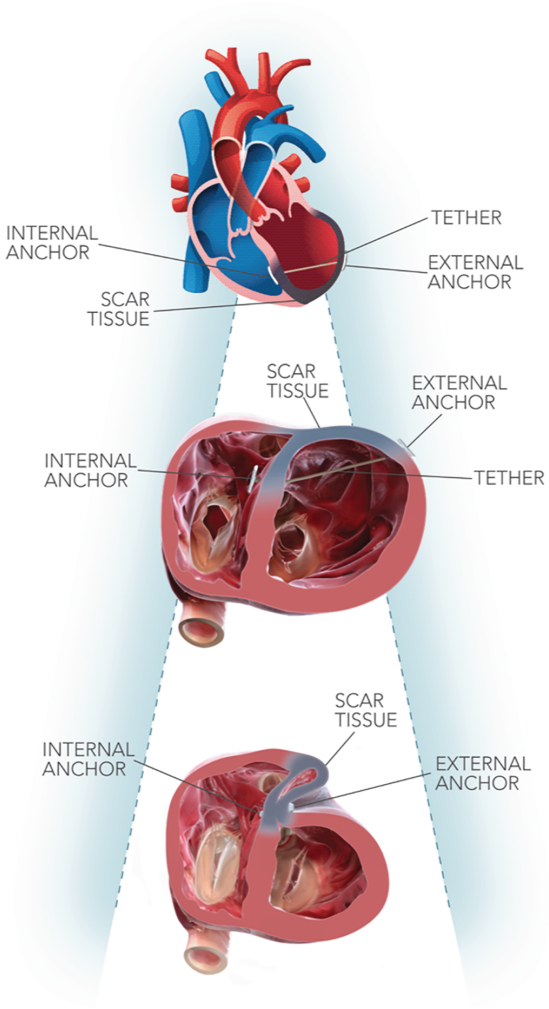


Figure 6 Areas of antero-septal akinetic and/or dyskinetic scarred myocardium are identified with placement of the internal hinged anchor in the right ventricle and placement of the external locking anchor on the epicardial surface, both attached to the tether (top). The anchors and tether are positioned on the leading edge of the scarred myocardium (middle). Once the anchors are drawn together, the scarred myocardium is excluded, and the volume of the left ventricle is reduced (bottom).

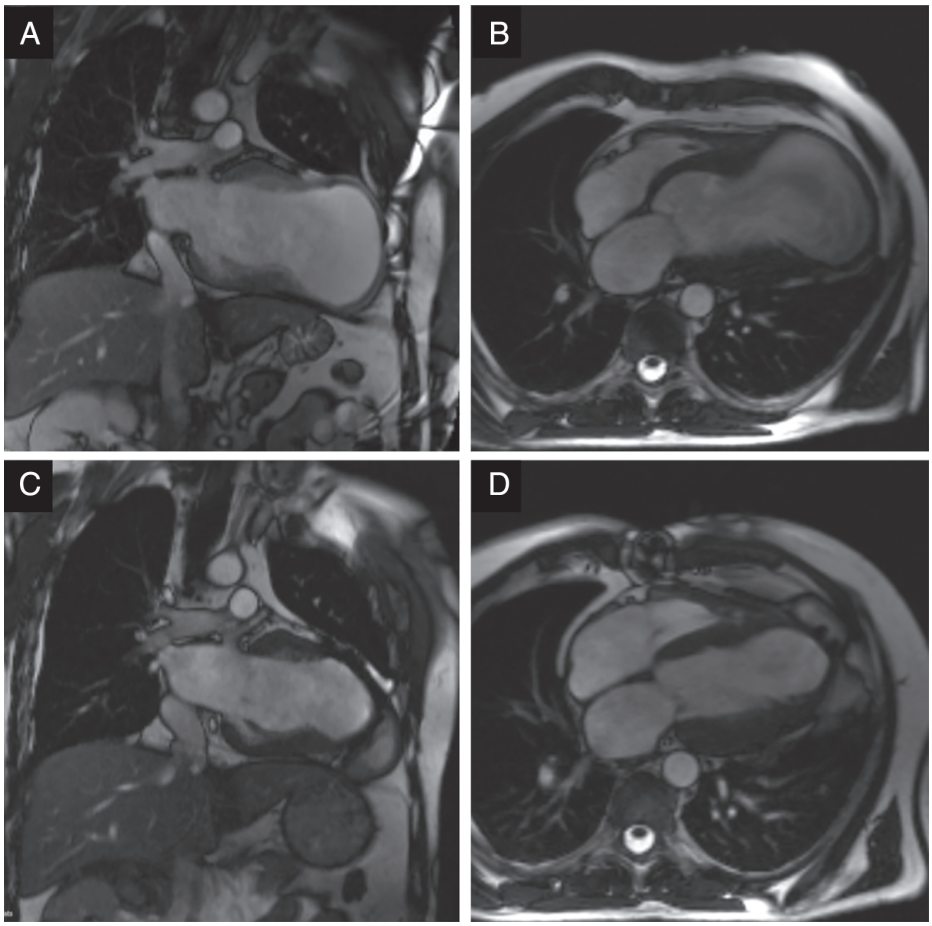


Figure 7 Magnetic resonance images of the heart pre- and post-surgery. On-site images taken before surgery show a large apical aneurysm post-myocardial infarction with increased ventricular volume and thinned wall [two-chamber orientation (*A*); four-chamber orientation (*B*)]. Images taken 6 months after surgery show significant volume reduction and reshaping of the left ventricle [two-chamber orientation (*C*); four-chamber orientation (*D*)].

The outcomes and the rate of adverse events during and after implantation of the Revivent TC System appear to be in an acceptable range when compared with SVR. The in-hospital operative mortality of 4.5% in this study is within the range of 3–14% reported in most SVR studies,[8,17,20–22] especially when considering the effects of the early operator's learning curve in this initial experience. Hospital stay could be significantly reduced by using the hybrid approach rather than the initial surgical approach. The observed 12-month survival of 90.6% is also comparable to SVR outcomes.[8,23–25] By comparison, the reported survival from the international Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical

shape to the left ventricle (RESTORE) registry of 1198 post-anterior infarction SVR cases at 18months was 89.2%. Improvement in outcomes after implantation of the Revivent TC System should be possible through application of experience gained in selecting candidates and in the technique of implantation. This might also offer an alternative in patients at high risk of perioperative complications or with a frail preoperative condition.

An important element of the Revivent TC System implantation technique is that the anchor pairs are set to a configuration parallel to the long axis of the heart. Each tether and the excluded portion of the scar are taken from the short axis of the heart. With this configuration, virtually all volume reduction decreases the radius of the left ventricle and is not just the result of amputation of an apical aneurysm. Reduction in wall tension, reorientation of myofibers, and improvement in torsional dynamics is, therefore, the most likely explanation for the functional improvement observed in the patients.

The focus of this study was to evaluate both safety and effectiveness of the device system. Clinical outcomes were essentially the same in all groups and were significantly improved through 12 months of follow-up. Both approaches are essentially less invasive compared to conventional SVR, and therapeutic volume reduction was achieved regardless of delivery method. These data compare favourably with the STICH sub-analysis, which established a survival benefit in patients realizing >30% reduction in LVESVI and/or postoperative LVESVI <60 mL/m^2.[11] Another finding from an additional STICH analysis was that patients with smaller ventricles (LVESVI <60 mL/m^2) and better LVEF (≥33%) at echocardiography may have benefited by SVR, while those with larger ventricles (LVESVI >90 mL/m^2) and lower LVEF (≤25%) did worse with SVR.[26] In this study we found weak evidence at univariate analysis that a smaller LVESVI is associated with patients that responded positively to treatment with the Revivent TC system (odds ratio 0.98, 95% CI 0.97–1,00; P = 0.051).

Many patients with ischaemic HF also experience (secondary or functional) MR. The presence of functional MR is associated with adverse clinical outcome. Although this therapy does not treat the mitral valve itself, reshaping of the left ventricle is expected to result in reduction in MR in some patients, particularly those with functional MR. Patients with moderate to severe MR (grade 4+) were excluded from this clinical study; however, enrolment of patients with functional MR grade 1+ to 3+ was allowed. At baseline, 68 of the 86 patients treated in this study had measurable MR of at least grade 1+, while 19 of the 86 patients enrolled in this study had MR grade 2+ or 3+. Of the 68 patients who entered the study with measurable

functional MR, the average MR grade was reduced from a mean of 1.12 at baseline to a mean of 0.57 at 6 months and 0.86 at 12months. Of the 19 patients who entered the study with at least grade 2+ MR, 12 (63%) experienced at least a 1 grade decrease in MR while the other seven patients remained unchanged. Due to reshaping of the left ventricle during and after treatment with the Revivent TC System, a reduction in MR was observed and should be considered as an additional potential benefit in patients who have MR but are not yet in need for mitral valve repair or replacement, or patients who have residual functional MR from previous repair of the mitral valve with ongoing progression of their HF symptoms.

Since CE Mark approval of the Revivent TC System in 2016, a registry of clinical data from treated patients has been maintained; publication of the results will be forthcoming. The results of this registry are important as there have been subtle refinements to the system, and experience with implantation has increased considerably.

Limitations

This study is limited by its moderate size in the number of patients treated, the non-randomized, non-controlled trial design and the limited follow-up of 12 months. Furthermore, the number of enrolled patients per centre is relatively low. Possibly, this is more related to the negative result of the STICH trial, than a real shortage of potential patients for this therapy.[27] In addition, patients with previous coronary artery bypass graft were excluded fromt his study.

Future trials will be randomized against guideline-directed medical therapy or conventional open chest surgery. Patients received the device either through a sternotomy or by mini-thoracotomy and internal jugular vein access and were not independently compared. The focus of these results was the effectiveness of the identical implanted device in both groups, not the delivery method. Nevertheless, both techniques are less invasive compared to conventional SVR, and therapeutic volume reduction was achieved regardless of delivery method. The imaging techniques used by the different centres for LV volume measurement were not uniform; consequently, our analysis was limited to patients that had the same measurement techniques. In future trials, longer follow-up is needed, especially in evaluation of the use in patients with severe HF after large anterior MI. However, in patients with less symptoms (NYHA class I), the use might be discussed to prevent the onset of LV remodelling. In addition, use of a three-dimensional method (magnetic resonance imaging or computed tomography) rather than echocardiography may result in a

more accurate assessment of LV remodelling and evaluation of parameters, such as LV strain in remote myocardium to test improvement in deformation.

To further assess the clinical benefit of the Revivent TC System over guideline-directed medical treatment, a randomized controlled trial (Revivent TC versus Guideline Determined Medical Therapy) has been set up and enrolment has started in 2019.

CONCLUSIONS

These data indicate that the Revivent TC System can be used as an HF therapy that results in good clinical outcomes. Selection of patients with appropriate anatomic features is a critical aspect for the achievement of durable clinical outcomes. This could be an additional personalized therapy for a specific type of patients with HF after MI with scar tissue in the anteroseptal or apical wall of the left ventricle.[28]

Benefits from LV volume reduction and ventricular reshaping have been demonstrated independent of myocardial revascularization or open chest surgery, using a hybrid approach. The ability to achieve these results without the need for sternotomy or cardiopulmonary bypass is an important advance for the treatment of patients suffering fromischaemic cardiomyopathy HF. This less invasive technique for LV volume reduction demonstrates efficacy and acceptable safety in this moderate sample size of highly selected patients.

Clinical perspective

Surgical SVR following anterior MI to exclude non-functioning myocardium returns the ventricle to a more normal size, thereby improving wall tension and LV function. Historical data have shown that SVR is an effective therapy for HF caused by ischaemic cardiomyopathy. Surgical techniques for SVR involve the use of cardiopulmonary bypass and incisions into the ventricle. The less invasive volume reduction and reshaping of the ventricle using the Revivent TC System has demonstrated its safety and good survival with reduced morbidity and improvement of clinical symptoms and exercise capacity in appropriately selected patients with severe HF.

SUPPLEMENTARY INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Detailed report of the three patients with unsuccessful implants that were not treated and removed from the study after 30 days.

Table S1. Revivent System study inclusion (*A*) and exclusion criteria (*B*).

Figure S1. Individual left ventricular end-systolic volume index change.

Video S1. Animation of the Revivent TC procedure.

Acknowledgements

We wish to thank the investigators who supported this research and our colleagues who provided insight and expertise to designing a successful trial. We wish to acknowledge the work of the echo core lab, The Ohio State University, who provided the results contained in this publication.

Funding

This study was sponsored by BioVentrix, Inc., San Ramon, CA. BioVentrix supported the design, conduct of the study and collection of the data. Analysis, interpretation of the data, preparation, review and approval of the manuscript was done independently by the authors.

Conflict of interest: P.K. reports consultancy, proctoring and speaker agreements with BioVentrix and Edwards LifeSciences, and speaking fee by LivaNova. S.K. reports consultancy and spear agreements with BioVentrix. The other authors have nothing to disclose.

REFERENCES

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30–41.
2. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJ. Estimates of global and regional premature cardiovascular mortality in 2025. Circulation 2015;132:1270–1282.
3. Buckberg G, Athanasuleas C, Conte J. Surgical ventricular restoration for the treatment of heart failure. Nat Rev Cardiol 2012;9:703–716.
4. Buckberg GD. Ventricular restoration – a surgical approach to reverse ventricular remodeling. Heart Fail Rev 2004;9:233–239.
5. Hamer AW, Takayama M, Abraham KA, Roche AH, Kerr AR, Williams BF, Ramage MC, White HD. End-systolic volume and long-term survival after coronary artery bypass graft surgery in patients with impaired left ventricular function. Circulation 1994;90:2899–2904.
6. Axelrad JE, Pinsino A, Trinh PN, Thanataveerat A, Brooks C, Demmer RT, Effner L, Parkis G, Cagliostro B, Han J, Garan AR, Topkara V, Takeda K, Takayama H, Naka Y, Ramirez I, Garcia-Carrasquillo R, Colombo PC, Gonda T, Yuzefpolskaya M. Limited usefulness of endoscopic evaluation in patients with continuous-flow left ventricular assist devices and gastrointestinal bleeding. J Heart Lung Transplant 2018;37:723–732.
7. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, di Donato M, Menicanti L, Almeida de Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy P, Oz MC, Fontan F, Scott ML, Accola KA; RESTORE Group. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. J Am Coll Cardiol 2004;44:1439–1445.
8. Di Donato M, Frigiola A, Benhamouda M, Menicanti L. Safety and efficacy of surgical ventricular restoration in unstable patients with recent anterior myocardial infarction. Circulation 2004;110 (11 Suppl 1):II169–II173.
9. Crespo-Leiro MG, Cuenca-Castillo JJ. Surgical treatment of heart failure: heart transplantation and ventricular restoration surgery. Eur Heart J Suppl 2006;8:E39–E42.
10. Athanasuleas CL, Stanley AW, Buckberg GD, Dor V, di Donato M, Siler W; RESTORE Group. Surgical anterior ventricular endocardial restoration (SAVER) for dilated ischemic cardiomyopathy. Semin Thorac Cardiovasc Surg 2001;13:448–458.
11. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, Holly TA, Oh JK, Dagenais F, Milano C, Wrobel K, Pirk J, Ali IS, Jones RH, Velazquez EJ, Lee KL, Di Donato M; STICH Trial Investigators. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg 2013;146:1139–1145.
12. Wechsler AS, Sadowski J, Kapelak B, Bartus K, Kalinauskas G, Rucinskas K, Samalavicius R, Annest L. Durability of epicardial ventricular restoration without ventriculotomy. Eur J Cardiothorac Surg 2013;44:e189–e192.
13. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. Cardiopulm Phys Ther J 2013;24:21–29.

14. Gonzalez-Saenz de Tejada M, Bilbao A, Ansola L, Quirós R, García-Perez L, Navarro G, Escobar A. Responsiveness and minimal clinically important difference of the Minnesota Living with Heart Failure Questionnaire. Health Qual Life Outcomes 2019;17:36.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.
16. Cooley DA. Endoaneurysmorrhaphy revisited. Tex Heart Inst J 1984;11: 8–9.
17. Dor V. Left ventricular aneurysms: the endoventricular circular patch plasty. Semin Thorac Cardiovasc Surg 1997;9:123–130.
18. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, DiDonato M, Menicanti L, de Oliveira SA, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy P, Oz MC, Fontan F, Scott ML, Accola KA; RESTORE Group. Surgical ventricular restoration: the RESTORE group experience. Heart Fail Rev 2004;9:287–297.
19. Broderick JP. The STICH trial: what does it tell us and where do we go from here? Stroke 2005;36:1619–1620.
20. Di Donato M, Castelvecchio S, Menicanti L. Surgical treatment of ischemic heart failure: the Dor procedure. Circ J 2009;73 Suppl. A:A1–A5.
21. Menicanti L, Castelvecchio S, Ranucci M, Frigiola A, Santambrogio C, de Vincentiis C, Brankovic J, di Donato M. Surgical therapy for ischemic heart failure: single-center experience with surgical anterior ventricular restoration. J Thorac Cardiovasc Surg 2007;134:433–441.
22. Hwang HY, Kim JS, Cho KR, Kim KB. Surgical anterior ventricular endocardial restoration performed with total arterial revascularization: serial 5-year follow-up. J Thorac Cardiovasc Surg 2014;148:529–535.
23. Castelvecchio S, Ranucci M, Bandera F, Baryshnikova E, Giacomazzi F, Menicanti L; Surgical and Clinical Outcome Research (SCORE) Group. The additional prognostic value of left atrial volume on the outcome of patients after surgical ventricular reconstruction. Ann Thorac Surg 2013;95:141–147.
24. Di Donato M, Castelvecchio S, Brankovic J, Santambrogio C, Montericcio V, Menicanti L. Effectiveness of surgical ventricular restoration in patients with dilated ischemic cardiomyopathy and unrepairedmild mitral regurgitation. J Thorac Cardiovasc Surg 2007;134:1548–1553.
25. O'Neill JO, Starling RC, McCarthy PM, Albert NM, Lytle BW, Navia J, Young JB, Smedira N. The impact of left ventricular reconstruction on survival in patients with ischemic cardiomyopathy. Eur J Cardiothorac Surg 2006;30: 753–759.
26. Oh JK, Velazquez EJ, Menicanti L, Pohost GM, Bonow RO, Lin G, Hellkamp AS, Ferrazzi P, Wos S, Rao V, Berman D, Bochenek A, Cherniavsky A, Rogowski J, Rouleau JL, Lee KL; STICH Investigators. Influence of baseline left ventricular function on the clinical outcome of surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. Eur Heart J 2013;34:39–47.
27. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and

outcomes following primary PCI: patient-level analysis from 10 randomized trials. J Am Coll Cardiol 2016;67:1674–1683.

28. Ahmad FA, Petrie MC, McMurray JJV, Lang NN. Personalized medicine and hospitalization for heart failure: if we understand it, we may be successful in treating it. Eur J Heart Fail 2019;21:699–702.

Chapter 10

Left ventricular volume reduction and reshape – 'Re-STICHING' the field

Patrick Klein[1], Stefan D. Anker[2,3,4], Andrew Wechsler[5], and Sebastian Kelle[6,7]

[1]Department of Cardiothoracic Surgery, St Antonius Hospital, Nieuwegein, The Netherlands; [2]BIH Center for Regenerative Therapies (BCRT), Charité, Universitätsmedizin Berlin, Berlin, Germany; [3]Division of Cardiology and Metabolism, Department of Cardiology (CVK), Charité, Berlin, Germany; [4]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; [5]Department of Cardiothoracic Surgery, Drexel University College of Medicine, Philadelphia, PA, USA; [6]Department of Internal Medicine, Cardiology German Heart Center Berlin, Berlin, Germany; and [7]Department of Internal Medicine/Cardiology, Charité Campus Virchow Clinic, Berlin, Germany

Reply to letter regarding the article 'Less invasive ventricular reconstruction for ischaemic heart failure'

LEFT VENTRICULAR VOLUME REDUCTION AND RESHAPE – 'RE-STICHING' THE FIELD.

Letter regarding the article 'Less invasive ventricular reconstruction for ischaemic heart failure'

We read with interest the study by Klein *et al.*[1] exploring the effect of a less invasive device in inducing left ventricular reconstruction in failing hearts post-myocardial infarction. Left ventricular remodelling following an anterior myocardial infarction has detrimental effects to the efficacy of the left ventricle. This stems not only from the Laplace law but in addition from the impaired blood flow kinetics within the remodelled left ventricle. The concept of surgical volume reduction of the dilated left ventricle is to exclude the infarcted myocardial tissue, reshape and increase the efficacy of the left ventricle.[2] This strategy faces two major challenges.

First, the final end-diastolic volume should be reduced enough in order to allow the Laplace low to take place effectively. However, the final volume should not be that small, otherwise restrictive phenomena will occur, stroke volume will be reduced, left ventricular filling pressures will rise and re-dilatation of the left ventricle might occur. In those cases, any potential benefit from volume reduction therapies will be eliminated.[3,4] In order to avoid the left ventricular excessive volume reduction during the procedure, surgeons are trying to keep the final left ventricular remaining volume close to 60 mL/m^2 using the 'balloon sizing' technique. However, even if it is true that a final volume at that level is sufficient for the normally working heart, we still do not know whether this is also true for an impaired left ventricle that has undergone remodelling.

The second challenge for left ventricular reconstruction surgeries is the restoration of a more conical shape of the left ventricle. Studies have shown that a conical shape results in better outcomes since this shape improves blood flow hydrodynamics. In the STICH trial, left ventricular geometry worsened after left ventricular reconstruction surgery and the left ventricle became more spherical.[5] Only those patients that obtained a conical left ventricular shape demonstrated improved outcomes.

Left ventricular reconstruction surgery is not a one size fits all patients, and a more individualized approach should be implemented. Klein *et al.*[1] in a less invasive approach attempted to reduce the volume of the infarcted left ventricle, excluding the non-functioning scarred myocardium. There was a significant reduction in left ventricular volumes and a significant increase in left ventricular ejection fraction.

A total of 46 out of 86 participants were characterized as 'responders' since they revealed improvement in the 6-min walk test and in their quality of life.

To the direction of a more individualized approach for ventricular volume reduction and reshaping therapies, it would be very helpful if authors could provide also parameters of the shape of the left ventricle before and following the application of the device (apical conicity index, left ventricular sphericity index). The device proposed by Klein *et al.*[1] has the advantage of requiring no cardiopulmonary bypass. In that way, haemodynamic parameters obtained by a Swan–Ganz catheter at the time of the deployment of the device could provide important prognostic information on the short- and long-term adaptation of the left ventricle to the newly acquired volume and shape in a real time way.

Again, we find the study of Klein *et al.*[1] a very important step for a more quantitative and personalized application of left ventricular reshaping and volume reduction therapies.

Michael J. Bonios, Nektarios Kogerakis, and Stamatis N. Adamopoulos

Heart Failure and Transplant Unit, Onassis Cardiac Surgery Center, Athens, Greece

REFERENCES

1. Klein P, Anker SD, Wechsler A, Skalsky I, Neuzil P, Annest LS, Bifi M, McDonagh T, Frerker C, Schmidt T, Sievert H, Demaria AN, Kelle S. Less invasive ventricular reconstruction for ischaemic heart failure. Eur J Heart Fail 2019;21:1638–1650.
2. Athanasuleas CL, Buckberg GD, Stanley AW, SilerW, Dor V, Di Donato M, Menicanti L, Almeida de Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, MooreW, McCarthy PM, Oz MC, Fontan F, Scott ML, Accola KA. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. J Am Coll Cardiol 2004;44:1439–1445.
3. Di Donato M, Fantini F, Toso A, Castelvecchio S, Menicanti L, Annest L, Burkhoff D. Impact of surgical ventricular reconstruction on stroke volume in patients with ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2010;140:1325–1331.e1–2.
4. Bonios MJ, Anastasiou-Nana M, Perrea DN, Malliaras K. A combined cellular and surgical ventricular reconstruction therapeutic approach produces attenuation of remodeling in infarcted rats. Hellenic J Cardiol 2017;58:135–142.
5. Choi JO, Daly RC, Lin G, Lahr BD, Wiste HJ, Beaver TM, Iacovoni A, Malinowski M, Friedrich I, Rouleau JL, Favaloro RR, Sopko G, Lang IM, White HD, Milano CA, Jones RH, Lee KL, Velazquez EJ, Oh JK. Impact of surgical ventricular reconstruction on sphericity index in patients with ischaemic cardiomyopathy: follow-up from the STICH trial. Eur J Heart Fail 2015;17:453–463.

LEFT VENTRICULAR VOLUME REDUCTION AND RESHAPE – 'RE-STICHING' THE FIELD.

Reply

We thank Bonios *et al.* for their interesting and relevant remarks to our study of the Revivent TC System as an additional personalized therapy for a specific type of patients with heart failure after myocardial infarction with scar tissue in the antero-septal or apical wall of the left ventricle.[1]

Multiple publications described the clinical and functional improvement after (open) surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. In line with these findings, we demonstrated at least equivalent functional and echocardiographic improvements by hybrid left ventricular (LV) reconstruction using the Revivent TC system. The basis for the rationale of LV reconstruction is, as Bonios *et al.* rightfully refer to, formed by the LaPlace law: decrease of LV volume reduces LV wall stress and both this and the (anatomic/physiologic) reconstruction improve LV contractile properties. Pressure–volume analysis provides the most comprehensive means of assessing ventricular contractile properties and the most rigorous means of measuring these relations in the clinical setting is with the conductance catheter as used by Tulner and colleagues from the Leiden University Medical Center.[2,3] They provided the scientific and pathophysiologic proof for LV reconstruction by demonstrating improvement in systolic and diastolic function, wall stress, dyssynchrony and mechanical efficiency by pressure–volume loop measurements. After surgical ventricular reconstruction, end-diastolic and end-systolic volumes were reduced from 211±54 to 169±34 mL (P =0.03) and from 147±41 to 110±59 mL (P =0.04), respectively. LV ejection fraction (from 27±7% to 37±13%, P =0.04) and end-systolic elastance (from 1.12±0.71 to 1.57±0.63 mmHg/mL, P =0.03) improved. Peak wall stress (from 358±108 to 244±79 mmHg, P <0.01) and mechanical dyssynchrony (from 26±4% to 19±6%, P <0.01) were reduced, whereas mechanical efficiency improved (from 0.34±13 to 0.49±0.14, P =0.03). With regard to pressure–volume relations, there were leftward shifts of both end-diastolic and end-systolic pressure–volume relationships towards more normal volumes. Decreased ventricular compliance has also been demonstrated by them and also in other studies on LV reconstruction and moreover also in settings of prolonged myocardial ischaemia. Hybrid LV reconstruction or the Revivent procedure is performed on the beating heart, without cardioplegic arrest and without the use of an akinetic/stiff Dacron patch. Therefore, the impact on diastolic functional properties should be less than in its open-surgical predecessor. Essentially, it all comes down to determine the balance between the relatively beneficial effects of decreasing wall stress and the detrimental effects of

increasing diastolic filling pressures as a consequence of reducing chamber volume. Michler *et al.*[4] found that an LV end-systolic volume of 60 mL/m^2 body surface area after reconstruction to be a threshold at or under which a mortality benefit was observed. As such, it does not represent a target, but rather the upper limit of the target volume. The fact that in the Revivent procedure, the heart is beating and anchors can be removed or adjusted, under-sizing would be recognized in real-time intraoperatively, and corrected. We fully agree with Bonios *et al.* that the exact/ideal volume that should be achieved after LV reconstruction in remodelled ventricles is still unclear and it could very well be that it should be personalized in every single patient.

Concerning the changes in LV shape, we agree that additional data on pre- and post-operative shape would be very interesting. However, DiDonato and the RESTORE Group published already in 2006 that the adverse effects of ischaemic cardiomyopathy are statistically evident in every parameter except global sphericity, which remained unchanged between normal patients and those with dilated hearts after anterior infarction. Both ventricular length and width increased following anterior infarction, and hence the dimensionless ratio between length and width did not change, so that the sphericity index was unaltered.[5] Classical parameters of LV shape such as the sphericity index therefore seem insufficient to assess improvements in LV shape post reconstruction and therefore there is a need for new (perhaps three-dimensional or fusion) imaging parameters on shape (and function) in LV reconstruction procedures.

REFERENCES

1. Klein P, Anker SD, Wechsler A, Skalsky I, Neuzil P, Annest LS, Bifi M, McDonagh T, Frerker C, Schmidt T, Sievert H, Demaria AN, Kelle S. Less invasive ventricular reconstruction for ischaemic heart failure. Eur J Heart Fail 2019;21:1638–1650.
2. Tulner SA, Bax JJ, Bleeker GB, Steendijk P, Klautz RJ, Holman ER, Schalij MJ, Dion RA, van der Wall EE. Beneficial hemodynamic and clinical effects of surgical ventricular restoration in patients with ischemic dilated cardiomyopathy. Ann Thorac Surg 2006;82:1721–1727.
3. Tulner SA, Steendijk P, Klautz RJ, Bax JJ, Schalij MJ, van der Wall EE, Dion RA. Surgical ventricular restoration in patients with ischemic dilated cardiomyopathy: evaluation of systolic and diastolic ventricular function, wall stress, dyssynchrony, and mechanical efficiency by pressure-volume loops. J Thorac Cardiovasc Surg 2006;132:610–620.
4. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, Holly TA, Oh JK, Dagenais F, Milano C, Wrobel K, Pirk J, Ali IS, Jones RH, Velazquez EJ, Lee KL, Di Donato M; STICH Trial Investigators. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg 2013;146:1139–1145.
5. Di Donato M, Dabic P, Castelvecchio S, Santambrogio C, Brankovic J, Collarini L, Joussef T, Frigiola A, Buckberg G, Menicanti L; RESTORE Group. Left ventricular geometry in normal and post-anterior myocardial infarction patients: sphericity index and 'new' conicity index comparisons. Eur J Cardiothorac Surg 2006;29:S225–S230.

Chapter 11

General Discussion

Left ventricular remodeling after myocardial infarction lead to left ventricular (LV) dilatation, change in LV shape and myocardial dysfunction. Both the LV dilatation and the dysfunction (either global or regional) can additionally cause secondary or functional mitral regurgitation. In a more advanced disease state, it can cause the clinical syndrome of heart failure (HF). Furthermore, the LV remodeling is associated with malignant ventricular tachyarrhythmias and sudden cardiac death.

Surgical reconstruction of akinetic or dyskinetic segments reduces LV volume and this has two important effects. First, based on the Laplace equation, which relates wall stress inversely to wall thickness and directly to chamber radius, volume reduction diminishes wall stress and thereby reduces myocardial oxygen consumption. Minimising the mass of abnormal myocardium improves wall compliance, reduces filling pressure, and further enhances diastolic coronary flow. Second, reduction of wall stress, as a critical determinant of afterload, enhances contractile performance of the ventricle by increasing the extent and velocity of systolic fibre shortening [ref. 1].

Early and late outcome of LV reconstruction surgery

LV reconstruction surgery originates from ventricular aneurysmectomy. Secondary to extensive transmural infarction, ventricular aneurysms occur commonly anterior, less commonly inferior and rarely involving the lateral wal [ref 1]. Classically and before the widespread application of thrombolysis and later primary percutaneous intervention (PCI), the native coronary artery was totally blocked and the distal vessel filled by collaterals. Almost 50% contained an organised thrombus. There was controversy concerning the natural history of patients with ventricular aneurysms that were managed conservatively. An early report by Schlichter in 1954 reported a mere 18% survival at 5 years [ref. 2]. In contrast, analysis from the CASS trial data showed a 71% survival at 4 years [ref. 3]. Possible explanations could be differences in contractility of the remote non-infarcted myocardium, size of the aneurysm and extent of coronary disease.

Beck reported the first attempt to surgically repair a ventricular aneurysm in 1944 attaching a fascia lata graft to the external surface of the aneurysm [ref. 4]. The fascia lata graft and aneurysm were thereafter plicated with interrupted sutures. The patient died 6 weeks postoperatively from empyema and sepsis. Bailey described in 1956 the repair of four ventricular aneurysms [ref. 5]. Using a large toothed clamp across the base of the aneurysms, excision and repair of the ventricular aneurysms was possible without the use of extracorporeal circulation. In 1958, Cooley used a

pump oxygenator to excise a ventricular aneurysm and repair the ventricle with a linear closing technique [ref. 6].

Coltharp reported in 1994 on their 25-year experience in 523 patients that underwent ventricular aneurysmectomy [ref 1]. Ventricular reconstruction was performed by either the linear, septal, purse-string or patch technique. Hospital mortality was 7.5%. The most frequent complication with 22% was low cardiac output. Mortality appeared to be related to technique of repair: 8.2% for septal and linear techniques to 3.9% for purse-string technique and 4.0% for the patch technique, although the differences in these rates were not statistically significant (p=0.433). Kaplan-Meier estimates of overall survival rates were 85% at 1 year, 68% at 5 years, and 51% at 10 years. Overall median survival was 128 months. Long-term survival was best in those patients with good contractility of the nonaneurysmal LV (54%) and worst in those with impaired nonaneurysmal LV (35%) (p = 0.027).

Since Cooley's initial report on surgical aneurysm repair, new techniques have been developed and reported that attempt a more physiological and anatomical reconstruction of the residual ventricular cavity. The premise was that a more physiological reconstruction would result in a more normal ventricular function and a better long-term result. Stoney described in 1973 a repair technique in which the free lateral ventricular wall of the aneurysm is brought down and sewn to the scar along the septum [ref. 7]. With this technique, also the a- or dyskinetic septal scar could be excluded and should result in an increased LV ejection fraction. Jatene reported in 1985 a purse-string technique that incorporated a suture to close the neck of aneurysm [ref. 8]. Dor and Cooly reported - both in 1989 – the technique of using a prosthetic patch in the closure of the defect after aneurysmectomy [ref. 9, 10]. Also these techniques aimed to eliminate a- or dyskinetic scar in the interventricular septum and create a more physiologic reconstructed LV to improve postoperative hemodynamic measurement. Coltharp already discussed technical caveats that should be applied to aneurysm resection and LV reconstruction: too extensive a ventriculotomy and scar excision could encroach inadvertently on coronary arterial supply to viable muscle and extensive excision of scarred ventricles invited reconstruction of a ventricular cavity with compromised diastolic volume [ref. 1]. In patients with compromised diastolic volume, the restricted stroke volume causes cardiac output to becomes a function of pulse rate and may results in low cardiac output and pump failure.

With the technique described by Dor, the use of a endoventricular patch instead of a large resection, both preserves epicardial vessels and adequate ventricular volume

[ref. 11]. The Dor procedure excludes akinetic or dyskinetic portions of the ventricle, reshapes the ventricle with a stitch that encircles the transitional zone between contractile and non-contractile myocardium, and uses a small patch to reestablish ventricular wall continuity at the level of the purse-string suture [ref. 12]. The Dor procedure was initially perceived as a functional amputation of the ventricle with exclusion of the entire akinetic or dyskinetic scar. This led to increased sphericity of the ventricle in some patients, but in general the volume reduction still improved function. However, a suboptimal short axis/long axis ratio may influence the development of late moderate mitral regurgitation [ref. 13]. To prevent a compromised diastolic volume, to help configure the ventricle (ensuring a more normal short axis / long axis radio and to provide the correct position of the new apex, the use of a pre-shaped elliptical balloon (Chase Medical, Dallas, Tex) has been added to the procedure.

In our systematic review of the published peer-reviewed literature (62 studies; 12,331 patients) on the early and late outcome of LV reconstruction in ischemic heart disease, we found that (weighted) average early mortality was 6.9%. Cumulative 1-year, 5-year and 10-year survival were 88.5%, 71.5% and 53.9%, respectively. The Endoventricular Reconstruction (EVR) technique showed a reduced risk for both early ($RR = 0.79$, $p < 0.005$) and late ($RR = 0.67$, $p < 0.001$) mortality compared to the linear repair (early: $RR = 1.38$, $p < 0.001$; late: $RR = 1.83$, $p < 0.001$) confirming the improved outcome with a more physiological and anatomical reconstruction of the LV. Also of influence could be that patients that underwent EVR were operated in a more recent era with improved myocardial protection, anesthesiologic techniques, and perioperative care. Another contributing factor could be that revascularization further reduced the risk for late ventricular arrhythmias. These factors probably outweigh the increase in operative and extra-corporal circulation time with EVR and thus did not result in higher early mortality. Early and late mortality were mainly cardiac in origin, with as predominant cause heart failure in respectively 49.7% and 34.5% of the cases. Ventricular arrhythmias caused 16.6% of early deaths and 17.2% of late deaths. Concomitant CABG significantly decreased late mortality ($RR = 0.28$, $p < 0.001$) without increasing early mortality ($RR = 1.018$, $p = 0.858$). This decreased late mortality could be caused by a combination of a reduction in ischaemia and improvement in function of the remote non-scarred myocardium in the patients that underwent concomitant CABG. Concomitant mitral valve surgery showed both an increased risk for early ($RR = 1.57$, $p = 0.001$) and late mortality ($RR = 4.28$, $p < 0.001$). The presence of important secondary or functional mitral regurgitation (FMR) in patients with previous large anterior myocardial infarction is a marker of a more advanced disease state. The pathological mechanism behind it is either more

advanced LV dilatation, with tethering of the mitral valve leaflets, displacement of the subvalvular apparatus and dilatation of the mitral annulus causing incompetence of the mitral valve. The other possible mechanism is that the FMR could be caused by ischaemia or infarction in the postero-inferior wall of the LV or posterior papillary muscle complex in addition to the infarcted tissue in the anterior wall. Either way, the ventricular disease state in these patients with FMR is most probably more advanced.

One third of patients included in the review analysis were operated for HF (14 studies; 4,135 patients). In this group we noted an early mortality of 11.0% with a late mortality (3-year) of 15.2%. The EVR technique showed in these patients an even more profound reduction in relative risk (RR = 0.66, p = 0.004). An explanation could be that the patients that underwent LV reconstruction for heart failure, probably have larger LV volumes with more septal scarring. The linear technique cannot exclude the septal scar and carries the risk of creating a restrictive residual LV cavity, leading to compromised volume and increased diastolic dysfunction with LV failure as a consequence.

Risk stratification and predictors for mortality or poor functional outcome

Numerous studies have identified risk factors for mortality and limited survival after LV reconstruction in patients with HF, including renal insufficiency, severe mitral regurgitation, concomitant mitral valve surgery, and progressive LV dilatation, however no plain single risk variable is yet available to identify patients who would have a poor outcome and should not undergo LV reconstruction. These patients could better be referred for implantation of a left ventricular assist device (LVAD) or heart transplantation. Additionally, better patient selection and preoperative risk stratification will reduce mortality and improve outcome of LV reconstruction procedures. Colthard reported already in 1994 that hospital mortality in patients that underwent ventricular aneurysmectomy was related to the contractility grade of the remote myocardium [ref. 1] . About half of the patients he studied (231 out of 523) presented with congestive HF or angina with congestive HF. Mortality varied from 4.9% for patients with contractility Grade A (good contraction of nonaeurysmal anterior and inferior wall), 8.7% for patients with contractility Grade B (good contraction of nonaeurysmal anterior wall and hypokinesis of the inferior wall) to 15.7% for patients with contractility grade C (good contraction of nonaeurysmal anterior anterior wall and akinesis of the inferior wall; p=0.031). Five- and 10- year survival rates were 82% and 57% for patients with Grade A contractility, 72% and 38% for patients with Grade B contractility, and 60% and 42% for patients with Grade

C contractility. The difference in survival for Grade A and B approached statistical significance ($p = 0.096$), and the difference in survival between Grade A and Grade C was statistically significant ($p = 0.027$).

We tested echocardiographic wall motion score index (WMSI) as a predictor for mortality or poor functional result. WMSI was found to be the only statistically significant predictor for poor outcome (odds ratio 139, 95% confidence interval (CI) 17—1116, $p < 0.0001$). The optimal cut-off value for WMSI in predicting mortality or poor functional result was 2.19 with a sensitivity and specificity of 82% (95% CI 81.5—82.5% and 81.4—82.6%). The area under the curve was 0.94 (95% CI 0.90—0.99). We found that the echocardiographically derived WMSI has a good ability to predict outcome after SVR surgery. This was the single statistically significant predictor for poor outcome at 1-year follow-up. Other preoperative variables including age, renal insufficiency, severe pulmonary hypertension, and moderate to severe mitral regurgitation proved not to be significant predictors of outcome. Sufficient residual remote myocardium is necessary to recover from a SVR procedure and to translate the surgically induced morphological changes into a functional improvement.

We found that preoperative LVEF, LVESVI and LVEDVI were not statistically significant in predicting poor outcome after SVR surgery. This is interesting since White described already in 1987 that LV dilatation after myocardial infarction was more closely related to outcome then a decreased LVEF [ref. 14]. Di Donato and Dor confirmed that in ventricular restoration procedures, relatively irrespective of LVEF, the mortality increased in parallel to preoperative LV volumes [ref. 12]. The explantation could be that heterogeneity in the capacity for functional recovery of the residual remote myocardium might influence operative risk in patients with equally increased LV volumes. The post-infarction remodelled LV consists of heterogeneous tissue: scar (with varying degrees of transmurality), and residual myocardium with varying contractility. Volume derived indices are incapable of predicting outcome since these parameters depend on global ventricular measurements.

Our initial strategy to use the function of the basal pyramid (in line with the findings and work of Colthard on the remote myocardium) to select patients eligible for SVR surgery, proved to be insufficient: about one quarter of the patients did not benefit from the procedure (26 out of 101 patients: mortality 15 patients, NYHA class >/= III 10 patients). Indeed using the function of the basal pyramid takes into account only part of the LV and does not differentiate between normo- and hypokinesia. WMSI considers the entire LV and uses quantitative segmental function.

Quantification of scar

Cardiac magnetic resonance (CMR) is often used to assess ventricular shape, volume, and viability before a revascularization or ventricular reconstruction procedure. Hüther postulated that differences in the outcome should be reflected in the basal scar distribution, because the residual contractility of the ventricle is generated in this area and should be affected by scar tissue [ref. 15]. Patients with poor improvement of postoperative LVEF had more basal scar than those with large LVEF improvement. Of interest, they also found that only 22% of all improvements of regional function were located in segments that have received revascularization and 77% of all regional functional improvements were located in non-revascularized segments. This might indicate that the functional improvement may be more influenced by the SVR procedure than by revascularization.

Yamazaki et al. reported that the actuarial survival rate after isolated coronary artery bypass grafting (CABG) in patients with preoperative indexed LV end-systolic volume (LVESVI) of >100 ml/m2 was significantly worse than that in patients with LVESVI of ≤100 ml/m2 [ref. 16]. They also showed that congestive HF was more common among patients with LVESVI of >100 ml/m2. Using delayed-enhancement MRI, the mean percentage of hyper-enhancement in the entire LV area was 31 ± 12 (range 13–67%). The mean number of segments where scarring was >50% of the area (non-viable) was 4.5 ± 2.4, and the mean number of segments where scarring was >25% of the area (LV segments with MI) was 8.1 ± 2.8. The infarct size was significantly correlated with the LVEDVI, LVESVI and LVEF values. Moreover, the number of LV segments with MI was correlated with the LVEDVI, LVESVI and LVEF values, although the number of non-viable segments was not correlated with these values.

With regard to Laplace's law, a larger ventricle may receive greater benefit from volume reduction surgery; however, many reports have indicated that a larger LVESV was a significant risk factor after the SVR procedure. Patel et al. demonstrated that patients with LVESVI of >100 ml/m2 had a significantly increased mortality after SVR, whereas Athanasuleas et al. (in their RESTORE registry) reported that preoperative LVESVI of ≥80 ml/m2 was a risk factor for death after SVR [ref. 17, ref. 18].

The 2017 ESC/EACTS Guidelines on myocardial revascularization defined CABG with SVR for scarred LAD territory to be a class IIb recommendation if a postoperative LVESVI of <70 ml/m2 can predictably be achieved [ref. 19]. Di Donato et al. reported that SVR for patients with a relatively low LVESVI (<73 ml/m2) leads to a poor response and may even be useless [ref. 20]. They concluded that the LVESVI at follow-up in patients without reverse remodelling was not markedly large; hence,

without reverse remodelling, they would paradoxically show good survival. Skelley et al. indicated that patients with lower preoperative LVESVI had greater preoperative LVEF; however, there was no difference in preoperative LVEF or change in LVEF, compared with patients with larger LVESVI [ref. 20]. Consistent with these reports, we observed that patients with low LVESVI had the lowest likelihood of LVEF and LVESVI improvement at follow-up, although this did not affect their good clinical outcomes due to the fairly good baseline cardiac function.

Secondary or functional mitral regurgitation

As we have found in our structured review of published literature on early and late outcome after LV reconstruction surgery, the presence of important secondary or functional mitral regurgitation (FMR) in patients with previous large anterior myocardial infarction is a marker of a more advanced disease state. The presence of chronic secondary MR is associated with an impaired prognosis [ref. 21]. The pathological mechanism behind it is either more advanced LV dilatation, with tethering of the mitral valve leaflets, displacement of the subvalvular apparatus and dilatation of the mitral annulus causing incompetence of the mitral valve. The other possible mechanism is that the MR could be caused by ischaemia or infarction in the postero-inferior wall of the LV or posterior papillary muscle complex in addition to the infarcted tissue in the anterior wall. Either way, the ventricular disease state in these patients with FMR is clearly more advanced.

The most recent 2017 ESC/EACTS Guidelines for the management of valvular heart disease state that in contrast to patients with primary mitral regurgitation, there is currently no evidence that a reduction of FMR improves survival [ref. 22]. The guidelines furthermore highlight the importance of decision making by the Heart Team and that HF and electrophysiology specialists should be involved in the decision making. Controversy still exist on optimal surgical approach. Mitral valve repair with an undersized complete ring to restore leaflet coaptation and valve competence is the preferred technique according to the ESC/EACTS guidelines. However, valve replacement should be considered in patients with echocardiographic risk factors for residual or recurrent mitral regurgitation such as a mitral diastolic annulus diameter ≥37 mm, a systolic tenting area ≥1.6 cm2, and a severe functional ischaemic MR [ref. 4, 5]. The probability of recurrence of regurgitation after mitral valve repair could be as high as 50%. Indications for surgery in secondary mitral regurgitation are particularly restrictive when concomitant revascularization is not an option, owing to significant operative mortality, high rates of recurrent mitral regurgitation and the absence of a proven survival benefit.

The impact of LV reconstruction on FMR – both early and at late follow-up – is unclear, as is the indication for concomitant correction of FMR during LVR. On the one hand, immediate decrease of LV volumes and diameters, with the reduction of the distances between annulus and papillary muscles and between the papillary muscles, can lead to improved mitral valve leaflet coaptation [ref. 23-25]. Reduction of wall stress by the decrease in LV volumes and dimensions contributes to improvement in ventricular and papillary muscle function [ref. 8]. On the other hand, it is possible that LV reconstruction leads to a distortion of the geometry of the LV and subvalvular apparatus, causing an increase in MR. Moreover, possible further LV remodeling over time with gradual increase of LV volumes and diameters might lead to the appearance or recurrence of FMR at midterm follow-up if FMR is left untreated. Our management of FMR in patients undergoing LV reconstruction encompassed performing a restrictive mitral annuloplasty (RMA) when FMR ≥ grade 2+, established either preoperatively or immediately after LV reconstruction. Direct concomitant RMA was planned and performed in 38 out of 40 patients (95%) with preoperative MR ≥ grade 2+. In 17 out of 52 patients (33%) with FMR < grade 2+ preoperatively, FMR increased after LV reconstruction to ≥ grade 2+ leading to additional RMA during a second period of aortic cross-clamping. Early mortality in the RMA group (n = 55) was 12.7% and survival at 36 months 78.2 ± 11.2%. Early mortality in the no-RMA group (n = 37) was 5.4% and survival at 36 months 81.1 ± 12.8%. Patients in the RMA group had significantly more reduced LV function with greater LV dimensions and volumes preoperatively. As such, the presence or occurrence of at least moderate (grade 2+) FMR pre- or during surgery confirms to be marker of a more advanced disease state and translates into a higher early or in-hospital mortality. However, the combination of LV reconstruction with RMA (+/- CABG) leads to a sustained improvement in LVEF with reduction of LV volumes and equal survival in both patient groups. Also, recurrence-rate of FMR at late follow-up was low in both groups (1 patient per group).

Di Donato et al. propose to leave FMR grade 2+ untreated. They demonstrated an excellent survival; however, a substantial percentage of patients (29%) was found to have at least a moderate degree of FMR (grade 2+) at follow-up [ref. 27]. Prucz et al. demonstrated an overall reduction in FMR grade with good functional results and excellent survival in a group of patients who underwent LVR with untreated moderate MR. However, 76% of the patients still had MR > grade 2+ at follow-up [ref. 26]. As such, a conservative approach to FMR grade 2+ will leave a significant proportion of patients at risk for the potentially deleterious effects of FMR, which are further LV remodeling and increased mortality. As has been demonstrated, a moderate degree of FMR proves to be of hemodynamic importance in patients with reduced LV func-

tion and imposes significant clinical implications in post-infarction patients, even in those with minimal symptoms [ref. 29, 30]. In the setting of ischemic F .MR, even a regurgitant volume as little as 30 ml is associated with a limited 5-year survival of 47%.

We also evaluated 10-year clinical outcomes in 159 patients after an integrated approach of LV reconstruction with concomitant procedures (based on well-defined indications by the Heart team), and to assess preoperative risk factors for long-term clinical outcomes, focusing on LV geometry, LV function, and the presence of FMR. Concomitant mitral valve repair was performed in 68 of 70 patients with preoperative FMR ≥ grade 2. Mitral valve repair was not performed in 2 patients because of a completely calcified posterior mitral annulus. Preoperative FMR ≥ grade 2 was absent in 89 patients. Nonetheless, intraoperative TEE showed an increase in FMR to ≥ grade 2 immediately after LVR in 24 patients. These patients underwent additional mitral valve repair during a second period of aortic cross-clamping. Intraoperative echocardiography after mitral valve repair showed no more than mild FMR in any of the patients and a leaflet coaptation height of 8 ± 1 mm. This approach resulted in LV reverse remodeling (LVESVI –36%, improved LVEF +46%) and absence of FMR ≥ grade 2 at mid-term follow-up. Event-free survival 10 years after surgery was 46%. Increased age, higher preoperative WMSI, preoperative presence of MR ≥ grade 2 and a longer time interval after myocardial infarction were associated with worse event-free survival after surgery. Event-free survival is favourable in patients with WMSI < 2.5 and significantly worse when WMSI is ≥ 2.5. In both groups, the presence of preoperative MR grade ≥ 2 negatively affects event-free survival, despite successful correction of FMR. The presence of preoperative FMR negatively affected event-free survival in both patients with WMSI < 2.5 and WMSI ≥ 2.5 despite successful mitral valve repair. Consequently, the presence of preoperative FMR could be interpreted as a marker of LV remodeling. Advanced LV systolic dysfunction and presence of FMR provide a fatal combination. Preoperative LV volumes were not associated with adverse outcomes in the present study, in contrast to previous reports. However, the extent and function of the remote myocardium—and consequently the ability to recover after LV reconstruction surgery— may differ between patients with equally increased LV volumes. This heterogeneity in remote myocardium may explain why global ventricular measures such as LV volumes may not accurately predict event-free survival after LV reconstruction surgery.

We identified risk factors that can easily be determined and may help the Heart team to decide on which intervention to choose for patients with refractory HF with reduced Ejection Fraction (HFrEF). LV reconstruction surgery with concomitant

procedures is favourable for patients with a preoperative WMSI < 2.5— both with and without FMR, provided that the mitral valve is successfully repaired. In patients with WMSI ≥ 2.5 without MR, LVR may still be considered a viable option, however with slightly worse outcomes at longer follow-up. For patients with WMSI ≥ 2.5 and presence of FMR, event-free survival is extremely poor despite durable correction of MR. For these patients, the Heart team might first consider alternatives such as LVAD implantation or HTx. LV reconstruction surgery might still have a place in patients with contraindications for these alternatives, and in those for whom it might be warranted to defer LVAD implantation or HTx. Given that a longer interval between myocardial infarction and surgery was associated with adverse event-free survival, LV reconstruction surgery should preferably be considered in an early stage if patients develop symptoms of HF.

Incidence of ventricular arrhythmias and sudden cardiac death and the indication for ICD after LV reconstruction surgery

Sudden cardiac death (SCD) is an important cause of mortality in patients with both ischemic and non-ischemic heart failure. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) randomised 1,232 post-myocardial infarction patients with systolic dysfunction (LVEF ≤30%) to prophylactic ICD or conventional medical therapy [ref 31]. Unlike the earlier MADIT-I (1996) and MUSTT (1999) trials, MADIT-II did not require electrophysiologic testing for inducible ventricular tachyarrhytmia prior to enrolment [ref 32, 33]. After a mean follow-up of 20 months, the trial was terminated early because prophylactic ICD reduced all-cause mortality (14.2% vs. 19.8%; P=0.016; NNT=18). A post-hoc analysis demonstrated that the mortality reduction appeared to be entirely attributed to a reduction in SCD (3.8% vs. 10.0%; P<0.01). Interesting, ICD implantation was also found to be associated with a higher rate of new or worsened HF (20% vs. 15%). More recent, the SCD-HeFT trial demonstrated the mortality benefit of ICD's in patients with either ischemic or nonischemic cardiomyopathy (LVEF ≤ 35%) also in comparison to medical treatment with amiodarone and to placebo [ref. 34].

Since LVEF is used a selection criterium in patient with ischemic cardiomyopathy to qualify for prophylactic ICD implantation and SVR improves LVEF routinely to values above the selection criterium, the value of LVEF as criterium for ICD implantation in HF patients undergoing SVR was examined in a study. There is some theoretic or indirect evidence that SVR promotes electrical stability in the heart by different mechanisms [ref 35]. Thirty-seven consecutive patients with end-stage HF who underwent ICD implantation and SVR were evaluated. During admission, two-dimensional (2D) echocardiography (LV volumes and LVEF) was performed before

surgery and was repeated at 3 months after surgery. During 18-month follow-up, 12 (32%) patients had ventricular arrhythmias, resulting in appropriate ICD therapy. No significant relations existed between baseline LVEF (P = 0.77), LVEF at 3-month follow-up (P = 0.34), change in LVEF from baseline to 3-month follow-up (P = 0.28), and the occurrence of ICD therapy during 18-month follow-up. Hence, we concluded that LVEF before and after SVR is of limited use as criterium for ICD implantation in patients with end-stage HF since these patients remain at risk for malignant ventricular arrhythmias and hence may benefit from prophylactic ICD implantation. O'Neill et al. confirmed this finding in their study prospectively evaluating 217 consecutive patients with left ventricular ejection fractions less than 40% undergoing SVR [ref. 36]. They found an high early event rate of ICD-therapy (occurring in the first 90 days after SVR) that supports the use of pre-discharge electrophysiologic studies, implantation of ICD before discharge from the hospital, or both. A major limitation of the O'Neill study is that ventricular volumes are not measured before and after SVR. Ventricular volume before and after surgical intervention is crucial for arrhythmia development based on the following considerations. A large ventricular volume brings high wall stress and stretch, and stretch is arrhythmogenic [ref 37, 38]. Patients with ventricular arrhythmias (spontaneous or inducible) have end-diastolic and end-systolic volumes significantly larger than those seen in non-inducible patients and that patients who die at follow-up have the largest ventricular volumes[ref 39, 40]. The antiarrhythmic effect of SVR has been demonstrated by several groups and is related to volume reduction (less tension and stretch) and to the exclusion of the myocardial scar, which constitutes the trigger for electrical instability, but also to complete revascularization, which relieves ischaemia (another important component of electrical instability), and to mechanical resynchronisation which brings a more homogeneous distribution of wall tension and reduces regional pre-stretch [ref. 37, 41-42].

SVR procedure while reducing volume and wall stress and hence pre-stretch, leaves a large part of the substrate (myocardial scar) for ventricular arrhythmias in place. The question remains whether or not adding specific anti-arrhythmic surgical procedures, such as endocardectomy and cryoablation to patients undergoing SVR, will provide us with potentially curative treatment option for potentially fatal ventricular tachyarrhythmias. Furthermore, EP studies could be used after SVR when surgical intervention for ventricular tachyarrhythmias has been included to identify surgical failures in which ICD therapy is warranted. Sartipy et al. recently reported their experience with such a treatment in a series of 53 consecutive patients undergoing SVR and surgical intervention for ventricular tachyarrhythmias. The success

rate in terms of ventricular tachyarrhythmias-control in their experience proved to be 90% [ref 43].

More studies (randomised) and larger experience are needed to provide a correct indication for ICD in patients with dilated ischemic cardiomyopathy and symptomatic HF submitted to LV volume reduction and reshaping surgery.

Minimal-invasive / hybrid LV reconstruction (the future?)

SVR reduces the LV volume and reconstructs the shape of the remodelled LV leading to improvement in systolic function. Consensus from expert centres for SVR is that appropriately selected patients could benefit from a well-conducted procedure sufficiently reducing the LV end-systolic volume (LVESV) and reconstructing the elliptical shape of a normal LV. Conventional SVR relies on full median sternotomy, the use of extracorporeal circulation, cardioplegic arrest and ventriculotomy, which inflicts a considerable physical burden on often vulnerable patients with ischaemic heart failure. A less invasive procedure able to achieve the same results as conventional SVR is appealing and is a logic strategy to explore.

We evaluated the use of a novel hybrid transcatheter technique to reconstruct the remodelled LV by plication of the anteroseptal LV scar tissue which relies on the micro-anchoring technology of the Revivent TC Ventricular System (BioVentrix Inc. San Ramon, CA, USA). This system consists of a number of paired anchors connected by a poly-ether-ether-ketone (PEEK) tether that, once properly positioned, are pulled together with a controlled force by means of a specialised force gauge and finally released. The Revivent TC System represents the evolution of its previous fully surgical version. The Revivent system offers a minimally invasive strategy for LV reconstruction in HF patients with LV antero-apical scar and/or aneurysm. The procedural concept is similar to SVR, except that it utilises titanium anchor pairs on the beating heart. The decrease in the radius of the LV cavity reduces the myocardial wall stress (according to Laplace's law), thus leading to more efficient contractile function. This hybrid procedure is performed off-pump, under general anesthesia with fluoroscopic and echocardiographic guidance. The Revivent TC system implantation has several advantages compared to surgical LV aneurysm repair, as it does not require a median sternotomy, ventriculotomy, cardioplegia, extracorporeal circulation or aortic clamping, therefore it may result in reduced bleeding and air embolism risk, shorter recovery time and hospital stay.

The preliminarily experience regarding the early outcome of 9 patients that underwent implantation of the Revivent TC system between October 2016 and April

2017 by 2 Dutch Heart Centers (the Academic Medical Center Amsterdam, currently Amsterdam University Medical Center and the St. Antonius Hospital in Nieuwegein) were evaluated. Procedural success was 100%. On average, 2.6 anchor pairs were used to reconstruct the LV. Comparing echocardiographic data preoperatively and directly postoperatively, LV ejection fraction increased from 28 ± 8% to 40 ± 10% (change +43%, P < 0.001) and LV volumes decreased: LV end-systolic volume index (LVESVI) 53 ± 8 ml/m2 to 30 ± 11 ml/m2 (change -43%, P < 0.001) and LVEDVI 75 ± 23 ml/m2 to 45 ± 6 ml/m2 (change -40%, P = 0.001). Hospital mortality was 0%. The median duration of intensive care unit stay was 2 days [interquartile range (IQR) 1–46 days], and the median length of hospital stay was 9 days (IQR 3–57 days).

SVR procedures have demonstrated—in selected patients—that the dysfunctional myocardium can be favourably remodelled. When these preliminary results of the Revivent TC procedure are compared to (open) SVR, the efficacy of the LV reconstruction appears to be similar. Safety profile of the procedure and impact on the patient (median length of hospital stay 9 days) seem to be favourable. However, it must be stated that these preliminary results of the Revivent TC procedure in patients with ischemic HF, are observational and describe only the short term outcome. However, apart from a case report and an experimental paper of the technique in an ovine model, this was the first report describing the clinical results of this novel technique.

A larger and more thorough evaluation was done by reporting the first multicenter and multinational European experience with the Revivent TC system in a total of 86 patients, 51 of whom had the first-generation delivery system through median sternotomy and 35 had the procedure through the hybrid approach of mini-thoracotomy and internal jugular access. Eligible patients had LVEF 25-45%, LVESVi 60-120 mL/m2, NYHA class II-IV symptoms and an akinetic or dyskinetic scar in the anteroseptal, anterolateral and/or apical regions as a result of MI more than 90 days prior to enrolment. Patients with severe (4+) FMR were excluded. 30-day in-hospital mortality after Revivent TC System implantation was 4.5%, overall lower than the reported range of 3-14% 30-day mortality in SVR cohorts [ref. 48]. Furthermore, the estimated survival rate at 12 months post-procedure was very good (90.6%). At baseline, 59% of HF patients were in NYHA class III compared with 22% at 12-month follow-up. Improvements in quality of life measures (Minnesota Living with Heart Failure Questionnaire 39 vs. 26 points, P <0.001) and 6-min walking test distance (363 m vs. 416 m, P = <0.001) were also significant. Besides the substantial improvement in clinical and LV parameters, a significant FMR reduction of about 1 grade was also observed. Based on the above safety and efficacy data, CE marking was awarded, and the Revivent TC System has been available in Europe since 2016. To further as-

sess the clinical benefit of the Revivent TC System, the Randomized Evaluation and Verification of Ventricular Enhancement (REVIVE-HF) randomized-controlled trial is currently being conducted in Europe, comparing the Revivent TC System plus GDMT to GDMT alone in patients with HF and previous MI. 126 patients will receive the investigational device and 60 will remain on GDMT. The primary outcome is improvement in 6-minute walk test (6MWT) distance. Secondary outcomes include changes in Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, New York Heart Association (NYHA) class, LV volumes, and LVEF by CMR. Preliminary data in a small cohort of patients has demonstrated a significant reduction in LVESVI and LVEDVI along with improvements in LVEF and cardiac output measured with CMR at 12 months.

The American Less Invasive Ventricular Enhancement (ALIVE) is a prospective, multi-center, dual-arm pivotal trial of the Revivent TC system, being conducted in US and UK sites. 126 patients will be allocated in 2:1 fashion to the study device and GDMT groups respectively. The key qualifying criteria for Revivent TC implantation are LV dysfunction (LVEF<45%) and dilatation (LVESVi >50 mL/m2), NYHA III-IVa symptoms despite GDMT, and presence of contiguous, akinetic scar involving the septum, anterior, apical or anterolateral LV walls. The control group will consist of patients on GDMT who meet all the inclusion criteria, except that the LV aneurysm/scar location does not permit treatment with the study device or the patient had previous open-heart surgery, pericardiotomy or left thoracotomy. Key exclusion criteria include the presence of a calcified LV wall near anchor targets, thrombus/mass in LA or LV, more than moderate SMR or degenerative MR, recent MI or stroke, need for coronary revascularization, significant pulmonary hypertension, renal dysfunction, and prior open-heart surgery or pericardiotomy. Safety data from patients treated with the Revivent TC system will be compared with surgical outcomes from the Society of Thoracic Surgeons database on LV aneurysm repair. The primary endpoint is freedom from device-related major adverse events including all-cause death, myocardial infarction, stroke, non-elective cardiac surgery and worsening HF requiring mechanical support more than 24 hours. Secondary endpoints to be assessed include improvement in quality of life and clinical parameters (NYHA class, 6MWT distance and MLHF score) and reduction in HF-related hospitalization rates.

The question still remains of whether patients with ischemic receiving optimal GDMT who have already undergone complete (functional) revascularization but continue to demonstrate symptomatic HF with LV dilatation (with or without FMR), benefit from an isolated structural intervention specifically targeting the LV. Because of the overall high surgical risk of these patients, as well as the complexity and

highly invasive nature of SVR, percutaneous ventricular remodeling devices may appear more attractive, and enhance our ability to answer this question due to easier patient selection and identification of independent device related effects. However, it needs to be stressed that most of our surgical patients underwent concomitant procedure (ventricular arrhythmia surgery, mitral and tricuspid repair, CABG) and it is likely that these procedures accounted to some extent to the succes of the procedure.

REFERENCES

1. Coltharp WH, Hoff SJ, Stoney WS, Alford WC Jr, Burrus GR, Glassford DM Jr, Lea JW 4th, Petracek MR, Starkey TD, Shuman TA. Ventricular aneurysmectomy. A 25-year experience. Ann Surg. 1994 Jun;219(6):707-13; discussion 713-4
2. Schlichter J, Hellerstein HK, Katz LN. Aneurysm of the heart: a correlative study of 102 proved cases. Medicine 1954; 33:43-86.
3. 3. Faxon DP, Ryan TJ, David KB, et al. Prognostic significance of angiographically documented left ventricular aneurysm from the coronary artery surgery study (CASS). Am J Cardiol 1982; 50:157-164.
4. Beck CS. Operation for aneurysm of the heart. Ann Surg 1944; 120:34-40.
5. Bailey CP, Bolton HE, Nichols H, Gilman R. Ventriculoplasty for cardiac aneurysm. J Thorac Surg 1958; 35:37-66.
6. Cooley DA, Collins HA, Morris GC, Chapman DW. Ventricular aneurysm after myocardial infarction: surgical excision with the use of temporary cardiopulmonary bypass. JAMA 1958; 167:557.
7. Stoney WS, Alford WC Jr, Burrus GR, Thomas CS Jr. Repair of anteroseptal ventricular aneurysm. Ann Thorac Surg 1973; 15: 394-404.
8. Jatene AD. Left ventricular aneurysmectomy: resection or reconstruction. J Thorac Cardiovasc Surg 1985; 89:321-33 1
9. Dor V, Sarb M, Coste P, et al. Left ventricular aneurysm: a new surgical approach. Thorac Cardiovasc Surg 1989; 39:11-19.
10. Cooley DA. Ventricular endoaneurysmorrhaphy: a simplified repair for extensive postinfarction aneurysm. J Card Surg 1989; 4:200.
11. Dor V. Surgery for left ventricular aneurysm. Curr Opin Cardiol. 1990;5:773-80
12. Menicanti L, Di Donato M. The Dor procedure: what has changed after fifteen years of clinical practice? J Thorac Cardiovasc Surg. 2002 Nov;124(5):886-90.
13. 13 Di Donato M, Sabatier M, Dor V, et al. Effects of Dor procedure on left ventricular dimension and shape and geometric correlates of mitral regurgitation one year after surgery. J Thorac Cardiovasc Surg. 2001;121:91-6.
14. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44—51.
15. Hüther J, Doenst T, Nitzsche S, Thiele H, Mohr FW, Gutberlet M, .Hüther J, et al. Cardiac magnetic resonance imaging for the assessment of ventricular function, geometry, and viability before and after surgical ventricular reconstruction. J Thorac Cardiovasc Surg. 2011 Dec;142(6):1515-22
16. Yamazaki S, Doi K, Numata S, Itatani K, Kawajiri H, Morimoto K, Manabe K, Ikemoto K, Yaku H. Ventricular volume and myocardial viability, evaluated using cardiac magnetic resonance imaging, affect long-term results after surgical ventricular reconstruction. Eur J Cardiothorac Surg. 2016 Oct;50(4):704-712.
17. Patel ND, Williams JA, Barreiro CJ, Bonde PN, Waldron MM, Chang DC e al. Surgical ventricular remodeling for multiterritory myocardial infarction:defining a new patient population. J Thorac Cardiovasc Surg 2005;130:1698–706.

18. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, Di Donato M et al. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. J Am Coll Cardiol 2004;44:1439–45.
19. Sousa-Uva M, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2019.
20. Buckberg GD. Questions and answers about the STICH trial: a different perspective. J Thorac Cardiovasc Surg 2005;130:245—9.
21. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–1764
22. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL; ESC Scientific Document Group.2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21;38(36):2739-2791
23. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, Blackstone EH, Lytle BW. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol 2007;49:2191–2201
24. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL, Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–644
25. Kongsaerepong V, Shiota M, Gillinov AM, Song JM, Fukuda S, McCarthy PM et al. Echocardiographic predictors of successful versus unsuccessful mitral valve repair in ischemic mitral regurgitation. Am J Cardiol 2006;98:504–8
26. Prucz RB, Weiss ES, Patel ND, Nwakanma LU, Shah AS, Conte JV. The impact of surgical ventricular restoration on mitral valve regurgitation. Ann Thorac Surg 2008;86:726–34.
27. Di Donato M, Castelvecchio S, Brankovic J, Santambrogio C, Montericcio V, Menicanti L. Effectiveness of surgical ventricular restoration in patients with dilated ischemic cardiomyopathy and unrepaired mild mitral regurgitation. J Thorac Cardiovasc Surg 2007;134:1548–53
28. Menicante L, Di Donato M, Castelvecchio S, Santambrogia C, Montericcio V, Frigriola A, Buckberg G, the RESTORE group. Functional ischemic mitral regurgitation in anterior ventricular remodelling: results of surgical ventricular restoration with and without mitral repair. Heart Fail Rev 2004;9:317–27
29. Bolling SF. Mitral valve reconstruction in the patient with heart failure. Heart Fail Rev 2001;6:177–85
30. Grigioni F, Detaint D, Avierinos J-F, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. JACC 2005;45:260–7.
31. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-883

32. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia: Multi- center Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996; 335: 1933 – 1940.
33. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999 Dec 16;341(25):1882-90.
34. Bardy GH, et al. "Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure". The New England Journal of Medicine. 2005. 252(3):225-37.
35. Koilpillai C. Quinones M.A. Greenberg B. et al. Relation of ventricular size and function to heart failure status and ventricular dysrhythmia in patients with severe left ventricular dysfunction. Am J Cardiol. 1996; 77: 606-611
36. O'Neill JO, et al. Residual high incidence of ventricular arrhythmias after left ventricularreconstructive surgery. J Thorac Cardiovasc Surg. 2005. PMID: 16256775
37. Ulrik Sartipy, Anders Albåge, Dan Lindblom. Implantable cardioverter-defibrillator after left ventricular reconstruction? LTTE J Thorac Cardiovasc Surg. 2006 May;131(5):1210-1; author reply 1211. doi: 10.1016/j.jtcvs.2005.11.048.
38. Babuty D. Lab M.J. Mechanoelectric contributions to sudden cardiac death. Cardiovasc Res. 2001; 50: 270-279
39. Di Donato M. Sabatier M. Dor V. RESTORE group Surgical ventricular restoration in patients with post-infarction coronary artery disease: effectiveness on spontaneous and inducible ventricular tachycardia. Semin Thorac Cardiovasc Surg. 2001; 13: 480-485
40. Di Donato M. Sabatier M. Dor V. Buckberg G. RESTORE Group. Ventricular arrhythmias after LV remodelling: surgical ventricular restoration or ICD?. Heart Fail Rev. 2004; 9: 299-306
41. Mikleborough L.L. Merchant N. Ivanov J. Rao V. Carson S. Left ventricular reconstruction: early and late results. J Thorac Cardiovasc Surg. 2004; 128: 27-37
42. Di Donato M. Toso A. Dor V. et al. Surgical ventricular restoration improves mechanical intraventricular dyssynchrony in ischemic cardiomyopathy. Circulation. 2004; 109: 2536-2543
43. Sartipy U. Albåge A. Stråât E. Insulander P. Lindblom D. Surgery for ventricular tachycardia in patients undergoing left ventricular reconstruction by the Dor procedure. Ann Thorac Surg. 2006; 81: 65-71
44. Menicanti L, Castelvecchio S, Ranucci M, Frigiola A, Santambrogio C, de Vincentiis C et al. Surgical therapy for ischemic heart failure: single- center experience with surgical anterior ventricular restoration. J Thorac Cardiovasc Surg 2007;134:433–41.
45. Jones RH, Velazquez EJ, Michler RE et al. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009;360: 1705–17.
46. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM et al. Insights from the STICH trial: change in left ventricular size af- ter coronary artery bypass grafting with and without surgical ventricular reconstruction. J Thorac Cardiovasc Surg 2013;146:1139–45.e6.
47. Constantine L Athanasuleas 1 , Gerald D Buckberg, Alfred W H Stanley, William Siler, Vincent Dor, Marisa DiDonato, Lorenzo Menicanti, Sergio Almeida de Oliveira, Friedhelm Beyersdorf, Irving L Kron, Hisayoshi Suma, Nicholas T Kouchoukos, Wistar Moore, Patrick M McCarthy, Mehmet C Oz, Francis Fontan, Meredith L Scott, Kevin

A Accola, RESTORE Group **Surgical ventricular restoration: the RESTORE Group experience** Heart Fail Rev. 2004 Oct;9(4):287-97. doi: 10.1007/s10741-005-6805-4.

48. Velazquez EJ, Lee KL, O'Connor CM, Oh JK, Bonow RO, Pohost GM, Feldman AM, Mark DM, Panza JA, Sopko G, Rouleau JL, Jones RH, STICH Investigators. The Rationale and Design of the Surgical Treatment for IsChemic Heart failure (STICH) Trial. J Thorac Cardiovasc Surg. 2007;134: 1540–1547

Chapter 12

Thesis Summary

Chapter 1 is a general introduction to the subject of matter of this thesis. The disease of ischemic cardiomyopathy, the relation with heart failure as a clinical syndrome and its cause - obstructive coronary artery disease - are explained. The pathophysiology of myocardial infarction and (negative) cardiac remodelling are described, followed by its clinical characteristics and implications. Next, the rationale for surgical ventricular reconstruction and its history are described. Followed by an explanation of the STICH-trial, the first randomised controlled trial to address whether or not contemporary CABG surgery is superior to contemporary medical/ secondary prevention therapy in prolonging survival in patients with heart failure and whether or not the addition of surgical ventricular reconstruction (SVR) to CABG improves hospitalisation-free survival among patients with significant anterior wall dysfunction. Last, the position and outcome of SVR after the STICH-trial is described followed by a detailed description of the aims and outline of this thesis.

Chapter 2 focuses on the early and late outcome of left ventricular (LV) reconstruction surgery in ischemic heart disease. A systematic review of the literature was performed to determine early and late mortality associated with LV reconstruction surgery and to assess the influence of different surgical techniques, concomitant surgical procedures, clinical and hemodynamic parameters on mortality. The MEDLINE database (January 1980—January 2005) was searched and from the pooled data, hospital mortality and survival were calculated. Summary estimates of relative risks (RR) were calculated for the techniques that were used and for concomitant CABG and mitral valve surgery. The risk-adjusted relationships between mortality and clinical and hemodynamic parameters were assessed by meta-regression. A total of 62 studies (12,331 patients) were identified. Weighted average early mortality was 6.9%. Cumulative 1-year, 5-year and 10-year survival were 88.5%, 71.5% and 53.9%, respectively. Endoventricular reconstruction (EVR) showed a reduced risk for both early (RR = 0.79, $p < 0.005$) and late (RR = 0.67, $p < 0.001$) mortality compared to the linear repair (early: RR = 1.38, $p < 0.001$; late: RR = 1.83, $p < 0.001$). Early and late mortality were mainly cardiac in origin, with as predominant cause heart failure in respectively 49.7% and 4.5% of the cases. Ventricular arrhythmias caused 16.6% of early deaths and 17.2% of late deaths. Concomitant CABG significantly decreased late mortality (RR = 0.28, $p < 0.001$) without increasing early mortality (RR = 1.018, $p = 0.858$). Concomitant mitral valve surgery showed both an increased risk for early (RR = 1.57, $p = 0.001$) and late mortality (RR = 4.28, $p < 0.001$). No clinical or hemodynamic parameters were found to influence mortality. It is noteworthy that only one third of patients included in the current analysis were operated for heart failure (14 studies, 4135 patients). In this group we noted an early mortality of 11.0% with a late mortality (3-year) of 15.2%. This analysis of pooled literature data

showed that LV reconstruction surgery is performed with acceptable mortality and EVR may be the preferred technique with a reduced risk for early and late mortality. Concomitant CABG improved outcome, whereas the need for mitral valve surgery appeared an index of gravity. No clinical or hemodynamic parameters were found to influence mortality; specifically LV ejection fraction and LV volumes both did not predict outcome.

Advanced ischemic heart failure can be treated with SVR. While numerous risk factors for mortality and recurrent heart failure have been identified, no plain predictor for identifying SVR patients with left ventricular damage beyond recovery is yet available. In **Chapter 3**, echocardiographic wall motion score index (WMSI) was tested as a predictor for mortality or poor functional result after SVR. One hundred and one patients electively operated between April 2002 and April 2007 were included for analysis. All patients had advanced ischemic heart failure (NYHA-class ≥ III and LVEF ≤ 35%). Mean logistic EuroSCORE was 10 ± 8. All patients were evaluated at 1-year follow-up. Risk factors for poor outcome, defined as mortality or poor functional result (NYHA class ≥ III) at 1-year follow-up were identified by univariable logistic regression analysis. Preoperatively, a 16-segment echocardiographic WMSI was calculated and receiver operating characteristic curve analysis was used to identify cut-off values for WMSI in predicting poor outcome. Early mortality was 9.9%, late mortality 6.6%. NYHA class improved from 3.2 ± 0.4 to 1.5 ± 0.7. At 1-year follow-up, 10 patients (12%) were in NYHA class III and the remaining patients were in NYHA class I or II (75 patients, 88%). WMSI was found to be the only statistically significant predictor for poor outcome (odds ratio 139, 95% confidence interval (CI) 17 - 1116, $p < 0.0001$). The optimal cut-off value for WMSI in predicting mortality or poor functional result was 2.19 with a sensitivity and specificity of 82% (95% CI 81.5 - 82.5% and 81.4 - 82.6%). The area under the curve was 0.94 (95% CI 0.90 - 0.99). Positive and negative predictive values were 67% and 92% respectively (95% CI 66.4 - 67.6% and 91.4 - 92.6%). We concluded that sufficient residual remote myocardium is necessary to recover from a SVR procedure and to translate the surgically induced morphological changes into a functional improvement. Preoperative WMSI is a surrogate measure of residual remote myocardial function and is a promising tool for better patient selection to improve results after SVR procedures for advanced ischemic heart failure.

Remodelling of the LV in ischemic cardiomyopathy frequently leads to functional mitral regurgitation (MR). The indication for correcting MR in patients undergoing LV reconstruction (LVR) is unclear.T he study in **Chapter 4** was set out to evaluate our strategy of correcting MR ≥ grade 2+ by restrictive mitral annuloplasty (RMA)

during LVR. We studied 92 consecutive patients (76 men, mean age 61 ± 10 years) who underwent LVR for ischemic heart failure (IHF). RMA was performed in all patients with MR ≥ grade 2+ on preoperative echocardiography and in patients who showed increased MR to ≥grade 2+ immediately after LVR. Patients were attributed to a RMA and no-RMA group, depending on whether or not concomitant RMA had been performed. Mean clinical and structured echocardiographic follow-up was 47 ± 20 months and was 100% complete. In 38 out of 40 patients (95%) with preoperative MR ≥ grade 2+, concomitant RMA was planned and performed. In 17 out of 52 patients (33%) with MR < grade 2+ preoperatively, MR increased after LVR to ≥grade 2+ leading to additional RMA during a second period of aortic cross-clamping. Early mortality in the RMA group (n = 55) was 12.7% and survival at 36 months 78.2 ± 11.2%. Early mortality in the no-RMA group (n = 37) was 5.4% and survival at 36 months 81.1 ± 12.8%. Patients in the RMA group had significantly more reduced LV function with greater LV dimensions and volumes preoperatively. Echocardiography demonstrated sustained improvement in LVEF with reduction of LV volumes in both patient groups. Recurrence of MR at late follow-up was observed in 2 patients (1 patient per group). We concluded that patients with IHF eligible for LV reconstruction have MR ≥ grade 2+ in 44% of cases. In one-third of IHF patients with MR < grade 2+ preoperatively, MR increases to ≥ grade 2+ after LVR. Concomitant mitral valve repair for MR ≥ grade 2+, on either preoperative echocardiography or immediately after LVR, results in favourable late clinical and echocardiographic outcome that proved to be similar to patients without concomitant mitral valve repair, despite more advanced disease.

Chapter 5 describes the study to evaluate outcomes after an integrated approach of left ventricular reconstruction with concomitant procedures (mitral/tricuspid valve repair, coronary revascularization), and assess risk factors for event-free survival, focusing on left ventricular geometry/function and presence of functional mitral regurgitation (MR). A total of 159 consecutive heart failure patients who underwent left ventricular reconstruction between 2002 and 2011 were included. Mid-term echocardiographic and long-term clinical outcomes were evaluated. Preoperative risk factors were correlated to event-free survival (freedom from mortality, left ventricular assist device implantation, and heart-transplantation). Mid-term echocardiography demonstrated decreased indexed left ventricular end-systolic volumes(89 ± 42 mL/m2 preoperatively; 51 ± 18 at mid-term, p < 0.001), and absence of MR ≥ grade 2. Event-free survival was 83% ± 3% at 1-year, 68% ± 4% at 5-year, and 46% ± 4% at 10-year follow-up. Preoperative wall motion score index (WMSI; hazard ratio [HR] 3.1, 95% confidence interval [CI] 1.7–5.8, p < 0.001) and presence of MR ≥ grade 2 (HR 1.9, 95% CI 1.1–3.1, p [0.014) were independently associated with adverse event-free

survival. We concluded that event-free survival is favourable in patients with WMSI < 2.5 and significantly worse when WMSI is ≥ 2.5. In both groups, the presence of preoperative MR ≥ grade 2 negatively affects event-free survival, despite successful correction of MR. Risk stratification by preoperative WMSI and MR grade supports the Heart team in choosing the optimal surgical strategy for patients with refractory heart failure.

Besides implantation of an implantable cardioverter-defibrillator (ICD), a proportion of patients with LV dysfunction due to ischemic cardiomyopathy are potential candidates for surgical LV reconstruction (Dor procedure), which changes LV ejection fraction (LVEF) considerably. In these patients, LVEF as selection criterium for ICD implantation may be difficult. The study in **Chapter 6** aimed to determine the value of LVEF as criterium for ICD implantation in heart failure patients undergoing surgical LV reconstruction. Consecutive patients with end-stage heart failure who underwent ICD implantation and LV reconstruction were evaluated. During admission, two-dimensional (2D) echocardiography (LV volumes and LVEF) was performed before surgery and was repeated at 3 months after surgery. Over a median follow-up of 18 months, the incidence of ICD therapy was evaluated. The study population consisted of 37 patients (59 ± 11 years). At baseline, mean LVEF was 23 ± 5%. Mean left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were 175 ± 73 mL and 225 ± 88 mL, respectively. At 3-month follow-up, mean LVEF was 41 ± 9% ($P < 0.0001$ vs. baseline), and mean LVESV and LVEDV were 108 ± 65 mL and 176 ± 73 mL, respectively ($P < 0.0001$ vs. baseline). During 18-month follow-up, 12 (32%) patients had ventricular arrhythmias, resulting in appropriate ICD therapy. No significant relations existed between baseline LVEF ($P = 0.77$), LVEF at 3-month follow-up ($P = 0.34$), change in LVEF from baseline to 3-month follow-up ($P = 0.28$), and the occurrence of ICD therapy during 18-month follow-up. We concluded that LVEF before and after surgical LV reconstruction is of limited use as criterium for ICD implantation in patients with end-stage heart failure.

Chapter 7 to **Chapter 10** describe the hybrid left ventricular reconstruction. In **Chapter 7**, a novel hybrid transcatheter technique is described to reconstruct the remodelled LV by plication of the anteroseptal LV scar, in order to reduce the enlarged LV volume, decrease the wall stress and increase the EF. The procedure, called less invasive ventricular enhancement (LIVE), has the objective of reconstructing the LV by plication of fibrous scar and relies on micro-anchoring technology. This system consists of a number of paired anchors connected by a poly-ether-ether-ketone (PEEK) tether that, once properly positioned, are pulled together with a controlled force by means of a specialised force gauge and finally released. Both

sternotomy and extracorporeal circulation are avoided. Patients eligible for the procedure present with symptomatic heart failure (NYHA Class ≥II) and ischaemic cardiomyopathy (EF <40%) after anteroseptal MI resulting in a dilated LV with an akinetic/dyskinetic scar in the anteroseptal wall and apex. Preoperative planning requires gadolinium-enhanced magnetic resonance imaging (MRI) (or alternatively contrast computed tomography [CT]) to define the scar morphology clearly. Scarred regions must comprise at least 50% of the wall thickness to enable safe anchor implantation. The LIVE procedure is a hybrid transcatheter procedure performed by both an interventional cardiologist(IC) and a cardiothoracic surgeon (CTS) in co-operation. Additional support is provided by the presence of a cardiologist skilled in three-dimensional transoesophageal echocardiography (3D-TEE). This minimally invasive and off-pump technique has the promise of offering an effective LV reconstruction at lower risk in a very high-risk group of patients. The main limitation of this technique is represented by its applicability only in patients with previous antero-septal-lateral infarction, while patients with infarctions in other territories are not candidates for this procedure. In **Chapter 8**, we describe preliminary multicenter results of the LIVE procedure in the Netherlands. Between October 2016 and April 2017, 9 patients (8 men, 1 woman; mean age 60 ± 8 years) were operated on in 2 Dutch centres. Procedural success was 100%. On average, 2.6 anchor pairs were used to reconstruct the LV. Comparing echocardiographic data preoperatively and directly postoperatively, LV ejection fraction increased from 28 ± 8% to 40 ± 10% (change +43%, P < 0.001) and LV volumes decreased LV end-systolic volume index 53 ± 8 ml/m2 to 30 ± 11 ml/m2 (change -43%, P < 0.001) and LVEDVI 75 ± 23 ml/m2 to 45 ± 6 ml/m2 (change -40%, P = 0.001). In 1 patient, an RV perforation occurred which necessitated conversion to full sternotomy. One patient underwent a postoperative revision because of RV restriction. After the removal of 1 'RV-LV' anchor pair, the patient recovered completely. Hospital mortality was 0%. The median duration of intensive care unit stay was 2 days [interquartile range (IQR) 1–46 days], and the median length of hospital stay was 9 days (IQR 3–57 days). We concluded that hybrid transcatheter LV reconstruction is a promising novel treatment option for patients with symptomatic heart failure and ischaemic cardiomyopathy after anteroseptal MI and that the early results demonstrate that the procedure is safe and results in a significant improvement in EF and reduction in LV volumes in the early postoperative period. In **Chapter 9** we present 12-months follow-up data of an international (European) multicenter study of the LIVE procedure with BioVentrix Revivent TC System. Patients were considered eligible for the procedure when they presented with symptomatic HF [New York HeartAssociation (NYHA) class ≥II], left ventricular (LV) dilatation and dysfunction caused by myocardial infarction, and akinetic and/or dyskinetic transmural scarred myocardium located in the anteroseptal, anterolat-

eral, and/or apical regions. A total of 89 patients were enrolled and 86 patients were successfully treated (97%). At 12months, a significant improvement in LV ejection fraction (29 ± 8% vs. 34 ± 9%, P <0.005) and a reduction of LV volumes was observed (LV end-systolic and end-diastolic volume index both decreased: 74 ± 28 mL/m2 vs. 54 ± 23 mL/m2, P <0.001; and 106 ± 33 mL/m2 vs. 80 ± 26 mL/m2, respectively, P <0.0001). Four patients (4.5%) died in hospital and survival at 12months was 90.6%. At baseline, 59% of HF patients were in NYHA class III compared with 22% at 12-month follow-up. Improvements in quality of life measures (Minnesota Living with Heart Failure Questionnaire 39 vs. 26 points, P <0.001) and 6-min walking test distance (363 m vs. 416 m, P = <0.001) were also significant. We concluded that treatment with the Revivent TC System in patients with symptomatic HF results in significant and sustained reduction of LV volumes and improvement of LV function, symptoms, and quality of life. Finally, in **Chapter 11**, the challenges of surgical ventricular volume reduction and reshaping in ischemic heart failure patients is discussed together with the concept of a more individualised or patient-tailored approach.

NEDERLANDSE SAMENVATTING (SUMMARY IN DUTCH)

Hoofstuk 1 is een algemene introductie over het onderwerp van dit proefschrift. De ziekte ischemische cardiomyopathie, de relatie met hartfalen als klinisch syndroom en de oorzaak - obstructief coronairlijden - worden uitgelegd. Vervolgens wordt de pathofysiologie van het myocardinfarct en negatieve cardiale remodelering beschreven, gevolgd door de klinische kenmerken en de implicaties. Hierna wordt de rationale voor chirurgische ventriculaire reconstructie en de geschiedenis hiervan beschreven, gevolgd door een uitleg van de STICH-trial, het eerste gerandomiseerde onderzoek dat opgezet was of de hedendaagse coronaire bypass operatie (CABG) superieur is aan de hedendaags medicamenteuze / secundaire preventie therapie om de overleving van patiënten met hartfalen te verlengen en of het toevoegen van chirurgische ventriculaire reconstructie (SVR) aan een CABG de overleving zonder heropnames in het ziekenhuis verbeterd bij patiënten met significante linker ventrikel voorwand dysfunctie. Tenslotte wordt de positie en uitkomsten van SVR in de periode na de STICH-trial beschreven, gevolgd door een gedetailleerde beschrijving van de doelen en overzicht van dit proefschrift.

Hoofdstuk 2 spitst zich toe op de vroege en late uitkomsten van de linker ventrikel (LV) reconstructie chirurgie bij ischemische hartziekten. Een systematische review van de literatuur werd uitgevoerd om de vroege en late sterfte geassocieerd met de LV reconstructie chirurgie in kaart te brengen en de invloed van verschillende chirurgische technieken, aanvullende cardiale ingrepen, klinisch en hemodynamische parameters op de sterfte vast te stellen. De MEDLINE database (januari 1980 - januari 2005) werd doorzocht en vanuit de gepoolde data werden de ziekenhuissterfte en overleving berekend. Samenvattende schattingen van het relatieve risico (RR) werden berekend voor de gebruikte technieken en voor de aanvullende CABG en mitralisklepchirurgie. De risico-gecorrigeerde relaties tussen sterfte en klinische en hemodynamische parameters werden onderzocht door middel van meta-regressie analyse. In totaal werden er 62 studies (12,331 patiënten) geïdentificeerd. De gewogen gemiddelde vroege sterfte was 6.9%. Cumulatieve 1-jaars, 5-jaars and 10-jaars overleving was respectievelijk 88.5%, 71.5% en 53.9%. De EndoVentriculaire Reconstructie techniek (EVR) liet een lager risico zien voor zowel vroege ($RR = 0.79$, $p < 0.005$) als late ($RR = 0.67$, $p < 0.001$) sterfte vergeleken met de lineaire reconstructie (vroege sterfte: $RR = 1.38$, $p < 0.001$; late sterfte: $RR = 1.83$, $p < 0.001$). Vroege en late sterfte waren met name cardiaal van origine, met as belangrijkste oorzaak hartfalen in respectievelijk 49.7% en 4.5% van de gevallen. Ventriculaire ritmestoornissen waren de oorzaak bij 16.6% van de vroeg overledenen en bij 17.2% van de late doden. Aanvullende CABG verlaagde significant het risico op late sterfte ($RR = 0.28$, $p <$

0.001) zonder dat het risico op vroege sterfte hierdoor verhoogd werd (RR = 1.018, p = 0.858). Aanvullende mitralisklepchirurgie liet zowel een verhoogd risico op vroege (RR = 1.57, p = 0.001) en late sterfte zien (RR = 4.28, p < 0.001). Er werden geen klinische of hemodynamische parameters geïdentificeerd die van invloed waren op de sterfte. Vermeldenswaardig is dat slechts een derde deel van de patiënten in de huidige analyse geopereerd werden in verband met hartfalen (14 studies, 4135 patienten). In deze groep noteerden we een vroege sterkte van 11.0% met een late sterfte (na 3-jaar) van 15.2%. Deze analyse van gepoolde data uit de literatuur laat zien dat LV reconstructie chirurgie wordt uitgevoerd met een acceptable sterfte en dat EVR de techniek van voorkeur is met een verminderd risico op vroege en late sterfte. Aanvullende CABG verbeterd de uitkomst, terwijl de noodzaak voor bijkomende mitralisklepchirurgie een uiting van ernst van de ziek te lijkt te zijn. Geen klinische of hemodynamische parameters werden geïdentificeerd die van invloed waren op sterkte, in het bijzonder waren noch LV ejectiefractie noch LV volumina voorspellers de uitkomst na LV reconstructieve chirurgie.

Gevorderd ischemisch hartfalen kan worden behandeld middels SVR. Hoewel er vele risico factoren voor sterfte en recidief hartfalen zijn geïdentificeerd, is er tot op heden geen eenduidige voorspeller beschikbaar om SVR patiënten met schade aan de linker ventrikel die niet meer hersteld kan worden te identificeren. In **Hoofdstuk 3** werd echocardiografische wall motion score index (WMSI) getest als een voorspeller voor sterfte of slecht functioneel resultaat na SVR. Honderd en een patiënten die elective geopereerd zijn tussen april 2002 en april 2007 werden geïncludeerd voor analyse. Alle patiënten had gevorderd ischemisch hartfalen (NYHA-klasse ≥ III en LVEF ≤ 35%). De gemiddelde logistische EuroSCORE was 10 ± 8. Alle patiënten werden geëvalueerd na 1-jaar follow-up. Risico-factoren voor slechte uitkomst, gedefinieerd als overlijden of slecht functioneel resultaat (NYHA class ≥ III) na 1-jaar follow-up werden geïdentificeerd door middel van unitaristen logistische regressie analyse. Preoperatief werd er een 16-segmenten WMSI berekend en ROC-analyse werd gebruikt om afkapwaardes voor de WMSI om slechte uitkomst te voorspellen te identificeren. Vroege sterfte was 9.9%, late sterfte was 6.6%. De NYHA klasse verbeterde van 3.2 ± 0.4 to 1.5 ± 0.7. Na 1-jaar follow-up waren 10 patiënten (12%) in NYHA klasse III en de overige patiënten waren in NYHA klasse I or II (75 patiënten, 88%). WMSI bleek de enige statistisch significante voorspeller voor een slechte uitkomst (odds ratio 139, 95% confidentie interval (CI) 17 - 1116, p < 0.0001). De optimale afkap-waarde van de WMSI om sterfte of slechte functionele uitkomst te voorspellen was 2.19 met een sensitiviteit en specificiteit van 82% (95% CI 81.5 - 82.5% en 81.4 - 82.6%). De oppervlakte onder de curve was 0.94 (95% CI 0.90 - 0.99). Positieve en negatieve voorspellende waarden waren 67% en 92% respectievelijk (95% CI 66.4 - 67.6%

en 91.4 - 92.6%). Onze conclusie was dat voldoende residueel “remote myocardium” (myocardweefsel op afstand / niet betrokken bij het infarct) noodzakelijk is om te herstellen van een SVR procedure en om de chirurgisch gecreëerde morfologische veranderingen tot een functionele verbetering te kunnen laten leiden. Preoperatieve WMSI is een surrogaat maat voor residueel remote myocardiale functie en is een veelbelovende instrument voor een betere patiënt selectie om daarmee de resultaten na SVR procedure voor gevorderd ischemisch hartfalen te verbeteren.

Remodelering van de LV bij ischemische cardiomyopathie leidt frequent to functionele mitralisklepinsufficientie (FMI). De indicatie voor het corrigeren van FMI bij patiënten die een LV reconstructie (LVR) ondergaan is onduidelijk. De studie in **Hoofdstuk 4** was opgezet om onze strategie te evalueren om FMI ≥ graad 2+ te corrigeren door middel van een restrictieve mitralisklepannuloplastiek (RMA) gelijktijdig met de LVR. We onderzochten 92 opeenvolgende patiënten (76 mannen, gemiddelde leeftijd 61 ± 10 jaar) die een LVR in verband met ischemisch hartfalen (IHF) ondergingen. Er werd een RMA uitgevoerd bij alle patiënten met FMI ≥ graad 2+ bij preoperatieve echocardiografie en bij patiënten die een peroperatief een toename van de FMI naar ≥ graad 2+ lieten zien direct na de LVR. De patiënten werden toegeschreven aan een RMA en een geen-RMA groep, afhankelijk of er wel of geen bijkomende RMA bij hen was uitgevoerd. De gemiddelde klinische en gestructureerde echocardiografische follow-up na 47 ± 20 maanden en was 100% compleet. Bij 38 van de 40 patiënten (95%) met een preoperatieve FMI ≥ graad 2+ was er een bijkomende RMA gepland en uitgevoerd. Bij 17 van de 52 patients (33%) met FMI < grade 2+ preoperatief, nam de FMI na de LVR toe tot ≥ graad 2+, wat er toe leidde dat er een additionele RMA werd verricht tijdens een 2e klemtijd. De vroege sterfte in de RMA groep (n = 55) was 12.7% en de overleving na 36 maanden was 78.2 ± 11.2%. De vroege sterfte in de geen-RMA groep (n = 37) was 5.4% en de overleving na 36 months 81.1 ± 12.8%. Patiënten in de RMA groep hadden een significant meer gereduceerde LV functie met grotere LV dimensies en volumina preoperatief. Echocardiografie liet in beide patiënten groepen een stabiele verbetering in LVEF zien met een reductie in LV volumina. Recief FMI bij late follow-up werd gezien bij 2 patiënten (1 patient per groep). Onze conclusies waren dat bij patiënten met IHF die geschikt waren voor een LV reconstructie, in 44% van de gevalen sprake was een FMI ≥ graad 2+. Bij eenderde van de IHF-patiënten met preoperatief FMI < graad 2, neem de FMI na de LVR toe tot ≥ graad 2+. Bijkomende mitralisklepchirurgie in verband met FMI ≥ graad 2+ danwel bij preoperatieve echocardiografie of direct na LVR, resulteert in een gunstige late klinische en echocardiocardiografische uitkomst, die gelijk blijkt te zijn aan die van patiënten zonder bijkomende mitralisklepchirurgie, ondanks het

feit dat er bij de eerstgenoemde groep sprake was verdergevorderde stadium van de ziekte.

Hoofdstuk 5 beschrijft de studie om de uitkomsten te evalueren van een geïntegreerde benadering van linker ventrikel reconstructie met bijkomende procedures (mitralis-/tricuspidalisklep reparatie, coronaire revascularisatie) en om risicofactoren voor gebeurtenis-vrije overleving vast te stelen gefocussed op linker ventrikel geometrie/functie en de aanwezigheid van functionele mitralisklepinsufficientie (FMI). In totaal 159 opeenvolgende patiënten met hartfalen die een linker ventrikel reconstructie tussen 2002 en 2011 onderging werden geincludeerd in de studie. De middenlange termijns echocardiografische en lange termijn klinische uitkomsten werden geëvalueerd. Preoperatieve risicofactoren werden gecorreleerd aan overleving-zonder negatieve gebeurtenissen (geen sterfte, geen linker ventrikel assist device en harttransplantatie). Middenlangetermijns echocardiografie liet een afname van geïndexeerde linker ventriculaire eind-systolische volumina (89 ± 42 mL/m2 preoperatief; 51 ± 18 bij middellange termijn ,$p < 0.001$), en afwezigheid van FMI ≥ graad 2. Gebeurtenis-vrije overleving was 83% ± 3% na 1-jaar, 68% ± 4% na 5-jaar, and 46% ± 4% na 10-jaar opvolging. Preoperatieve wall motion score index (WMSI; hazard ratio [HR] 3.1, 95% confidentie interval [CI] 1.7–5.8, $p < 0.001$) en aanwezigheid van FMI ≥ graad 2 (HR 1.9, 95% CI 1.1–3.1, p [0.014) waren onafhankelijk geassocieerd met gebeurtenis-vrije overleving. We concludeerden dat gebeurtenis-vrije overleving gunstig is in patiënten met WMSI < 2.5 en significant slechter wanneer WMSI ≥ 2.5. In beide groepen beïnvloed de preoperatieve aanwezigheid van FMI ≥ graad 2 de gebeurtenis-vrije overleving negatief, ondanks succesvolle correctie van de FMI. Risico stratificatie op basis van preoperatieve WMSI en ernst van FMI ondersteunt het hartteam om de optimale chirurgische strategie te bepalen voor patiënten met hardnekkig hartfalen.

Naast implantatie van een implanteerbare cardioverter-defibrillator (ICD), is een deel van de patiënten met LV dysfunctie als gevolg van ischemische cardiomyopathie potentiele kandidaten voor chirurgische LV reconstructie (Dor-procedure), wat de LV erectie fractie aanzienlijk veranderd.Het gebruik van LVEF als selectiecriterium voor ICD-implantatie bij deze patient kan moeilijk zijn. De studie in **Hoofdstuk 6 b**eoogde de waarde van LVEF als criterium voor ICD-implantatie bij hartfalen patiënten die een chirurgische LV reconstructie ondergingen vast te stellen. Opeenvolgende patiënten met eind-stadium hartfalen die een ICD-implantatie en LV reconstructie ondergingen werden geëvalueerd. Tijdens opname werd er preoperatief een 2-dimensionaal echocardiogram verricht (LV volumina en LVEF) en dit werd 3 maanden postoperatief herhaald. Na een mediane opvolging van 18

maanden werd de incidentie van de ICD-therapie geëvalueerd. De studie bevatte 37 patiënten (59 ± 11 years). Op het beginpunt van de studie was de gemiddelde LVEF 23 ± 5%. De gemiddelde linker ventrikel eind-systolische volume (LVESV) en linker ventrikel eind-diastolische volume (LVEDV) waren respectievelijk 175 ± 73 mL end 225 ± 88 mL. Na 3 maanden opvolging was de gemiddelde LVEF 41 ± 9% (P < 0.0001 vs. beginpunt), en de gemiddelde LVESV en LVEDV respectievelijk 108 ± 65 mL en 176 ± 73 mL (P < 0.0001 vs. beginpunt). Tijdens 18-maanden opvolging hadden hadden 12 (32%) patiënten ventriculaire ritmestoornissen die resulteerden in passende ICD-therapie. Er waren geen significante relaties tussen beginpunt LVEF (P = 0.77), LVEF na 3 maanden opvolging (P = 0.34), verandering in LVEF van beginpunt tot 3-maanden opvolging (P = 0.28), en het optreden van ICD-therapie tijdens de 18 maanden opvolging. We concludeerden dat LVEF vóór en na chirurgische LV reconstructie van beperkt nut is als criterium voor ICD-implantatie bij patiënten met eind-stadium hartfalen.

Hoofstuk 7 tot **Hoofdstuk 10** beschrijven de hybride linker ventrikel reconstructie. In **Hoofdstuk 7** wordt een nieuw uitgevonden hybride transcatheter techniek beschreven om de geremodelleerde LV te reconstrueren door plicatie van het anteroseptale LV littekenweefsel om het vergrote LV volume te reduceren, de wandspanning te verminderen en de LVEF vergroten. Deze procedure, genaamd less invasive ventricular enhancement (LIVE) heeft al doel om de LV te reconstrueren door plicatie van het vezelige litteken en is gebaseerd op micro-anker technologie. Dit systeem bestaat uit een aantal gekoppelde ankers, die verbonden worden via een poly-ether-ether-ketone (PEEK) ketting of band, die - wanneer goed gepositioneerd - onder gecontroleerde kracht gemeten via een speciale krachtmeter samengetrokken worden. Zowel een sternotomie als hartlongmachine worden hierbij vermeden. Patiënten die in aanmerking komen voor deze procedure hebben symptomatisch hartfalen (NYHA klasse ≥II) en ischemische cardiomyopathie (EF <40%) na een antero-septaal MI, wat geresulteerd heeft in een gedilateerde LV met een akinetisch/dyskinetisch litteken in de anteroseptale wand en apex. Preoperatieve planning vereist gadolinium-versterkte magnetic resonance imaging (MRI) (of als alternatief computed tomography [CT] met contrast) om de morfologie van het litteken duidelijk vast te stellen. De gebieden met een litteken moeten tenminste 50% van de wanddikte omvatten om veilig anker implantatie mogelijk te maken. De LIVE procedure is een hybride transcatheter procedure die in samenwerking uitgevoerd wordt door een interventie-cardioloog (IC) en een cardiothoracaal chirurg (CT). Aanvullende ondersteuning wordt geleverd door de aanwezigheid van een cardioloog die bekwaam is in drie-dimensionale transoesofageale echocardiografie (3D-TEE). Deze minimaal-invasieve en 'off-pump' techniek belooft een effectieve LV recon-

structie tegen een lager risico aan te bieden aan een groep hoog-risico patiënten. De belangrijkste beperking van deze techniek wordt gevormd doordat deze alleen kan worden toegepast bij patienten met een eerder antero-septo-lateraal infarct, terwijl patienten met infarceringen in andere gebieden geen kandidaten voor deze procedure zijn. In **Hoofdstuk 8** beschrijven we de voorlopige multicenter resultaten van de LIVE procedure in Nederland. Tussen oktober 2016 and april 2017, werden er 9 patiënten (8 mannen, 1 vrouw; gemiddelde leeftijd 60 ± 8 jaar) geopereerd in 2 Nederlandse centra. Procedurele succespercentage was 100%. Gemiddeld waren er 2.6 paar ankers nodig om de LV te reconstrueren. Waneer de echocardiografische data van preoperatief en direct postoperatief worden vergeleken, nam de LV ejectiefractie toe van 28 ± 8% naar 40 ± 10% (verandering +43%, P < 0.001) en namen de LV volumina: LV eind-systolisch volume index van 53 ± 8 ml/m2 naar 30 ± 11 ml/m2 (verandering -43%, P < 0.001) en LVEDVI van 75 ± 23 ml/m2 naar 45 ± 6 ml/m2 (verandering -40%, P = 0.001). In 1 patiente trad er een RV perforatie op, die een conversie naar volledige sternotomie noodzakelijk maakte. Eén patient onderging een postoperatieve revisie in verband met RV restrictie. Na het verwijderen van 1 paar 'RV-LV' ankers herstelde de patient volledig. De ziekenhuissterfte was 0%. De mediane opnameduur op de intensive care was 2 dagen [interquartile range (IQR) 1–46 dagen], en de mediane duur van de ziekenhuisopname was 9 dagen (IQR 3–57 dagen). Onze conclusies waren dat hybride transcatheter LV reconstructie een veelbelovende nieuwe behandelingsoptie is voor patiënten met symptomatisch hartfalen en ischemische cardiomyopathie na een anteroseptaal MI en dat de eerste resultaten laten zien dat de procedure veilig is een leidt tot een significante verbetering in EF en vermindering van LV volumina tijdens de eerste postoperatieve periode. In **Hoofdstuk 9** presenteren we de 12-maanden opvolgingsdata van een internationale (Europese) multicenter studie van de LIVE procedure met het BioVentrix Revivent TC systeem. Patiënten kwamen in aanmerking komen voor deze procedure indien zij symptomatisch hartfalen (NYHA klasse ≥II) hadden , linker ventrikel (LV) dilatatie en dysfunctie veroorzaak door een myocard infarct en een kinetisch en/of dyskinetisch transmuraal myocardiaal litteken gelokaliseerd in de anteroseptaal, anterolateral en/of apicale gebieden. In totaal 89 patiënten werden geincludeerd en 86 patiënten succesvol behandeld (97%). Na 12 maanden werd een significante verbetering in LV ejectiefractie 29 ± 8% vs. 34 ± 9%, P <0.005) en reductie van LV volumina gezien (LV end-systolisch en eind-diastolisch volume index name beide af: respectievelijk 74 ± 28 mL/m2 vs. 54 ± 23 mL/m2, P <0.001; en 106 ± 33 mL/m2 vs. 80 ± 26 mL/m2, P <0.0001). Vier patiënten 4.5%) overleden in het ziekenhuis en de overleving na 12 maanden was 90.6%. Bij de aanvang van de studie was 59% van de hartfalen patiënten in NYHA klasse III, vergeleken met 22% na 12 maanden opvolging. Vebetering in kwaliteit van leven maten (Minnesota Living with Heart Failure

Questionnaire 39 vs. 26 punten , P <0.001) en 6-min. looptest (363 m vs. 416 m, P = <0.001) waren eveneens significant. Onze conclusies waren dat behandeling van patiënten met symptomatische hartfalen met het Revivent TC systeem resulteert in een significante en aanhoudende reductie van de LV volumina en verbetering van de LV functie, symptomen en kwaliteit van leven. Tenslotte worden in **Hoofdstuk 10** de uitdagingen van chirurgische ventriculaire volume reductie en hervorming bij patiënten met ischemisch hartfalen en het concept van een meer geïndividualiseerde or op maat gemaakt benadering van patiënten bediscussieerd.

Chapter 13

Curriculum Vitae

De auteur van dit proefschrift werd geboren op 19 mei 1977 in Oegstgeest. Na het middelbare schoolexamen (VWO - Atheneum) in 1995 volgde hij een summerschool natuurkunde aan het James Boswell Instituut in Utrecht en haalde hij aanvullende tentamens natuurkunde en scheikunde. Datzelfde jaar begon hij met de studie Geneeskunde aan de Universiteit Utrecht. In 1998 liep hij klinische stages bij de Cardiothoracale chirurgie, Plastische chirurgie en Kinderchirurgie in het St. Marianne University Hospital, Tokyo, Japan (begeleider: prof. dr. N. Yamate). Het doctoraalexamen werd behaald in 1999 en het artsexamen in oktober 2002. Hij deed zijn wetenschapsstage bij de afdeling Experimentele Cardiologie van het Academisch Ziekenhuis Utrecht (AZU, thans Universitair Medisch Centrum Utrecht - UMC Utrecht, begeleiders prof. dr. C. Borst en dr. P.F. Gründeman). Zijn keuze coschap liep de auteur bij de afdeling Cardiothoracale chirurgie van het UMC Utrecht (afdelingshoofd: prof. dr. A. Brutel de la Rivière)

In november 2002 begon hij als AGNIO Thoraxchirurgie in het St. Antonius Ziekenhuis Nieuwegein (maatschapsvoorzitter en opleider: dr. ir. H.A. van Swieten), gevolgd door een AGNIO-aanstelling per januari 2004 bij de afdeling Thoraxchirurgie van het Leids Universitair Medisch Centrum - LUMC, afdelingshoofd prof. dr. R.A.E. Dion). Van januari t/m september 2005 werkte hij als AGNIO Cardiologie in het UMC Utrecht (afdelingshoofd: prof. dr. P.A.F.M. Doevendans). Per 1 januari 2006 startte hij met de opleiding tot cardiothoracaal chirurg in het LUMC. De vooropleiding Algemene heelkunde werd gevolgd in het Gelre Ziekenhuis in Apeldoorn (opleiders: dr. W.H. Bouma en dr. E.J. Hesselink) van 1 januari 2006 tot en met 31 januari 2008. Daarna werd de opleiding Cardiothoracale chirurgie voltooid in het LUMC (opleiders: drs. M.I.M. Versteegh en prof. dr. R.J.M. Klautz). De goede ervaringen van de afdeling Thoraxchirurgie van het LUMC op het gebied van de chirurgische behandeling van hartfalen vormde de aanleiding voor de totstandkoming van dit proefschrift. Gedurende de periode dat de auteur als AGNIO en AGIO/AIOS in Leiden werkzaam was, werd hiervoor de basis gelegd. Aansluitend aan zijn opleiding tot cardiothoracaal chirurg werkte hij vanaf januari 2012 als staflid in het LUMC (afdelingshoofd: prof. dr. R.J.M. Klautz), waarna hij in januari 2013 toetrad tot de maatschap Cardiothoracale chirurgie van het St. Antonius Ziekenhuis in Nieuwegein. Sinds september 2014 vervult hij de rol van voorzitter van de maatschap. Persoonlijke aandachtsgebieden zijn - naast chirurgie voor hartfalen - reconstructieve klepchirurgie, aortachirurgie, minimaal-invasieve aortaklepchirurgie en de chirurgische behandeling van hypertrofische obstructieve cardiomyopathie In 2011 trouwde hij met Marleen A.D. Pietersen en samen hebben zij 4 kinderen: Stella (2012), Friso (2014), Thijme (2015) en Thibeau (2018).

Chapter 14

Dankwoord (Acknowledgements)

Graag besluit ik mijn proefschrift met het bedanken voor van iedereen zonder wiens inspiratie, hulp, steun en bijdrage over de afgelopen jaar dit niet tot stand had kunnen komen.

Professor dr. Klautz, beste Robert, vanaf onze allereerste kennismaking op de afdeling Thoraxchirurgie van het Leids Universitair Medisch Centrum in 2004 ben je altijd een inspirerend en motiverend rolmodel geweest (en ik geef ruiterlijk toe toch wel erg veel van jouw altijd goed doordachte operatietechnieken gekopieerd te hebben). Jouw onafgebroken persoonlijke support is cruciaal geweest voor de totstandkoming van dit proefschrift.

Professor dr. Braun, beste Jerry, ook jouw bijdrage aan dit proefschrift is majeur geweest. Veel dank voor je immer messcherpe en kritische wetenschappelijke blik, welke in combinatie met je spitsvondigheid nog altijd een groot voorbeeld zijn.

Dr. Swaans, beste Martin, als 'imaging interventionalist' behoor jij wat mij betreft onmiskenbaar tot de top. Onze voortdurende samenwerking op gebied van wetenschap, innovatie en dit proefschrift in het bijzonder waardeer ik – uiteraard tezamen met alle gezelligheid op locatie – zeer.

Emeritus professor dr. Dion, dank voor het vertrouwen om mij indertijd in opleiding te nemen en voor al uw support bij het wetenschappelijk onderzoek. Uw leidende rol op het gebied van mitralisklepchirurgie en chirurgie voor hartfalen was onmiskenbaar en uw slides met tekst in primaire kleuren staan op mijn netvlies gebrand.

Dr. Agostini, beste Pierfrancesco, veel dank ook aan jou voor de wetenschappelijke samenwerking. Jouw voortdurende streven naar innovatie op het gebied van transcatheter interventies, maar zeker ook de wetenschappelijke focus was inspirerend. Jammer dat we niet meer samenwerken in Nieuwegein.

Voormalig cardiothoracaal chirurg en opleider cardiothoracale chirurgie **drs. Versteegh**, beste Michel, ook jou ben ik veel dank verschuldigd. Zowel als opleider, maar zeker ook als technisch meester in de chirurgie voor hartfalen ben jij van groot belang geweest voor dit proefschrift.

(Voormalig) collegae cardiologen van het LUMC en in het bijzonder **professor dr. Bax**, **dr. Verwey** en **dr. Holman**, veel dank voor jullie steun en de samenwerking bij het onderzoek dat aan de basis ligt van dit proefschrift.

Graag wil ik ook alle andere cardiothoracaal chirurgen, arts-assistenten, datamanagers en medewerkers van het secretariaat van de Thoraxchirurgie van het LUMC bedanken. Jullie hebben allemaal direct of indirect bijgedragen aan de totstandkoming van dit proefschrift.

Dr. Petrus, beste Annelieke dank voor de fijne samenwerking bij een belangrijk hoofdstuk van dit proefschrift. Ik hoop dat je een heel succesvolle carrière in de huisartsgeneeskunde zult hebben.

Drs. Veltema, beste Gabrielle, dank voor al jouw hulp bij het afronden van de laatste loodjes van dit proefschrift.

Dr. van Putte, beste Bart, collega in de cardiothoracale chirurgie, wiens professionele wegen de mijne herhaaldelijk blijven kruisen. Dank voor alle goede gesprekken aan de bar doorheen onze carrières, maar zeker ook voor de huidige wetenschappelijke samenwerking en onze vriendschap. Ik was indertijd paranimf bij jouw promotie, veel dank dat je nu mijn paranimf wilt zijn.

Mijn maten cardiothoracale chirurgie in het St. Antonius Ziekenhuis, Thom, Hans, Bart, Edgar, Erik, Uday en Geoffrey: wij delen een b(l)oeiende praktijk, die op meerdere vlakken zelden saai is. Dank voor de samenwerking.

Pappa en mamma, dank voor jullie liefdevolle en nimmer aflatende support. Pap, dank voor de o zo belangrijke gesprekken laat op de avond met een glas wijn (uiteraard door mamma uitgekozen).

Cindy, lieve grote kleine zus en paranimf: wij zijn zo compleet anders, maar toch ook zo enorm hetzelfde. Veel dank voor al jouw steun en ook dat je naast me wil staan bij de verdediging van dit proefschrift.

Stella, Friso, Thijme en Thibeau, geweldige kinderen, jullie zijn echt mijn raison d'etre! Lieve Stella, dank voor de prachtige tekeningen in dit proefschrift en op de cover; je blijft me toch steeds verbazen! Lieve Thijme, op je vraag wanneer ik nu eindelijk eens een doctor wordt, is vandaag een antwoord gekomen.

Marleen, liefste, zonder jouw steun en talent om het thuis met ons drukke gezin zo goed te organiseren – en dit nog naast je eigen fulltime baan en carrière - was het nooit gelukt om dit proefschrift af te schrijven. Ik hou van je.