Left ventricular reconstruction in ischemic cardiomyopathy

Klein, P.

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

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