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Personalised surgical treatment of functional mitral regurgitation

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Personalised surgical treatment of functional mitral regurgitation

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Voor mijn ouders en zusje

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Chapter 1

General introduction

Background

Mitral regurgitation (MR) can be classified as either organic or functional. Organic MR – also known as primary MR – is caused by structural or degenerative abnormalities of the mitral valve leaflets, annulus, chordae tendinae or papillary muscles. In functional MR, on the other hand, the mitral valve is structurally normal and becomes insufficient due to a combination of annular dilatation, increased mitral leaflet tethering and decreased closing forces, as a consequence of regional or global left ventricular (LV) remodelling.[1] As such, it is also referred to as secondary MR. Based on aetiology of LV remodelling, functional MR can be classified as either ischaemic or non-ischaemic.

MR is the most common valvular heart disease in high-income countries. The estimated prevalence of moderate to severe MR is 1.7% in the overall population, markedly increasing to 9.3% in patients of 75 years and older.[2] Functional MR represents approximately 30-56% of patients with significant MR and is – regardless of aetiology – associated with adverse clinical outcome.[3, 4] Consequently, functional MR carries a substantial burden of disease, which is – given its association with increasing age, and the rising age of the European population – likely to increase.[5-7]

Over the past decades, tremendous advances have been made in the medical and device therapy of functional MR and many different surgical and percutaneous interventions have been introduced. However, functional MR comprises a very heterogeneous disease and the optimal surgical treatment strategy for patients with functional MR is still a topic of debate.

In this thesis the surgical treatment of patients with functional MR – with undersized or restrictive mitral annuloplasty as the mainstay – is investigated. In particular, long-term clinical and echocardiographic outcomes after surgery and preoperative identification of patients likely to benefit from each treatment strategy are explored, in order to personalise the surgical approach and optimise outcomes for each patient.

Anatomy and function of the mitral valve

The mitral valve – also known as the left atrioventricular valve – is a complex apparatus, comprised of the (saddle-shaped) mitral annulus, anterior and posterior mitral valve leaflets, subvalvular apparatus (consisting of the chordae tendinae and the anterolateral and posteromedial papillary muscles), and adjacent LV wall. This complex anatomical structure is finely tuned to actively facilitate the dynamic process of mitral valve opening – enabling unrestricted inflow of blood from the left atrium (LA) to the LV – during diastole, and mitral valve closing – preventing the passage of blood from the LV back into the LA – during systole.

The mitral valve opens at the beginning of diastole, when LV pressure decreases and becomes lower than LA pressure, resulting in a blood flow down the pressure gradient. Mitral valve closure involves several forces acting on the mitral valve. Mitral valve closure starts at the end of diastole and beginning of systole, with a decrease in mitral valve orifice area due to anterior movement of the aortic root, contraction of the atrial fibres encircling the posterior annulus and contraction of the LV base.[8, 9] The decreased mitral valve orifice area moves the anterior and posterior mitral leaflet together and enables the first phase of mitral valve closure. Further coaptation of the mitral valve leaflets is facilitated by contraction of the LV during systole. On the one hand, LV contraction causes inward movement of the LV wall and papillary muscles, thereby relieving traction on the chordae tendinae and mitral valve leaflets, resulting in decreased tethering forces. On the other hand, LV contraction increases LV pressure resulting in increased closing forces acting on the mitral valve. Together, the balance of decreased tethering and increased closing forces results in adequate mitral leaflet closure during systole, while preventing prolapse of the mitral valve leaflets into the LA. Disruption in any of the forces acting on the mitral valve may disturb this delicate balance and result in MR.[1, 10]

Pathophysiology of functional mitral regurgitation

Definition and pathophysiologic mechanisms

Functional MR can be defined as a disease condition in which the mitral valve becomes insufficient as a consequence of LV remodelling, whereas the valve itself is – at least macroscopically – normal. Consequently, functional MR should be distinguished from organic MR – MR caused by structural or degenerative alterations of the mitral valve – in the coincidental presence of LV disease. Furthermore, papillary muscle rupture due to an acute myocardial infarction can result in acute ischaemic MR requiring urgent cardiac surgery.[11] However, such acute MR represents a different subset of disease and is not discussed in this thesis.

Left ventricular remodelling is a term used to describe genome expression, molecular, cellular and interstitial changes in response to myocardial injury, manifested clinically as changes in LV size, geometry and function.[12] Depending on the aetiology of LV remodelling, functional MR can be defined as either ischaemic or non-ischaemic. Ischaemic MR results from regional or global ischaemia, myocardial infarction, or both. MR in non-ischaemic cardiomyopathy has a multifactorial aetiology, in which toxic damage (e.g. alcohol, cocaine), immune mediated and inflammatory damage, infiltration (e.g. malignancy, hemochromatosis), metabolic (hormonal and nutritional) derangements and genetic abnormalities may play a role.[13]

Functional MR develops when LV remodelling results in incomplete mitral leaflet closure due to a combination of mitral annular alterations, increased tethering forces and decreased closing forces.[1] In the past, development of functional MR was primarily attributed to mitral annular alterations (mitral annular dilatation, flattening of its saddle shape and loss of systolic annular contraction).[9, 14, 15] However, a study by Otsuji et al.,[16] demonstrated that patients with isolated mitral annular dilatation due to lone atrial fibrillation did not develop moderate or severe functional MR, whereas patients with LV dilatation and dysfunction, who had comparable annular sizes but greater tethering lengths, did frequently develop important MR. These data suggest that isolated mitral annular enlargement is insufficient to cause significant MR and that development of MR depends on an altered force balance on the mitral leaflets due to LV dilatation and dysfunction.[16] Increased mitral leaflet tethering forces are characterised by restriction of the mitral valve leaflets into the LV cavity, thereby preventing adequate mitral leaflet coaptation. Mitral leaflet tethering proved to be determined by outward (apical, posterior and lateral) displacement of the papillary muscles, which in turn was found to be associated with altered LV geometry.[17, 18] Several in vitro and animal studies suggested that local rather than global LV geometrical alterations are the primary determinant of increased mitral leaflet tethering.[19-21] In a clinical study, Yiu and co-workers indeed demonstrated that local LV remodelling is the primary determinant of mitral leaflet tenting and effective regurgitant orifice area (EROA) – independent of global LV remodelling.[17] Decreased closing forces due to reduced LV contractility and LV dyssynchrony, were found to contribute to the development of functional MR as well. However, an experimental study showed that outward papillary muscle displacement (tethering forces) with maintained LV pressures (closing forces) leads to MR, whereas a pharmacological reduction of LV contraction to a left ventricular ejection fraction (LVEF) < 20% without concomitant LV dilatation does not.[19] These findings were confirmed by clinical studies.[15, 17] Nowadays, functional MR is generally assumed to be primarily related to increased mitral leaflet tenting. However, concomitant mitral annular alterations and decreased closing forces do augment the effects of mitral leaflet tethering and further increase the severity of functional MR.[16]

The complex pathophysiological mechanism and forces involved in functional MR, explain why it comprises such a dynamic and heterogeneous disease. Severity of MR may vary with changing loading conditions and during exercise[22], as will be discussed later. Even during a cardiac cycle, severity of MR was found to vary, with a typical decrease in EROA at midsystole – at the time of peak LV closing forces.[23] Furthermore, the degree of LV dysfunction can highly vary among patients developing functional MR.[17] In patients with non-ischaemic cardiomyopathy, MR develops when considerable LV remodelling has taken place and is therefore always accompanied by heart failure. Ischaemic MR may develop in the same way when diffuse ischaemia or extensive infarction leads to global LV remodelling. However, more frequently ischaemic MR results from local LV remodelling, following local myocardial infarction or ischaemia. In this situation LVEF can be relatively preserved and symptoms of heart failure may not yet have become manifest. The location of a myocardial infarction therefore plays an important role in the development of ischaemic MR. For example, patients with an inferior myocardial infarction generally have more papillary muscle displacement and consequently more tethering and a higher severity of MR, compared to patients with an anterior infarction, even though an anterior infarction results in more global LV remodelling with higher LV volumes and lower LVEF.[24, 25]

The mitral valve and left ventricle

In functional MR, the LV suffers from both the intrinsic myocardial disease and from the volume overload that ensues with MR. The (sub)cellular rearrangements in response to this myocardial injury, result in repair of myocardial injury and scar formation, which may – to some extent – be considered beneficial. Initially, this remodelling process is associated with maintained or improved cardiac output, but at the expense of significantly increased LV volumes. Over time, when LV remodelling continues, these changes become pathological. Left ventricular size (end-systolic volume) progressively increases, resulting in a decline in LVEF and altered geometry (resulting in a more spherical rather than elliptical LV). Furthermore, progressive ventricular dilation leads to increased LV wall stress, which may precipitate the energy imbalance and increase myocardial oxygen demand – which in ischaemic cardiomyopathy is already limited – leading to even more LV dilatation and contractile dysfunction.[12, 26] Consequently, functional MR results in a vicious cycle of progressive LV remodelling and worsening of MR (**Figure 1**), in which it is difficult to distinguish the ventricular and valvular component. Due to this vicious cycle, functional MR is found to be associated with an increased risk of heart failure and adverse prognosis, as will be discussed in more detail later.

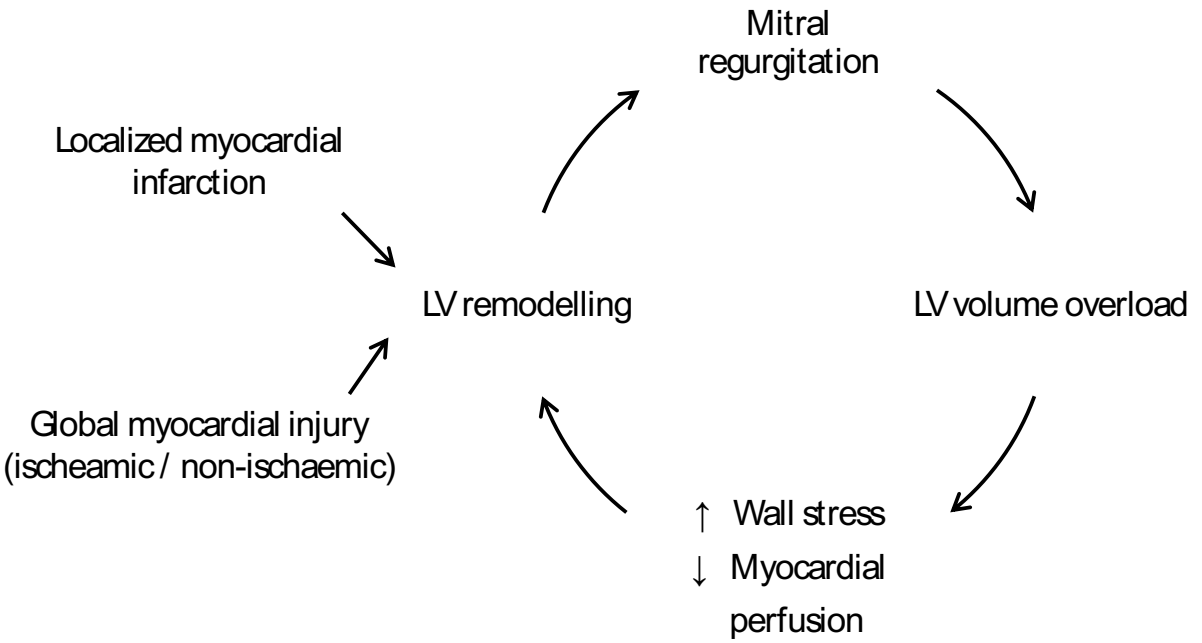

Figure 1. Vicious cycle of functional mitral regurgitation.

Many treatment options have been proposed to break the vicious cycle that ensues with functional MR. Their common aim is twofold: to restore mitral valve competence and initiate sustained LV reverse remodelling in order to improve clinical outcome. Left ventricular reverse remodelling, is a term used to describe an LV which is no longer in the circle of ongoing LV dilation and contractile dysfunction, but on a way back to a normal LV size, geometry and function. As in LV remodelling, the exact cellular and structural pathways of LV reverse remodelling are not fully elucidated. A decrease in LV size (volume or diameter) or improvement in LV function (LVEF) is often used as a clinical surrogate measure of reverse remodelling. Presence of LV reverse remodelling is associated with improved clinical outcome.[12, 27, 28]

Prevalence and clinical impact of functional mitral regurgitation

The exact epidemiology of functional MR is difficult to determine. Clinical assessment is imprecise since patients with functional MR are often asymptomatic and severity of symptoms (e.g. dyspnoea, fatigue) may be related to the underlying ventricular disease as well.[11] Furthermore, detection of a cardiac murmur lacks sensitivity and specificity, and the intensity of a murmur weakly correlates with the degree of MR, due to the decreased LV systolic function and atrial compliance.[11, 29-31] Consequently, the prevalence of functional MR can only be established by systematic echocardiographic assessment in a representative population. Available data regarding the prevalence and clinical impact of functional MR in the general population, following a myocardial infarction and in patients with heart failure will be discussed.

Mitral regurgitation in the general population

Data regarding the prevalence of (functional) MR in the general population is limited and the epidemiology of valvular heart disease has changed substantially over the past decades.[5]

In a population-based study investigating the prevalence of moderate to severe left-sided valvular heart disease by echocardiography in 11,911 patients in the United States, MR was the most commonly diagnosed valvular heart disease, with an overall prevalence of 1.7% and increasing with age to 9.3% in patients ≥75 years of age.[2] However, this study did not distinguish between different pathophysiological mechanisms of MR.[2]

In a community-based study in Olmsted county, isolated moderate or severe MR was diagnosed by echocardiography in 1,294 community residents.[32] The prevalence of MR in the overall adult population was 0.59% and increased with age. Secondary MR accounted for 56% of patients with MR. The 5- and 10-year survival rates of patients with secondary MR were 46% and 23% respectively, which was significantly lower than expected for the general county population of same sex and age (HR 2.7 [2.5 – 3.0], p <0.001).[32]

Finally, in a study including 63,463 patients referred for an echocardiogram in 19 European hospitals, moderate or severe MR was observed in 3,309 patients (5.2%).[3] Within this subgroup, 30% of patients had functional MR. Aetiology of functional MR was ischaemic in 51%, non-ischaemic in 32% of patients and unknown in 17%.[3]

Functional mitral regurgitation after myocardial infarction

Over the past decennia, the frequency and prognostic impact of functional MR after a myocardial infarction has been investigated in many studies. In the earliest reports, the prevalence of angiographically assessed functional MR ranged from 1.6 – 19%.[11] Currently, echocardiography is the recommended technique for assessment of MR, since it provides more adequate information on aetiology and severity of the regurgitation. An overview of studies reporting on the frequency of functional MR assessed by echocardiography, including >100 patients and published from the year 2000 onwards, is presented in Table 1. Reports regarding post-hoc analysis of randomised controlled trials (RCTs) and case-series are not discussed, since these studies are subject to selection and referral bias.

The reported prevalences of moderate to severe (or ≥ grade 2) functional MR after a myocardial infarction range from 6 – 37% (Table 1). This variation can be explained by the heterogeneity of the different reports. Study design was a cohort study in most reports,[33-38] whereas Bursi and co-workers were the first to perform a community-based study.[29] Furthermore, study populations are heterogeneous due to the fact that the definition of myocardial infarction has

changed over time and because some studies only included patients after a first myocardial infarction,[29, 36, 39] while others also included patients with a history of prior myocardial infarction or coronary artery disease.[33-35, 37, 38] The moment of imaging differed considerably between studies as well, with some performing an echocardiography within a few days to a week after myocardial infarction[33-38, 40-43] and others in the chronic phase.[29, 39] Finally, the method of quantification of the severity of MR varied between studies, with most reports using qualitative measurements (maximum regurgitant jet area)[29, 33-35, 38, 40, 43], whereas only a few reports used quantitative measurements (EROA, regurgitant volume [RVol]).[36, 37, 39, 42]

Survival 5 years after an acute myocardial infarction in patients with moderate to severe MR ranged from 67 – 37% (Table 1). In the study by Bursi et al.,[29] patients with moderate to severe MR had a 5-year survival of 40%, which was comparable to the 5-year survival rate of 38% in patients with MR in the study by Grigioni and colleagues.[39] In a report by Mentias and colleagues,[42] 4,005 patients underwent an echocardiography within 3 days following primary percutaneous coronary intervention for a STEMI. In this study, a graded association between severity of MR and survival was observed, with a 5-year survival of 84% in patients without MR, 77% in patients with grade 1 MR, 64% in patients with grade 2 MR, 46% in patients with grade 3 MR and 37% in patients with grade 4 MR.

The clinical impact of functional MR after a myocardial infarction was studied in many of the abovementioned reports (Table 1). An independent association between MR and increased all-cause mortality was observed in many reports, with hazard ratios for moderate to severe MR ranging from 1.7 to 5.0 (Table 1).[29, 33-35, 37-40, 42, 44] Even the presence of mild MR was found to be associated with adverse survival in several reports.[34, 35, 42] Grigioni et al. were the first to demonstrate that an EROA ≥20 mm^2 and RVol ≥30 mL are independently associated with mortality, which led to adjustment of the definition of severe functional MR in the guidelines, as will be discussed later.[39] Furthermore, an increased risk of heart failure was observed in patients with significant MR in several studies.[29, 33, 34, 36, 38, 40]

Presence of MR was found to be associated with clinical parameters such as increasing age,[29, 33-35, 37, 38, 40, 42-44] female gender,[29, 33, 34, 38, 40-42, 44] previous myocardial infarction,[33, 35, 38] diabetes,[33, 34, 38, 40] hypertension,[33, 35, 40] atrial fibrillation,[36] lower body mass index (BMI),[42] anaemia[42] and smoking.[33, 40, 42] Interestingly, studies regarding the association between MR and the location of myocardial infarction are conflicting. Although some reported that MR was associated with inferior[38, 42, 43] myocardial infarction, others observed no difference.[29, 35, 37, 40] The extent of myocardial infarction – assessed by Creatine Kinase[29] or Troponin I levels[34] – was not significantly associated with MR, and neither was the presence of STEMI compared to non-STEMI.[34] Echocardiographic parameters such as larger LV volumes[29, 44] and diameters,[34, 36, 40]

larger LA volume,[42] lower LVEF[29, 33, 36-38, 40-43], greater wall motion score index[29, 35, 36], higher sphericity[41] and higher RV pressure[29, 42] were associated with presence of MR. The association between MR and these echocardiographic parameters underlines the close relation between the mitral valve and LV, showing more (severe) MR in patients with more advanced LV remodelling. Finally, a longer door-to-balloon-time was found to be associated with the presence of MR as well[41, 42], indicating the need for rapid revascularization.

Functional mitral regurgitation in ischaemic or non-ischaemic heart failure

The epidemiology of functional MR in patients with heart failure has been described in many reports as well. An overview of the studies in which MR is assessed by echocardiography in a study population of >100 patients and published starting from the year 2000, is presented in Table 2.

The prevalence of moderate to severe (or ≥ grade 2) functional MR in patients with heart failure ranges from 20 – 60% (Table 2). As in the reports on the frequency of MR after a myocardial infarction, this wide variety can be explained by differences in study design, study population and the moment and method of echocardiographic assessment. Study design was cross-sectional in one report[31] and a cohort study in the other reports. Differences in study population are mainly due to variation in the definition of heart failure. Some studies simply state that patients with congestive heart failure were included without providing a further definition,[31, 45, 46] while others define heart failure by severity of LV dysfunction (LVEF <50%[47-49], ≤40%[50-52] or ≤35%[53-55]) or symptoms (New York Heart Association (NYHA) classification III/IV).[55] Except for one study including patients with non-ischaemic cardiomyopathy,[48] all studies included both patients with ischaemic and non-ischaemic heart failure. Of these reports, only two performed separate analysis for both aetiologies.[46, 55] Furthermore, severity of MR was either assessed using qualitative[49, 50, 52, 53] or quantitative parameters.[31, 45-48, 51, 54, 55] Finally, in only a few reports, patients received optimal guideline-directed medical therapy at time of inclusion.[47-49, 51]

Due to the abovementioned differences and due to variation in follow-up duration, survival rates of different reports are not comparable. The survival rates of each report are described in Table 2. Presence of moderate to severe MR was independently associated with all-cause mortality (HR 1.6 – 4.5) in many,[45, 46, 48-51, 53] but not in all reports.[47, 52, 54, 55] Moreover, moderate to severe MR was found to be related to heart failure hospitalizations or worsening heart failure symptoms in three reports,[47, 48, 54] whereas another study did not observe such a relation.[50]

Bursi and co-workers[49] performed a study in 469 patients with LVEF < 50% due to ischaemic (36%) or non-ischaemic (54%) cardiomyopathy, and observed absence of MR in 5%, grade 1

MR in 32%, grade 2 MR in 19%, grade 3 MR in 30% and grade 4 MR in 14% of patients. At 5 years follow-up, survival free of HTx was 83% in patients with no or grade 1 MR, 64% in patients with grade 2 MR, 59% in patients with grade 3 MR and 47% in patients with grade 4 MR. In this study, a worsening degree of functional MR was associated with a progressively increased risk of death or HTx (grade 3 MR: HR 2.0 [1.4– 3.0], grade 4 MR: HR 2.6 [1.6 – 4.1]), regardless of the aetiology of MR.

As mentioned, separate assessment of patients with ischaemic and non-ischaemic cardiomyopathy was performed in only two reports.[46, 55] Rossi et al.[46] included 1256 patients with chronic heart failure of which 27% had no MR, 49% had mild to moderate MR and 24% severe MR. Severe functional MR was a strong independent predictor for survival in both patients with ischaemic (HR 2.0 [1.4 – 2.7], p<0.001) and non-ischaemic (HR 1.9 [1.3 – 2.9], p = 0.002) cardiomyopathy. In patients with ischaemic cardiomyopathy, 5-year survival was 60% for patients with mild to moderate MR versus 23% in patients with severe MR; in patients with non-ischaemic cardiomyopathy, 5-year survival was 50% and 27%, respectively.

The presence of MR proved to be associated with clinical variables such as age,[46, 53, 54], worse NYHA functional class,[45, 46, 49, 51] and AF[51, 54], but also with echocardiographic characteristics namely lower LVEF[46, 47, 49, 51, 53, 54, 56]larger LV volumes,[45, 49, 50] LV diameters,[46, 53, 54, 56] and LA size,[45, 49, 53, 54, 56] degree of TR,[53, 56] and higher sPAP.[45, 56] These finding again demonstrate that an increasing MR prevalence is associated with increasing heart failure severity. However, Bursi and co-workers assessed the clinical impact of MR within different stages of heart failure and demonstrated that functional MR was an independent predictor of mortality in patients with NYHA class I-II, whereas in patients with NYHA class III-IV, MR was no longer a significant predictor of HTx-free survival after adjustment for confounders.[49] Similar findings were reported by Goliasch and co-workers[51] In this study, including 576 patients with heart failure (LVEF < 40%) receiving optimal medical therapy, 47% of patients had no or mild MR, 32% moderate MR and 21% severe MR. Increasing MR severity was independently associated with increasing mortality. However, after stratification for heart failure symptoms, severe MR was significantly associated with mortality in patients with NYHA class II (adjusted HR 2.2 [1.1 – 4.4], p = 0.03) and III (adjusted HR 1.8 [1.2 – 2.8], p = 0.008) but not in patients with NYHA class I (p = 0.73) or IV (p = 0.71). Furthermore, severe MR was associated with survival in patients with reduced LV function (LVEF 30-40%; adjusted HR 2.4 [1.4 – 4.2], p = 0.002), but not in patients with severely reduced LV function (LVEF < 30%; HR 1.3 [0.95 – 1.8], p = 0.10). The same applied for LV size (≤ moderately dilated LV; adjusted HR 2.0 [1.4 – 2.9], p <0.001 vs severely dilated LV: adjusted HR 1.4 [0.9 – 2.2], p = 0.11) and NT-proBNP levels (an association between severe MR and patients within the 2nd quartile of NT-proBNP (adjusted HR 2.2 [1.2 – 3.9], p = 0.009) but not within the 1st and 4th quartile). These results again reflect the complex interaction

between mitral valve and LV. Although MR seems to have a significant impact on clinical outcomes in patients with moderate degrees of heart failure, LV dysfunction rather than presence of MR seems to determine outcomes in patients with severe heart failure. This may also explain why some reports did not observe an independent association between functional MR and all-cause mortality and should be taken into account when considering surgical or percutaneous interventions to treat functional MR.

Overall, we can conclude that functional MR is a common phenomenon with an estimated prevalence of 6 – 37% following a myocardial infarction and 20 – 60% in patients with ischaemic or non-ischaemic heart failure. The prevalence of functional MR is higher in patients who are older, more often female and with a more advanced stage of LV remodelling. Presence of MR was found to have a graded and independent association with all-cause mortality and heart failure, which is already present in patients with only mild MR. However, in patients with severe heart failure outcomes seem primarily related to LV dysfunction rather than presence of MR.

Table 1. Prevalence and clinical impact of functional mitral regurgitation in patients after a myocardial infarction.

Study	n	Study population	TTE	Assessment	FU	LVEF	Prevalence of MR	Survival	HR and remarks
Abate 2016[44]	1599	STEMI treated with PCI + OMT	12 m	VCW, PISA	50 m	47±9%	30% grade 1 5% grade 2 3% grade 3	1 and 4 year: 98%, 93% no MR 93%, 86% with MR	MR ≥grade 2 independently associated with all-cause mortality (HR 1.7 [1.0-2.7]).
Aronson 2006[33]	1190	Acute MI survivors	2 [1-3] d	Max reg jet area	24 m	45%	40% mild 5.6% moderate 0.6% severe	3.3 years: 85% mild MR 67% moderate/severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 2.0 [1.2-3.4]) and HF (HR 3.6 [2.0-6.4]).
Barra 2012[34]	796	Acute MI (45% STEMI, 54% non-STEMI)	<1 w	Max reg jet area	24 m		55% none 30% mild 12% moderate 3% severe	2 years: 88% no MR 78% mild MR 62% moderate MR 61% severe MR	MR severity (each increment) independently associated with all-cause mortality (HR 1.4 [1.0-2.0]). No difference between STEMI/non-STEMI.
Bursi 2005[29]	757	First acute MI	<30 d	Max reg jet area	4.7 y	46±14%	50% none 38% mild 12% moderate/severe	5 years: 72% no MR 62% mild MR 40% moderate/severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 1.5 [1.1-2.0]) and HF (HR 3.4 [1.7– 6.8]).
Feinberg 2000[35]	417	Acute MI	< 48 h	Max reg jet area	1 y		65% none 29% mild 6% moderate/severe	1 year: 95% no MR 88% mild MR 76% moderate/severe MR	MR independently associated with 1-year mortality (HR 2.3 [1.0–5.2] for mild MR and HR 2.9 [1.0–8.5] for moderate/severe MR).
Grigioni 2001[39]	303	Q-wave MI	>16 d	RVol, EROA	5 y	33±13%	N/A	5 years: 61% without MR 38% with MR	MR independently associated with all-cause mortality (HR 1.9 [1.2-2.9]). ERO≥ 20mm2 and RVol ≥30ml independently associated with mortality. Study population: 194 patients with IMR matched to 109 without IMR
Lopez-Perez 2014[40]	1036	STEMI treated by primary PCI	< discharge	Max reg jet area	2.8 y	54%	45% none 44% mild 9% moderate	3 years FU: ± 98% no MR ± 97% mild MR	Moderate/severe MR independently associated with all-

							3% severe	± 95% moderate MR ± 80% severe MR	cause mortality (HR 3.1[1.3–7.2]) and HF (HR 3.3 [1.2–9.4]).
MacHaalany 2014[41]	174	STEMI treated by PCI	<1–3 d	Max reg jet area, VCW	366 d	46±12%	55% none 34% mild 11% moderate/severe	N/A	Moderate/severe MR independently associated with 1-year MACE (HR 2.6 [1.1 – 5.5]).
Mentias 2017[42]	4005	STEMI treated by primary PCI	<3 d	RVol, VCW, EROA, max reg jet area	5.9 y	45%	80% none 11% grade 1 6.5% grade 2 2.3% grade 3 0.7% grade 4	5 years: 84% no MR 77% grade 1 MR 64% grade 2 MR 46% grade 3 MR 37% grade 4 MR	MR independently associated with all-cause mortality (HR 1.3 for grade 1 MR, 1.7 for grade 2 MR, 2.4 for grade 3 MR and 2.5 for grade 4 MR).
Nunez-Gil 2013[36]	237	First non-STEACS and NYHA I-II	2 [1 – 3] d	EROA	7.0 y	56±15%	60% none 30% grade 1 6% grade 2 2.5% grade 3 1.3% grade 4	N/A	MR (per degree) independently associated with HF (HR 1.7 [1.1–2.6]) and MACE (HR 1.5 [1.2–1.9]).
Perez de Isla 2006[37]	300	First non-STEACS	<1 w	EROA	426 d	55%	63% grade 1 20% grade 2 14% grade 3 3% grade 4		MR independently associated with all-cause mortality (HR 5.0 [1.0–24]).
Persson 2010 [38]	725	ACS (STEMI n=343, non-STEMI n=256, unstable angina pectoris n=126)	<5 d	Color and continuous wave doppler	98 m		88% none/grade 1 12% ≥ grade 2	5 and 10 years: ±82%, ±75 no/grade 1 MR ±51%, ±30% ≥grade 2 MR	MR independently associated with all-cause mortality (HR 1.5 [1.1–2.2]) and HF (HR 2.1 [1.3 – 3.4]).
Uddin 2012[43]	888	STEMI treated by primary PCI	<72 h	Max reg jet area	3.1 y	48%	53% none/trace 36% mild 11% moderate/severe	5 years: 87% no/trace MR 82% mild MR 67% moderate/severe	After adjustment for age, moderate/severe MR not associated with survival (HR 1.3 [0.7 – 2.2]).

ACS = acute coronary syndrome, FU = follow-up, EROA = effective orifice area, HR = hazard ratio, LVSD = left ventricular systolic dysfunction, MI = myocardial infarction, MR = mitral regurgitation, NYHA = New York Heart Association, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, STEACS = ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction, TTE = transthoracic echocardiography, RVol = regurgitant volume, VCW = vena contracta width

Table 2. Prevalence and clinical impact of functional mitral regurgitation in patients with heart failure.

Study	n	Study population	Assessment	FU	LVEF	Prevalence of MR	Aetiology	Survival	HR and remarks
Agricola 2009[47]	404	≥ mild MR and HF (LVEF < 50%) receiving OMT	EROA, VCW	3.3 y	34±11%	41% mild 48% moderate 11% severe	77% IMR 24% NIMR	4 years: 64% mild MR 50% moderate MR 49% severe MR	Compared to mild MR, moderate/severe MR independently associated with cardiac mortality (HR 2.7 [1.2-6.1] and HF (HR 3.2 [1.9 – 5.2]), but not all-cause mortality.
Agricola 2011[48]	198	HF (LVEF < 50%), normal coronary vessels, receiving OMT	EROA, VCW	37 m	33±9%	35% none 32% mild 17% moderate 24% severe	100% NIMR	6 years: 72% no MR 63% mild MR 46% moderate MR 36% severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 2.1 [1.2-3.6]) and HF (HR 2.1 [1-4.5]).
Bruch 2007[45]	370	Congestive HF	VCW, EROA, RVol, max reg jet area	790 d	31±10%	10% none 65% mild/moderate 25% severe	56% IMR 44% NIMR	4 years, event-free survival: 81% no, mild or moderate MR 51% severe MR	Severe MR independently associated with all-cause mortality (HR 2.4 [1.4–4.1]).
Bursi 2010[49]	469	Congestive HF (LVEF < 50%) receiving OMT	Max reg jet area	5 y	30%	5% none 32% grade 1 19% grade 2 30% grade 3 14% grade 4	36% IMR 64% NIMR	5 years, HTx-free survival: 83% no/grade 1 MR 64% grade 2 MR 59% grade 3 MR 47% grade 4 MR	MR independently associated with event-free survival: MR grade 2 HR 1.3 [0.8–2.1], grade 3 (HR 2.0 [1.4– 3.0], grade 4 (HR 2.6 [1.6 – 4.1]).
Cioffi 2005[50]	175	HF (LVEF < 40%) and age >70 y	Max reg jet area	12 m	29%	80% no/mild MR 20% moderate /severe	51% IMR 49% NIMR	1 year: 90% no or mild MR 51% moderate or severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 4.5 [1.5–13.0]). No association MR and HF readmissions.
Goliasch 2018[51]	576	HF (LVEF < 40%) receiving OMT	VCW, EROA	62 m	27%	47% no/mild MR 32% moderate 21% severe	39% IMR 61% NIMR	N/A	Severe MR independently associated with all-cause mortality (HR 1.6 [1.2-2.1]).
Koelling 2002[53]	1436	HF (LVEF ≤ 35%)	Max reg jet area	369 d	20±5%	30% moderate 19% severe	59% IMR 41% NIMR	3 years: 57% mild MR 50% moderate MR 35% severe MR	Severe MR independently associated with all-cause mortality (HR 1.9 [1.4– 2.4]).

Mowakeaa 2018[42]	615	HF (LVEF ≤ 35%)	VCW, EROA, RVol, max reg jet area	2.9 y	27%	29% none 31% mild 40% moderate/severe	65% IMR 26% NIMR 4% mixed 5% unknown	3 years: ±82% no MR ±68% mild MR ±60% moderate or severe MR	MR associated with all-cause mortality (mild MR: HR 1.6; moderate/severe MR: HR 2.6), but not after adjustment for covariates. MR independently associated with HF hospitalizations (mild MR HR 1.7, moderate/severe HR 2.2).
Patel 2004[55]	558	HF (LVEF ≤ 35% and NYHA III/IV)	EROA, RVol, max reg jet area	5 y	21±7%	10% none 51% mild/moderate 22% moderate 17% moderate/severe	54% IMR 46% NIMR	5 years: 25% for IMR 54% for NIMR	MR not independently associated with all-cause mortality (moderate/severe MR HR 0.99 [0.8–1.3]).
Robbins 2003[52]	221	Congestive HF (LVEF ≤ 40%)	Max reg jet area	47 m	28±8%	59% moderate/severe (74% in-hospital patients, 45% outpatients)	Not specified	5 years: 81% none or mild MR 61% moderate or severe MR	MR not independently associated with all-cause mortality. Study population: 111 in-hospital patients, 110 outpatients.
Rossi 2011[46]	1256	Chronic HF	EROA, VCW, RVol	2.7 y	32±8%	27% none 49% mild/moderate 24% severe	61% IMR 39% NIMR	5 years: IMR: 60% mild-moderate MR 23% severe MR NIMR: 50% mild-moderate MR 27% severe MR (at 4 years)	Severe MR independently associated with all-cause mortality (HR 2.0 [1.5–2.6]; IMR HR 2.0 [1.4–2.7] and NIMR HR 1.9 [1.3–2.9]).
Varadarajan 2006[31]	370	Congestive HF	Max reg jet area, EROA, VCW	n/a	21±12%	5% none 44% grade 1 22% grade 2 15% grade 3 14% grade 4	39% IMR 61% NIMR	n/a	

FU = follow-up, EROA = effective orifice area, HF = heart failure, HR = hazard ratio, IMR = ischaemic mitral regurgitation, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, NIMR = non-ischaemic mitral regurgitation, NYHA = New York Heart Association, OMT = optimal medical therapy, TTE = transthoracic echocardiography, RVol = regurgitant volume, VCW = vena contracta width

Assessment of functional mitral regurgitation

Echocardiographic assessment of functional mitral regurgitation

Echocardiography is the recommended imaging technique for the assessment of functional MR.[57, 58] Two-dimensional transthoracic echocardiography (TTE) is usually the first-line imaging modality to assess the presence, severity and impact of functional MR. However, transoesophageal echocardiography can be performed if TTE is suboptimal or to obtain additional information on for example mitral valve geometry or eligibility for interventional/surgical procedures. A 3D echocardiography may provide an even more comprehensive evaluation of mitral valve morphology and is increasingly being used. Echocardiography also allows assessment of LV and LA geometry and function, right ventricular geometry and function, pulmonary artery pressure and function of the other valves.[59, 60]

Mitral valve morphology

Functional MR is characterised by restricted mitral leaflet closure during systole and can be classified as class IIIb according to Carpentier's classification (Table 3).[61] Restriction of the mitral leaflets can be symmetric (resulting in a central regurgitant jet) when restriction of both mitral leaflets results in incomplete coaptation, which is seen in patients with non-ischaemic cardiomyopathy and in patients with global ischaemia or after an anterior/inferior myocardial infarction. On the other hand, asymmetric restriction of the posterior mitral leaflet can be observed in patients with local LV remodelling after a posterior myocardial infarction, resulting in the so-called 'sea-gull sign' and an eccentric regurgitant jet.[59, 60]

Table 3. Carpentier's classification of mitral regurgitation.[61]

Type I	Normal leaflet motion
Type II	Excessive leaflet motion
Type III	Restrictive leaflet motion; restricted leaflet opening during diastole/systole (IIIa) or restricted leaflet closure during systole (IIIb)

Assessment of the severity of functional mitral regurgitation

Evaluation of the severity of MR should be performed pre-operatively. Since functional MR is dynamic and dependent on loading conditions, intra-operative assessment may lead to an underestimation of its severity due to decreased contractility and loading conditions caused by administration of general anaesthesia. [22, 60, 62, 63]

Severity of functional MR should be assessed by an integrative approach, using a combination of qualitative and quantitative parameters, as recommended by both the European and

American echocardiography societies.[59, 60] Qualitative findings include mitral valve morphology and visualization of the colour flow and continuous wave regurgitant jet. Semi-quantitative measures include vena contracta width, pulmonary vein flow and mitral inflow patterns. Finally, quantitative parameters of MR severity include EROA and RVol. Additional LV and LA dilation, and increased systolic pulmonary arterial pressure are supportive for severe functional MR. No single criterion is sufficient to establish the severity of MR.[59, 60]

The regurgitant colour flow jet area into the LA can provide information on the presence and direction of the jet and a semi-quantitative assessment of its severity. In general, a larger jet area represents more severe MR. However, the colour flow area of the regurgitant jet is dependent on many technical and haemodynamic factors (such as LA size and pressure) and is therefore not recommended to quantify the severity of MR.[59, 60]

The vena contracta is the narrowest area of the jet, just at or beyond the regurgitant orifice area, and is characterised by high velocities and laminar flow. The cross-sectional area of the vena contracta reflects the EROA – which is the narrowest area of actual flow – and can be used to quantify MR. The size of the vena contracta is independent of flow rate and driving pressure for a fixed orifice. However, if the EROA is dynamic, such as in functional MR, the vena contracta may vary with changing haemodynamics or during the cardiac cycle. Furthermore, the vena contracta area is based on the assumption that the regurgitant orifice is circular. Although the orifice is fairly circular in organic MR, it is usually crescent along the coaptation line of the mitral valve leaflets rather than circular in functional MR.[59, 60]

The flow convergence or proximal isovelocity surface area (PISA) is the most recommended approach to quantify the severity of MR. This method is derived from hydrodynamic principles, stating that as blood approaches a regurgitant orifice, its velocity increases and forms concentric shells of increasing velocity and decreasing surface area. The radius (r) of PISA is measured at mid-systole. Flow rate (Q) through the regurgitant orifice is than calculated as the hemisphere surface area multiplied by the aliasing velocity: $Q = 2\pi r^2 * V_{a.}$ The maximal EROA is assumed to occur at the time of peak regurgitant flow and peak regurgitant velocity (V_{pkreg}), and is consequently derived as: $EROA = (2\pi r^2 * V_a)/V_{pkreg.}$ The RVol can be estimated as the product of the estimated EROA and the velocity time integral (VTI) of the regurgitant jet: RVol = EROA * VTI. The PISA method provides a peak flow rate. EROA estimated by PISA is therefore the maximal EROA and may be slightly larger than EROA derived by other methods. Furthermore, the PISA method is based on the assumption that the velocity distribution proximal to the circular regurgitant orifice has a symmetric hemispheric shape. However, in functional MR, PISA may have an ellipsoid shape and two separate jets (one from the medial

and one from the lateral side of the coaptation line). In that case, the PISA method may underestimate severity of MR.[59, 60]

Pulsed wave Doppler can be used for the quantification of MR when the PISA and VC method are not accurate or applicable. Mitral regurgitant volume is then estimated by calculating the difference between total stroke volume and systemic stroke volume. However, this calculation is time-consuming and inaccurate in the presence of significant aortic regurgitation.

Defining the severity of functional mitral regurgitation

The guidelines' recommendations regarding the cut-off values to define severe functional MR have been changed several times.[57-60, 64, 65] Currently, the threshold for severe functional MR is defined as an EROA of ≥ 40 mm^2 and an RVol of ≥ 60 ml in the guidelines of the American College of Cardiology/American Heart Association[58] and American Society of Echocardiography[60], which is consistent with the threshold for severe organic MR. In the European guidelines,[57, 59] these cut-off values apply for organic MR as well. However, the guideline on the management of valvular heart disease of the European Society of Cardiology[57] states "In secondary mitral regurgitation, lower thresholds have been proposed to define severe mitral regurgitation compared with primary mitral regurgitation [20 mm^2 for EROA and 30 ml for RVol], owing to their association with prognosis.". The guideline of the European Association of Echocardiography[59] states "In functional ischaemic MR, an EROA ≥ 20 mm^2 or an RVol ≥ 30 ml identifies a subset of patients at an increased risk of cardiovascular events".

The threshold for identifying patients with severe functional MR remains a topic of debate.[66-68] The rationale for adjusting the threshold of severe functional MR is that the risk of total and cardiac mortality in patients with ischaemic MR with an EROA ≥ 20 mm^2 or an RVol ≥ 30ml were found to be high.[39, 48] Furthermore, quantifying the severity of functional MR is challenging compared to organic MR, as pointed out before. In functional MR, the reduced total LV forward stroke volume and crescent shaped regurgitant orifice may result in underestimation of RVol, EROA and vena contracta width. Consequently, a lower EROA cut-off may still quantify severe functional MR. However, those in favour of an EROA of ≥ 40 mm^2 and a RVol of ≥ 60 ml as threshold for severe functional MR argue that it is not clear whether the prognostic significance of an EROA ≥ 20 mm^2 is primarily due to the MR itself or to confounding factors such as age, LV status, the underlying heart disease and comorbidities. Furthermore, they argue that lowering the threshold to define severe functional MR, may also lower the threshold for (surgical) interventions, while RCTs have not yet proven a survival benefit for correction of MR.[68]

Further research is warranted to refine the severity criteria for functional MR. More accurate and reproducible measurements of vena contracta and EROA may be provided by 3D echocardiography, which is gaining more and more ground. In the meantime, it is important to keep in mind which definition of severe MR is used when interpreting results of studies on the treatment of functional MR.

Exercise echocardiography

Exercise echocardiography may be useful in evaluating patients with functional MR. Since functional MR comprises a dynamic phenomenon, exercise may unmask the presence of symptoms and an exercise induced increase in MR severity.[57, 60, 69] The preferred method to quantify severity of MR during exercise is EROA derived by PISA, although it may be technically challenging due to tachypnoea and tachycardia.[60, 69] The Doppler method is an alternative if the flow convergence region is inappropriate for PISA. The regurgitant jet is not reproducible and should not be used.[69]

Pathophysiologic mechanisms involved in an increase in MR severity during exercise are LV dilatation due to an increase in volume load, and LV dyssynchrony due to a rate-dependent conduction delay.[70, 71] Significant contractile reserve – in particular of the postero-basal segment – and/or a reduction in LV dyssynchrony, on the other hand, may decrease tethering forces and consequently reduce the severity of functional MR during exercise.[71, 72]

Functional MR severity was found to increase during exercise in over 75% of patients with heart failure, with both ischaemic and non-ischaemic aetiology.[70-74] Interestingly, predictors of increasing MR during exercise all proved to be related to (local) LV geometry – which in turn was related to papillary muscle displacement and mitral valve tenting.[72] These findings indicate that increased tethering forces are the primary mechanism for increased MR severity during exercise.

An exercise-induced increase in functional MR proved to be associated with poor exercise capacity.[73, 75] The mechanism for the association between dynamic MR and impaired exercise capacity was found to be the inability to increase forward stroke volume during exercise, and the fact that LA and pulmonary artery pressure increased excessively. Furthermore, a study by Lancellotti et al. showed that an increase in EROA of $\geq 13mm^2$ during exercise in patients with heart failure was observed in 30% of patients, and was associated with increased mortality and hospital readmissions for heart failure.[76, 77] Additionally, a resting EROA $\geq 20mm^2$ was associated with adverse clinical outcome as well – which supports the lower threshold of severe functional MR, as adopted in the European guidelines.[76]

Other imaging techniques

Cardiac magnetic resonance imaging (MRI) may provide additional information and can be considered when echocardiographic images are suboptimal or when there is a discrepancy between clinical symptoms and severity of MR by echocardiography. Cardiac MRI can provide highly accurate information on the mechanism and severity of MR. Since severity of MR is assessed by the difference between LV stroke volume and forward stroke volume, its evaluation does not rely upon the characteristics of the regurgitant jet. Furthermore, cardiac MRI is the golden standard for assessment of LV and LA volume and function and provides additional information on myocardial fibrosis (scar) and viability, which may have important implications for surgical intervention. When compared to echocardiography, disadvantages of cardiac MRI are its limited availability, higher costs, and uncertainty about safety in patients with metallic implants such as pacemakers and/or cardiac resynchronization/defibrillator devices.[60, 78]

Finally, multi-slice computed tomography may also provide a comprehensive assessment of mitral valve geometry and anatomy of the subvalvular apparatus. Furthermore, multi-slice computed tomography allows a detailed analysis of the papillary muscles and their relation with the adjacent LV wall. Such information may be of value to guide surgical procedures for functional MR, especially procedures addressing the subvalvular apparatus or LV geometry. A disadvantage of multi-slice computed tomography is the associated radiation exposure.[79]

Treatment of functional mitral regurgitation

The treatment of functional MR is included in many guidelines.[13, 57, 58, 65, 80-85] Optimal medical and device therapy are the cornerstone in the treatment of patients with functional MR. In patients with persisting MR and symptoms of heart failure despite optimal medical and device therapy, more invasive treatment options may be considered.[13, 57, 58, 65, 80-85] In line with the broad spectrum of disease and different aetiologies involved in functional MR, many interventions have been proposed, aiming at the mitral valve (mitral valve repair, mitral valve replacement or percutaneous interventions), the subvalvular apparatus (papillary muscle interventions), the LV (coronary artery bypass grafting (CABG), implantation of a CorCap cardiac support device (CSD) or left ventricular reconstruction [LVR]), or a combination thereof. In patients unlikely to benefit from these interventions, HTx or implantation of a left ventricular assist device (LVAD) may be considered.

The wide variety of treatment options reflect the fact that the optimal treatment strategy for patients with functional MR remains a topic of debate. Recommendations in the guidelines are not unequivocal and are based on many heterogeneous – predominantly observational – studies, whereas data from RCTs is scarce. The guidelines' recommendations on mitral valve interventions for the treatment of functional MR are summarised in Table 4.

This thesis will focus on the surgical treatment of functional MR, by mitral valve repair using an undersized or restrictive mitral annuloplasty ring. Mitral valve repair is always combined with optimal medical and device therapy, and for specific indications concomitant surgical procedures – such as CABG, LVR and implantation of a CSD – are performed. Alternative (surgical) interventions, such as subvalvular procedures, mitral valve replacement, percutaneous interventions and implantation of an LVAD, are beyond the scope of this thesis and will therefore only briefly be discussed in Chapter 2.

Optimal medical therapy

Optimal medical therapy – according to the guidelines for the treatment of heart failure – is the mainstay of therapy for patients with functional MR.[13, 57, 58, 83] Optimal medical therapy includes the administration of angiotensin converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers [ARBs]/angiotensin receptor neprilysin inhibitors [ARNIs]), beta-blockers and mineralocorticoid/aldosterone receptor antagonists (MRAs). These drugs proved to reduce the risk of heart failure hospitalization and death in patients with heart failure and should be up-titrated to the maximum tolerated target dose. Furthermore, diuretics are recommended

in patients with signs and symptoms of congestion. In specific situations, other drugs such as digoxin, hydrazaline and isosorbide dinitrate can be considered.[13]

Potential mechanism of individual drugs on the treatment of functional MR

Data regarding the effect of individual heart failure drugs on the severity of functional MR are limited. We may however understand their potential effect by relating the pharmacological mechanism of each drug to the balance of forces involved in functional MR.

ACE inhibitors reduce the activity of the renin-angiotensin-aldosteron system by blocking the conversion of angiotensin I to angiotensin II and the breakdown of bradykinin. Consequently, they reduce ventricular pre- and afterload by inducing arterial and venous vasodilation, depressing sympathetic activity and promoting renal natriuretic and diuretic effects. Additionally, ACE inhibitors were found to inhibit cardiac remodelling. ARBs and ARNIs have similar effects. ARBs can be considered in patients not able to tolerate ACE inhibitors. ARNIs can be considered as a replacement for an ACE inhibitor in patients who remain symptomatic despite treatment with an ACE inhibitor, beta-blocker and MRA.[13]

Beta-blockers block the effects of (nor)epinephrine by binding to beta-adrenoreceptors and thereby reduce the deleterious effects of chronic sympathetic activation in patients with heart failure. Long-term administration of beta-blockers is associated with decreased pre- and afterload (by reducing peripheral vasoconstriction), improved myocardial contractility (due to restored beta-receptor responsiveness of the myocardium, reduced myocardial oxygen consumption and increased diastolic perfusion), and a lower heart rate and risk of arrhythmias. Finally, chronic administration of beta-blockade was found to have beneficial effects on LV remodelling.[86, 87]

MRAs inhibit the action of aldosterone. As such, these drugs have modest diuretic and natriuretic effects, resulting in a decrease in pre- and afterload. Furthermore, MRAs reduce the risk of LV remodelling, myocardial fibrosis and arrhythmias (due to decreased fibrosis and preservation of serum potassium levels).[88]

Diuretics increase excretion of sodium and water, thereby decreasing preload due to reduced blood volume and venous pressure. Long-term administration of diuretics may also reduce afterload by promoting systemic vasodilation.[89]

The impact of the abovementioned drugs on preload, afterload and LV remodelling, and consequently their potential effect on mitral leaflet tethering, closing forces and EROA, are summarised in Table 5. Preload reducing medication – such as diuretics – unload the LV and decrease LV volumes, which may result in reduced mitral leaflet tethering and consequently a

reduction in EROA. Furthermore, a decrease in preload may enhance closing forces, since LA pressure is reduced more than systolic LV pressure and since reduced LA overstretching may enhance LA contractility. A decrease in afterload – as caused by ACE inhibitors – can relieve mitral leaflet tethering by decreasing LV volumes and improving LV geometry. As a consequence of pre- and afterload reduction, LV wall stress and subsequently myocardial oxygen demand decrease which may improve myocardial contractility. Improved myocardial contractility may improve both closing forces (due to increased LV pressure) and tethering forces (due to improved geometry) acting on the mitral valve. Myocardial contractility may improve after long-term administration of beta-blockers as well. Finally, several drugs were found to reduce LV remodelling. Reverse remodelling may increase closing forces due to improved contractility and decrease tethering forces due to reduced LV dilation and improved LV geometry. Consequently, these drugs may reduce severity of functional MR by this mechanism as well.[70, 90]

Table 5. Potential effect of heart failure medication on the forces involved in functional MR.

	Preload	Afterload	LV remodelling	Closing force	Tethering force	EROA
ACEI	↓	↓↓	↓	=↑	↓	↓
BB	↓	↓	↓	=↑	↓	↓
MRA	↓	↓	↓	=↑	↓	↓
Diuretics	↓↓	=	=	↑	↓	↓↓

ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; EROA = effective regurgitant orifice area; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation

Impact of optimal medical therapy on functional mitral regurgitation and outcomes

The impact of guideline-directed optimal medical therapy on functional MR has been investigated by Nasser and co-workers. In this study, the clinical management of 163 patients with heart failure (LVEF ≤ 40%) was standardised according to the heart failure guidelines and doses of heart failure medications were titrated to the maximally tolerated dose. At baseline, 31% of patients had severe functional MR. After optimization of medical therapy, 38% (19 of 50) of patients with severe functional MR evolved to non-severe MR, whereas 18% (21 of 113) of patients with non-severe MR evolved to severe MR. Patients with sustained severe functional MR or a deterioration to severe MR had increased LV end-diastolic volumes and significantly worse prognosis (MACE, mortality and hospitalizations for heart failure or VT/VF) compared to patients without severe functional MR or with improvement in MR.[91] Other studies also demonstrated that functional MR is still frequently observed in patients receiving optimal medical therapy, and that presence of functional MR despite optimal medical therapy is associated with adverse prognosis.[47-49, 51]

Recently, the Pharmacological Reduction of Functional Ischemic Mitral Regurgitation (PRIME) trial was conducted in South-Korea.[92] In this trial, 118 patients with heart failure and functional MR were randomised to receive valsartan (an ARB, n = 58) or sacubitril/valsartan (a novel complex of an ARB and an ARNI, n = 60). A significantly greater decrease in EROA was observed in the sacubitril/valsartan group (–0.058 cm^2 or –30%) compared to the valsartan group (–0.018cm^2 or –9%, p = 0.032). A significant decrease in MR (defined as absolute change in EROA >0.1 cm2 or a percentage change > 50%) was observed in 21 patients in the sacubitril/valsartan group versus 14 in the valsartan group; a significant increase in MR was only observed in 5 patients in the valsartan group. Furthermore, follow-up LV volumes were significantly smaller in the sacubitril/valsartan group. Although the beneficial effects of an ARNI in patients with heart failure and functional MR need to be confirmed in other, larger trials, these results are promising.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) should be considered in symptomatic patients with functional MR, a reduced LVEF ≤ 35% and QRS duration ≥ 130ms, despite optimal medical therapy.[13]

Mechanism of CRT in the treatment of functional MR

Minimization of intraventricular and atrioventricular dyssynchrony by CRT may reduce the severity of functional MR by means of several mechanisms. First, CRT increases mitral closing forces by improving the efficiency of global LV contraction. These increased trans-mitral closing forces counterbalance the tethering forces involved in functional MR and consequently reduce EROA. Second, local synchronization may reduce mitral leaflet tethering forces due to improvement of the time delay between activation of the papillary muscles. Third, mitral annular geometry and function may be improved by coordination of the contraction of myocardial segments at the LV base. Fourth, atrioventricular synchronization may correct diastolic MR – if present – and consequently reduce LA pressure.[93]

CRT may affect functional MR both at short-term (immediately after CRT implantation) and long-term (weeks to months after CRT implantation). An immediate reduction of MR is predominantly due to improved contraction of the papillary muscle bearing LV segments, resulting in acute reduction of tethering forces. An immediate response to CRT results in an acute reduction of LV volume overload and contributes to LV reverse remodelling. Immediate reduction of MR was found to be an important determinant of a favourable response to CRT. The long-term reduction of functional MR is caused by LV reverse remodelling, which may

reduce both closing forces due to improved LV contractility and tethering forces due to a reduction in LV volumes and improvement in LV geometry. Consequently, the reduction of the volume overload that ensues with MR breaks the vicious cycle of LV wall stress and myocardial oxygen demand, which may further improve LV function and consequently MR.[93]

Impact of CRT on functional mitral regurgitation and outcomes

Several RCTs have investigated outcomes after CRT with optimal medical therapy as compared to optimal medical therapy alone in patients with heart failure and cardiac dyssynchrony. These trials demonstrated that CRT can reduce severity of functional MR and LV volumes, and improve symptoms, quality of life and survival.[94, 95]

The evolution of functional MR in patients undergoing CRT was studied by Cabrera-Bueno et al.[96] In this study, 76 patients with advanced dilated cardiomyopathy were included. At baseline 42% (32 of 76) of patients had significant MR (EROA > 20mm^2); in 34% (11 of 32) of these patients, MR had become insignificant 6 months after CRT, while seven (9%) patients developed significant MR. Persistence or development of functional MR after CRT was associated with a higher rate of clinical events (death, transplantation or readmission for heart failure), arrhythmic events and less reverse remodelling. Similar outcomes were described by van Bommel et al.[97], who demonstrated a significant reduction in MR (by ≥ 1 grade) 6 months after CRT in 49% (42 of 85) of patients with moderate-severe functional MR and high operative risk. Patients with an improvement in MR after CRT had better survival.

Coronary artery bypass grafting

Coronary artery revascularization directly addresses the underlying cause of ischaemic MR. Consequently, CABG forms a key element in the treatment of patients with ischaemic MR. The indications for CABG are described in the guidelines on myocardial revascularization.[80, 98]

Mechanism of CABG in the treatment of functional MR

The rationale behind CABG in the treatment of ischaemic MR is that revascularization may improve LV geometry and function, and consequently reduce papillary muscle displacement and mitral leaflet tethering forces. As such, there has been much debate on the question whether CABG alone would be sufficient in the treatment of patients with ischaemic MR, especially in patients with less than severe MR. Leaving the mitral valve untouched would also avoid the perioperative risks associated with a concomitant mitral valve procedure.

Impact of CABG on functional mitral regurgitation and outcomes

The impact of CABG on the severity of ischaemic MR has been studied in several observational studies,[99-101] but much information can also be obtained from the results of RCTs comparing CABG alone versus CABG with mitral valve repair for patients with moderate ischaemic MR.[102-104] In the RIME trial,[102] MR improved to no/mild in 50% of patients one year after CABG, whereas 47% of patients still had moderate MR and MR had worsened to moderate-severe in 3% of patients. One-year results of the CTSN trial demonstrated less than moderate MR in 59%, moderate MR in 26% and severe MR in 5% of patients after CABG. Outcomes of the RIME and CTSN trial will be discussed in detail in Chapter 2.

The clinical and echocardiographic impact of ischaemic MR in patients undergoing CABG alone was studied in several observational studies as well. A retrospective study by Fattouch et al.[101] evaluated 180 patients with coronary artery disease and moderate ischaemic MR who underwent CABG and 360 matched patients without ischaemic MR who also underwent CABG. Echocardiographic follow-up (mean 30 months) in 130 surviving patients with preoperative MR, demonstrated that MR had decreased to mild in 30%, remained moderate in 35% and had increased to severe in 35%. Patients without MR showed a significant reduction in LV diameters, whereas LV diameters increased in patients with residual MR. Additionally, 5-year survival was significantly worse in patients with preoperative ischaemic MR compared to patients without MR (74% versus 91%), as was freedom from cardiac-related events (62% versus 88%). Similar results were obtained by Grossi and colleagues, who demonstrated a graded relation between the degree of preoperative ischaemic MR and survival in 2242 patients undergoing CABG alone (5-year survival 86% in patients without MR, 84% in patients with mild MR and 70% in patients with moderate MR).[105]

These studies indicate that outcome after CABG alone is highly unpredictable with MR remaining unchanged or worse in 31-50% of patients undergoing CABG alone, and that presence of ischaemic MR is associated with ongoing LV remodelling and adverse clinical outcomes after CABG.

Table 4. Guidelines' recommendations for the interventional treatment of functional MR.

Guidelines of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS)			
Guideline	Recommendations	COR	LOE
CABG[80]	MV surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF > 30%.	I	C
	MV surgery should be considered in symptomatic patients with severe secondary MR and LVEF < 30%, but with evidence of myocardial viability and an option for surgical revascularization.	IIa	C
Valvular heart disease [57]	Surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF > 30%.	I	C
	Surgery should be considered in symptomatic patients with severe secondary MR, LVEF < 30% but with an option for revascularization and evidence of myocardial viability.	IIa	C
	When revascularization is not indicated, surgery may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.	IIb	C
	When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	IIb	C
	In patients with severe secondary MR and LVEF < 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	IIb	C
Heart Failure[13]	Combined surgery of secondary MR and CABG should be considered in symptomatic patients with LV systolic dysfunction (LVEF < 30%), requiring coronary revascularization for angina recalcitrant to medical therapy.	IIa	C
	Isolated surgery of non-ischaemic MR in patients with severe functional MR and severe LV systolic dysfunction (LVEF < 30%) may be considered in selected patients in order to avoid or postpone transplantation.	IIb	C

Guidelines of the American Heart Association (AHA) and American College of Cardiology (ACC)			
Guideline	Recommendations	COR	LOE
CABG[81]	In patients undergoing CABG who have moderate ischemic MR not likely to resolve with revascularization, concomitant MV repair or replacement at time of CABG is reasonable.	IIa	B
	Patients undergoing CABG who have severe ischemic MR not likely to resolve with revascularization should have concomitant MV repair or replacement at the time of CABG.	I	B
Valvular heart disease[58, 65]	In patients with moderate ischemic MR undergoing CABG, the usefulness of mitral valve repair is uncertain.	IIb	B-R
	MV surgery is reasonable for patients with severe secondary MR who are undergoing CABG or AVR.	IIa	C
	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with severe ischemic MR and persistent symptoms despite GDMT for heart failure.	IIa	B-R
	MV repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with severe secondary MR who have persistent symptoms despite optimal GDMT for heart failure.	IIb	B
Heart failure[82, 83]	Transcatheter mitral valve repair or mitral valve surgery for functional MR is of uncertain benefit and should only be considered after careful candidate selection and with a background of GDMT.	IIb	B
Guidelines of the American Association of Thoracic Surgery (AATS)			
Guideline	Recommendations	COR	LOE
Ischemic MV surgery[84]	In patients with moderate ischemic MR undergoing CABG, MV repair with and undersized complete rigid annuloplasty ring may be considered.	IIIb	B
	MV replacement is reasonable in patients with severe ischemic MR who remain symptomatic despite guideline directed medical and cardiac device therapy and who have a basal aneurysm/dyskinesis, significant leaflet tethering and/or severe LV dilatation (LVEDD >65mm).	IIa	B
	MV repair with an undersized complete rigid annuloplasty ring may be considered in patients with severe ischemic MR who remain symptomatic despite guideline directed medical and cardiac device therapy and who do not have a basal aneurysm/dyskinesis, significant leaflet tethering, or severe LV enlargement.	IIb	B

MR = mitral regurgitation, MV = mitral valve, CABG = coronary artery bypass grafting, COR = classification of recommendations, CRT = cardiac resynchronization therapy, GDMT = guideline directed medical therapy, LOE = level of evidence, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction.

Restrictive mitral annuloplasty

History

Restrictive mitral annuloplasty (RMA) was first introduced by Bach and Bolling from the University of Michigan in 1994. In the first report on early outcomes after mitral annuloplasty, they demonstrated improved NYHA functional class, reduced LV volumes and increased LVEF in nine patients with end-stage cardiomyopathy (mean LVEF 15%).[106] In the next paper, reporting similar outcomes and a 1-year survival of 75% in 16 patients after mitral annuloplasty, Bolling first mentions the use of a ring undersized by "perhaps one size" (mean ring size 29).[107] In the discussion of a subsequent manuscript, Bolling states: "We started downsizing more and more. Now we are basically putting in the smallest rings that we can, and we have not seen mitral stenosis clinically in any patient."[108] These publications led to the introduction of RMA, which nowadays forms the mainstay of the surgical treatment of functional MR and is the subject of this thesis.

Rationale and surgical technique

The rationale behind mitral valve repair using an RMA ring is that it corrects mitral annular dilatation and enforces mitral leaflet coaptation, thereby abolishing MR. Furthermore, RMA reduces the size of the LV base, thereby re-establishing LV shape, lowering LV wall stress and initiating LV reverse remodelling.[108, 109] This mitral valve repair technique can be used in both patients with ischaemic and non-ischaemic MR.

Initially, RMA was performed using (semi-)flexible and incomplete mitral annuloplasty rings.[107] Nowadays, complete (semi-)rigid rings are generally recommended for the performance of RMA.[85] These (semi-)rigid rings may better reduce the septal-to-lateral dimension of the mitral annulus and a complete ring may also account for dilatation of the anterior mitral annulus. Indeed, a study comparing flexible rings with complete (semi-)rigid rings, observed less recurrent MR in patients who underwent RMA with a complete (semi-)rigid ring.[110]

In our hospital, RMA is performed by a structured approach. This approach consists of the implantation of a complete rigid or semi-rigid ring. The size of the ring is carefully determined by measuring the anterior leaflet height and then downsizing by 2 ring sizes (i.e. size 26 when measuring size 30). Mitral valve repair is considered successful in case of no or mild MR and a leaflet coaptation length of ≥ 8mm on intraoperative transoesophageal echocardiography. If these criteria are not met, further downsizing is performed. In patients with ischaemic MR, we always combine RMA with complete revascularization to address both the valvular and

ventricular component of functional MR. In patients with non-ischaemic MR, treatment of the intrinsic ventricular disease remains an uncovered area.

Results after RMA

Many observational studies on outcomes after RMA for ischaemic MR have been published. Several of these studies demonstrated that RMA results in durable correction of MR, reversal of LV remodelling and beneficial clinical outcomes,[111-113] whereas others could not confirm these beneficial outcomes.[114-116] Data regarding RMA for patients with non-ischaemic MR are limited, but improved NYHA functional class, better quality of life and LV reverse remodelling have been reported in these patients as well.[117, 118] Outcomes of observational studies are difficult to compare since they are highly heterogeneous due to differences in included patient populations, aetiology of MR, surgical technique, concomitant procedures and follow-up duration.

Over the last years, several RCTs on the surgical treatment of functional MR in the setting of ischaemic heart disease have been conducted. Three trials compared CABG alone versus CABG with concomitant mitral valve repair for moderate ischaemic MR[102-104, 119], whereas one trial compared mitral valve repair versus replacement for severe ischaemic MR.[120, 121] Although these trials were conducted to provide answers in the optimal surgical treatment of ischaemic MR, results regarding incidences of residual/recurrent MR, LV reverse remodelling and clinical outcome are not unequivocal and none of the trials was powered to detect a survival difference. Results of these trials will be discussed in Chapter 2.

RCTs comparing RMA versus optimal medical and device therapy for non-ischaemic MR have thus far not been conducted. However, much information regarding RMA for non-ischaemic MR can be obtained from the Acorn trial, which will be discussed in Chapter 2 as well.

Recurrent mitral regurgitation

Recurrence of MR after RMA was found to be associated with adverse outcome after RMA. Reported incidences of recurrent MR highly differ between studies. Although several studies demonstrated that RMA can ensure a durable correction of MR,[102, 111-113, 119] others report considerable incidences of MR recurrence.[114-116, 120, 121] When interpreting these studies, it is important to differentiate between residual and true recurrent MR. Residual MR is observed early after surgery and can partly be explained by the surgical technique – whether adequate downsizing is performed and whether absence of MR and a coaptation length of ≥8mm are confirmed on intra-operative echocardiography. Recurrent MR, on the other hand, was found to be associated with disease progression – ongoing LV remodelling – and may develop despite

a well-conducted mitral valve repair.[122] However, since in functional MR the mitral valve and LV are interrelated in a complex way, the causality between the two remains to be distinguished.

Many studies have focused on preoperative predictors for recurrent MR. Although several predictors – mainly reflecting mitral valve or LV configuration – have been identified, it remains difficult to identify individual patients most likely to benefit from mitral valve repair.

Functional mitral valve stenosis

A downsized mitral annuloplasty ring reduces mitral septal-to-lateral distance and also decreases mitral valve orifice area. Use of small, undersized mitral annuloplasty rings (ring size 24 and 26) has therefore raised concerns, in that extensive reduction of mitral annular dimension may obstruct antegrade mitral flow and may consequently induce a functional mitral valve stenosis.[123]

Since such a functional mitral stenosis may be even more pronounced during exercise, exercise echocardiography studies have been performed.[124-126] These studies demonstrated that functional mitral stenosis – when present after RMA – does not simply result from implantation of an undersized annuloplasty ring. Although the mitral orifice at annular level is fixed after implantation of a complete (semi-)rigid annuloplasty ring, the functional mitral valve area proved to be dynamic in response to exercise and was determined by the degree of diastolic anterior leaflet tethering.[124, 125]

Left ventricular reconstruction

According to the guidelines, LVR may be considered in selected heart failure patients, with intractable heart failure symptoms (NYHA III/IV), a large LV aneurysm, large thrombus formation, or ventricular arrhythmias.[80, 82] In our hospital, LVR is predominantly performed in patients with a post-infarction antero-septal LV aneurysm and refractory heart failure despite optimal medical and device therapy.

Rationale and surgical technique

The rationale behind LVR is that exclusion of the scar tissue will reduce LV volume (thereby reducing LV wall stress and improving the oxygen supply/demand relationship), reshape LV geometry (which realigns cardiac muscle fiber orientation) and consequently improve LV function. Left ventricular reconstruction is usually combined with myocardial revascularization, which may also enhance LV function.[127]

LVR is generally performed as described by Dor and colleagues.[128] After careful inspection of the transitional zone between scarred and non-scarred tissue, a shaping Fontan-stitch is placed at the transitional zone. The sizing and shaping of the residual ventricular cavity is performed using a shaping device filled to a volume of 55 ml/m^2 BSA, to avoid diastolic dysfunction by creating a too small LV cavity. After exclusion of the dyskinetic or akinetic LV wall, the LV is closed with a direct suture or in case of a remaining defect, using an endoventricular patch.

Functional mitral regurgitation at the time of LVR

Functional MR is frequently observed in patients with ischaemic heart failure, but although its presence is known to be associated with poor survival, the management of MR at the time of LVR remains controversial.[127] On the one hand, LVR may reduce tethering forces and thus severity of MR by reducing LV volumes and restoring LV geometry. Additionally, the reduction in LV wall stress and myocardial oxygen demand may increase mitral leaflet coaptation due to improved LV function and hence closing forces. On the other hand, LVR may lead to distortion of LV geometry and the subvalvular apparatus and consequently induce or exacerbate MR. Moreover, ongoing LV remodelling after LVR may lead to development or recurrence of functional MR if left untreated at the time of surgery.[129, 130]

Results after LVR combined with RMA

In our institution, concomitant mitral valve repair is performed in patients with MR ≥ grade 2 on preoperative echocardiography, and in patients with an increase of MR to ≥ grade 2 on intraoperative transoesophageal echocardiography directly after LVR. Other concomitant procedures are performed when indicated. In a previous report, Klein et al. demonstrated sustained improvement in LVEF, reduction of LV volumes, and favourable clinical outcomes (approximately 80% survival) 36 months after this integrated approach of LVR with concomitant mitral valve repair and other procedures.[131]

Cardiac support device

Rationale and surgical technique

The CorCap CSD (Acorn Cardiovascular, St. Paul, MN, USA) is an external fabric mesh device for patients with heart failure due to non-ischaemic cardiomyopathy. The CSD is implanted surgically around the heart and reduces LV wall stress by providing circumferential diastolic support, in order to prevent further LV remodelling.

The CSD can be used in combination with mitral valve repair. In our hospital, the CSD implantation was performed in patients with non-ischaemic MR and advanced LV remodelling,

i.e. preoperative LV end-diastolic diameter (LVEDD) ≥ 65mm or indexed LVEDD ≥ 30mm/m^2. The CSD is than implanted after mitral valve surgery has been performed, on the beating heart along the atrioventricular groove. At the end of the surgical procedure, the CSD is tailored to meet the preoperative LV dimensions measured on transoesophageal echocardiography. Currently, the CorCap CSD has been taken off the market and is no longer used.

Results after CSD combined with RMA

The Acorn trial has studied the effect of a CSD in 192 patients with non-ischaemic MR and heart failure (EF ≤ 35%, LV end-diastolic diameter ≥ 60mm and a 6-minute walking test < 450m, NYHA functional class III or IV). Patients were randomised to receive either RMA alone (n = 102) or RMA with implantation of a CSD (n = 91). At 5-year follow-up, LV volumes were decreased in both strata, but addition of a CSD resulted in a more extensive decrease in LV volumes. Change in MR grade and LVEF were similar between both groups and CSD did not improve survival. The results of the Acorn trial are discussed in more detail in Chapter 2.

In another study, Braun and co-workers from our institution reported outcomes of 69 patients with non-ischaemic MR and heart failure, who received optimal medical therapy combined with mitral valve repair (n = 28) or – in case of advanced LV remodelling – mitral valve repair and concomitant CSD implantation (n = 41). Overall actuarial survival at 1 and 5 years was 86 ± 4% and 63 ± 7%, respectively. Addition of the CSD to mitral valve repair resulted in similar clinical outcome compared to mitral valve repair alone, a greater decrease in LV end-diastolic volume (33 versus 18%, p = 0.007) and a trend towards less recurrent MR.

Other concomitant procedures

Tricuspid regurgitation is frequently observed in patients with functional MR. In patients undergoing mitral valve surgery, tricuspid valve repair should be considered in case of severe tricuspid regurgitation and in patients with mild or moderate tricuspid regurgitation and annular dilatation (≥ 40 mm or ≥ 20mm/m^2).[57] Tricuspid valve repair for these indications was found to reverse right ventricular remodelling and improve functional status without increasing the operative risk.[132] In heart failure patients with LV ejection fraction ≤ 30%, an implantable cardiac defibrillator is advised, to reduce sudden death due to cardiac arrhythmias.[13]

Thesis outline

The aim of this thesis was to study the surgical treatment of patients with functional MR, focusing on identification of patients likely to benefit from each treatment strategy, in order to be able to further personalise the surgical approach and optimise outcomes for each patient.

Chapter 2, provides an overview of the different surgical and interventional treatment strategies for patients with both ischaemic and non-ischaemic MR. The rationale, indication, surgical technique, results and limitations of each of these techniques is discussed by experts in the field.

Studies regarding the surgical treatment of ischaemic MR are presented in chapters 3 and 4. Chapter 3 is a comment on the two-year results of the Cardio-Thoracic Surgery Network trial comparing mitral valve repair versus mitral valve replacement. In chapter 4, long-term outcomes after mitral valve repair with revascularization for ischaemic MR are evaluated. This study specifically focuses on the mortality-adjusted incidence of recurrent MR, the clinical impact of recurrent MR and its pre-operative determinants.

Chapter 5 presents the long-term outcomes after an integrated medico-surgical approach for patients with non-ischaemic MR, focusing on the prevalence and prognostic impact of LV reverse remodelling and recurrent MR. Furthermore, the analysis of preoperative risk factors for adverse clinical outcomes are presented.

In chapter 6, ten-year outcomes of patients with heart failure due to a post-infarction anteroseptal LV aneurysm, who underwent an integrated approach of LVR with concomitant procedures – mitral and tricuspid valve reconstruction, coronary revascularization and arrhythmia surgery – are presented.

In chapter 7, mitral valve exercise haemodynamics are assessed in patients who underwent an RMA, and related to LV geometry and function, and to clinical outcomes.

In chapter 8, analyses the incidence and clinical impact of vasoplegia after mitral valve repair for patients with ischaemic and non-ischaemic MR.

Finally, chapter 9 provides a summary, clinical implications, conclusions and future perspectives.

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Chapter 2

The optimal treatment strategy for secondary mitral regurgitation: A subject of ongoing debate

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Introduction

Secondary mitral regurgitation (MR) is a disease condition in which the mitral valve (MV) becomes insufficient as a result of left ventricular (LV) dysfunction. As such, it is also referred to as functional MR. A thorough comprehension of the forces involved in MV opening and closing is necessary to understand the mechanism of secondary MR, which in turn has implications for the (interventional) treatment of this condition.

In secondary MR (as opposed to primary MR), the MV is macroscopically normal, and incomplete mitral leaflet closure results from a combination of annular dilatation, papillary muscle displacement with increased systolic leaflet tethering, and reduced closing forces due to regional or global LV remodelling (Figure 1).[1]

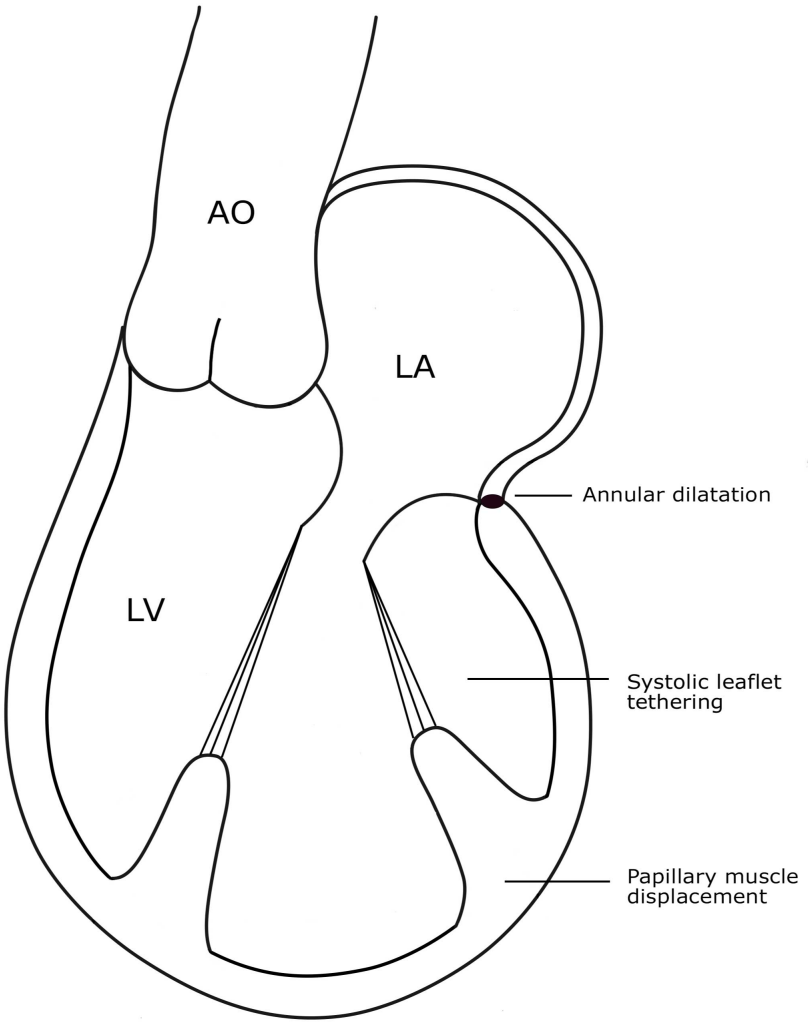

Figure 1. Pathophysiology of secondary mitral regurgitation.
AO = aorta, LA = left atrium, LV = left ventricle

Secondary MR is a common phenomenon and can be classified based on the aetiology of LV dysfunction as either ischaemic or non-ischaemic. Although there are many similarities between ischaemic and non-ischaemic MR, there are also distinct differences. In non-ischaemic cardiomyopathy, MR develops when considerable LV remodelling has taken place and is therefore always accompanied by heart failure with reduced ejection fraction. Ischaemic MR may develop in the same way when diffuse ischaemia or extensive infarction leads to global LV remodelling. However, more frequently ischaemic MR results from local LV remodelling, following local myocardial infarction or ischaemia. In this situation, LV ejection fraction can be relatively preserved and symptoms of heart failure may not yet have become manifest.

Echocardiography is the recommended imaging technique to evaluate secondary MR and its severity should be assessed using an integrative approach consisting of a combination of qualitative, quantitative and additional supportive echocardiographic parameters.[2, 3] The threshold for the definition of severe secondary MR is a topic of debate. Currently, severe secondary MR is defined as an effective regurgitant orifice area (EROA) of ≥40 mm^2 and a regurgitant volume of ≥60 ml in the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines,[3] whereas the European Society of Cardiology (ESC) guidelines use an EROA of ≥20 mm^2 and regurgitant volume of ≥30 ml.[2]

Secondary MR, regardless of its aetiology, has a poor prognosis.[4, 5] This is easily explained by the fact that the LV suffers from both intrinsic myocardial disease and volume overload that ensues with MR, resulting in a vicious cycle of progressive LV remodelling and worsening MR (Figure 2). In the past decades, many treatment options have been proposed to break this vicious cycle. The common goal is two-fold: to restore MV competence and to initiate sustained LV reverse remodelling, in order to improve clinical outcome.

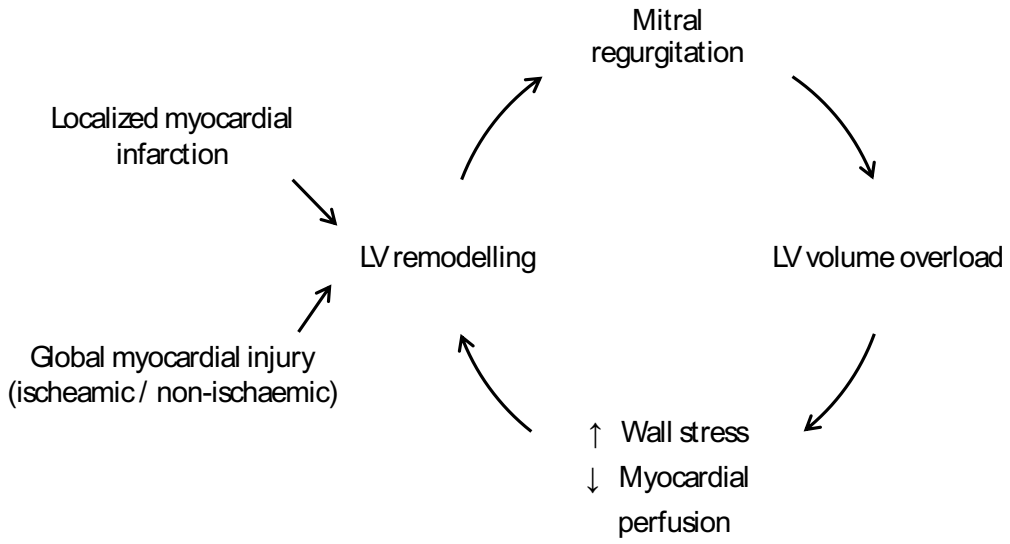

Figure 2. Vicious cycle of secondary mitral regurgitation.

The treatment of secondary MR is included in many guidelines.[2, 3, 6–13] Optimal guideline-directed medical therapy (GDMT) is the cornerstone in the treatment of patients with secondary MR. Effective medical therapy lowers LV afterload, reverses LV remodelling and consequently reduces MR. Cardiac resynchronization therapy improves LV systolic function in selected patients — both acute-term (by reduction of dyssynchrony) and long-term (by means of LV reverse remodelling) — resulting in increased closing forces and reduced tethering forces acting on the MV.[7, 11] In patients with persisting MR despite GDMT (including cardiac resynchronization therapy, when indicated), more invasive treatment options may be considered. In line with the broad spectrum of disease manifestations and the different aetiologies, many different interventions have been proposed, aiming at the valve (surgical MV repair, MV replacement and percutaneous approaches), at the subvalvular apparatus, at the ventricle (coronary revascularization, surgical ventricular restoration and external cardiac constraint devices), or a combination thereof. In patients who are unlikely to benefit from these interventions, implantation of an LV assist device (LVAD) may be considered.

This vast array of interventional treatment options reflects the fact that the optimal treatment strategy for patients with secondary MR is a topic of ongoing debate, also in current guidelines (Table 1).[2, 3, 6–13] Guideline recommendations are not unequivocal and are based on the results of many studies — predominantly observational in nature — with conflicting outcomes, whereas data from randomized controlled trials (RCTs) on the surgical treatment of secondary MR is scarce, and only available for ischaemic MR.[2, 3, 6–13] In this Great Debate, different approaches for the treatment of secondary MR, their rationale, outcomes and limitations are described by experts in this field.

Mitral valve repair

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Rationale and indication

Bolling and Bach introduced the concept of MV repair using an undersized (or: restrictive) annuloplasty ring.[14, 15] Undersizing corrects mitral annular dilatation and enforces leaflet coaptation, thereby abolishing MR, and reduces the size of the LV base, consequently lowering LV wall stress and initiating LV reverse remodelling.[16] This technique can be considered in both patients with ischaemic and non-ischaemic MR.

Theoretically, secondary MR in patients with ischaemic cardiomyopathy may improve after coronary artery bypass grafting (CABG) due to improvement in LV geometry and function. In practice, the outcome after CABG alone is highly unpredictable, with MR severity being

Table 1. Guidelines' recommendations for the surgical treatment of secondary MR.

Guideline	Recommendations	LOE	COR
ESC and EACTS[5]	Surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF >30%	C	I
	Surgery should be considered in symptomatic patients with severe secondary MR, LVEF <30% but with an option for revascularization and evidence of myocardial viability.	C	IIa
	When revascularization is not indicated, surgery may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite OMT (including CRT if indicated) and have a low surgical risk.	C	IIb
	When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite OMT (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	C	IIb
	In patients with severe secondary MR and LVEF <30% who remain symptomatic despite OMT (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	C	IIb
AHA and ACC[8, 9]	In patients with moderate ischemic MR undergoing CABG, the usefulness of mitral valve repair is uncertain.	B-R	IIb
	MV surgery is reasonable for patients with severe secondary MR who are undergoing CABG or AVR.	C	IIa
	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with severe ischemic MR and persistent symptoms despite OMT for heart failure.	B-R	IIa
	MV repair or replacement may be considered for severely symptomatic patients (NYHA class III-IV) with severe secondary MR who have persistent symptoms despite OMT for heart failure.	B	IIb
AATS[12, 13]	In patients with moderate ischemic MR undergoing CABG, MV repair with an undersized complete rigid annuloplasty ring may be considered.	B	IIIb
	MV replacement is reasonable in patients with severe ischemic MR who remain symptomatic despite OMT and cardiac device therapy and who have a basal aneurysm/dyskinesis, significant leaflet tethering and/or severe LV dilatation (LVEDD >65mm).	B	IIa
	MV repair with an undersized complete rigid annuloplasty ring may be considered in patients with severe ischemic MR who remain symptomatic despite OMT and cardiac device therapy and no basal aneurysm/dyskinesis, significant leaflet tethering, or severe LV enlargement.	B	IIb

ACC = American College of Cardiology, AHA = American Heart Association, AATS = American Association of Thoracic Surgery, CABG = coronary artery bypass grafting, COR = classification of recommendations, CRT = cardiac resynchronization therapy, EACTS = European Association for Cardio-Thoracic Surgery, ESC = European Society of Cardiology, LOE = level of evidence, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, MV = mitral valve, OMT = optimal medical therapy.

unchanged or worse in 31–50% of patients undergoing surgical revascularization only.[17–20] The combination of MV repair and CABG addresses both the valve and the underlying ventricular component in patients with ischaemic MR. In patients with non-ischaemic MR, the intrinsic ventricular disease cannot be addressed, which therefore remains an uncovered area.

Surgical technique

In our institution, the ring size is carefully determined by measuring the anterior leaflet height and then downsizing by 2 ring sizes (i.e. size 26 when measuring size 30). Restrictive mitral annuloplasty (RMA) is performed with a complete rigid or semirigid ring to reduce the septal-to-lateral dimension of the mitral annulus; using a complete ring also accounts for dilatation of the anterior mitral annulus. Repair is considered successful in case no or mild MR and a leaflet coaptation length ≥8 mm are observed on intraoperative transoesophageal echocardiography. If these criteria are not met, further downsizing is performed. In ischaemic MR patients, we always aim at complete revascularization.[21]

Results - Mitral valve repair for ischaemic mitral regurgitation

Several observational studies showed that RMA results in durable correction of MR, LV reverse remodelling and beneficial clinical outcomes in patients with ischaemic MR,[18, 21–23] whereas others negated these benefits.[24–26] Outcomes of observational studies are difficult to compare due to differences in baseline characteristics, completeness of revascularization and technique of MV repair. Therefore, we will focus on 2 RCTs — the Randomized Ischaemic Mitral Evaluation (RIME) and Cardiothoracic Surgical Trials Network (CTSN) trial — comparing CABG alone versus CABG + RMA for moderate ischaemic MR.[18–20, 27] The CTSN trial regarding RMA versus MV replacement for severe MR will be discussed later.[28, 29]

In both the RIME and CTSN trial patients with coronary artery disease and moderate secondary MR were randomized to undergo CABG alone or CABG + RMA. RMA was performed using a complete (semi-)rigid ring in both trials, but downsizing by 2 ring sizes was mandated in the RIME trial whereas the degree of downsizing and addition of supplementary repair techniques were left at the discretion of the surgeon in the CTSN trial. No difference in 30-day mortality was observed in both trials (RIME: 3% in both groups, p = 1.00; CTSN: 2.7% after CABG vs 1.3% after CABG + RMA, p = 0.68). One year after CABG, moderate-to-severe residual MR was observed in 50% of patients in the RIME trial and in 31% in the CTSN trial. After CABG + RMA, recurrent MR was observed in 4% in the RIME trial, compared with 11% in the CTSN trial. LV reverse remodelling 1 year after surgery was defined as an endpoint in both trials. The RIME trial demonstrated a significantly better decrease in indexed LVESV after CABG + RMA (-28%)

compared with CABG alone (-6%). By contrast, in the CTSN trial change in indexed LVESV was similar for both groups (-16% after the combined procedure vs -17% after CABG alone), with comparable results at 2-year follow-up (-25% vs -26%, respectively). Mortality at 1-year was equal between treatment groups in both trials (RIME: 9% after CABG + RMA vs 5% after CABG, p = 0.66; CTSN: 6.7% vs 7.3%, respectively, p = 0.81). However, neither trial was powered to detect a mortality difference. The RIME trial showed a higher increase in peak oxygen consumption (defined as primary endpoint) after CABG + RMA compared with CABG alone, but no difference in readmissions for heart failure. In the CTSN trial, no differences in major adverse cardiac or cerebrovascular events or hospital readmissions were demonstrated. However, more serious adverse neurological events and supraventricular arrhythmias were observed in patients after the combined procedure.

How can we explain the fact that the RIME trial observed a difference in LV reverse remodelling in favour of CABG + RMA, whereas the CTSN trial did not? First, LV reverse remodelling after CABG alone was better in the CTSN trial. This may be explained by the lower rate of previous myocardial infarction and smaller indexed LVESV at baseline, indicating that MR was most likely caused by reversible ischaemia rather than scar tissue in a large proportion of patients in this trial. Second, less LV reverse remodelling was observed after CABG + RMA in the CTSN compared with the RIME trial. Since MR recurrence was higher in the CTSN trial, the degree of LV reverse remodelling seems to be related to the durability of MV repair. Indeed, patients without recurrent MR after CABG + RMA showed a 29% reduction in indexed LVESV, compared with only 6% in patients with recurrent MR.

Results - Mitral valve repair for non-ischaemic mitral regurgitation

Data regarding RMA for MR due to non-ischaemic cardiomyopathy are limited. Observational studies report improved New York Heart Association (NYHA) functional class, better quality of life and LV reverse remodelling after RMA.[30–33] Much information regarding the effect of RMA in non-ischaemic cardiomyopathy has been obtained from the Acorn trial.[34, 35] Primary objective of this RCT was to examine the effect of an external cardiac support device (CSD). The trial enrolled 300 patients with non-ischaemic cardiomyopathy and heart failure into a no MV surgery (n = 107) or MV surgery stratum (n = 192), based on the presence of significant MR. Patients in the MV surgery stratum were then randomized to MV surgery + CSD (n = 91), or MV surgery alone (n = 102). In the MV surgery stratum, baseline LV end-diastolic volume was 270 ml, ejection fraction 24% and all patients had MR ≥ grade 3. The MV was replaced in 16% of patients; the remainder underwent MV repair by RMA. Perioperative mortality was low (1.6% at 30-day). Echocardiography 1 year after surgery demonstrated recurrent MR ≥ grade 2 in 16.5% of patients and a decrease in LVESV of approximately -25 ml. LV reverse remodelling

remained stable at 5-year follow-up. Cumulative mortality was 13% at 1-year, 15% at 2-year and 30% at 5-year follow-up. Concomitant implantation of a CSD resulted in an additional decrease in LVESV (15 ml on average), whereas change in MR and ejection fraction was similar between both groups; addition of the CSD did not improve survival.

Limitations and pitfalls

Reported incidences of MR recurrence after RMA highly differ between studies.[24–26] Although this difference can be partly explained by surgical technique — whether RMA was performed using stringent downsizing and aiming at a coaptation length of ≥8 mm — a subgroup of patients may develop recurrent MR despite a well-conducted MV repair.[21, 33, 36] Several echocardiographic parameters can be used to identify these patients (Table 2).[36–39] Furthermore, some surgeons are reluctant to perform RMA due to the risk of inducing functional MV stenosis. However, recent exercise echocardiography studies challenge the concept that functional mitral stenosis — when present after RMA — simply results from implantation of a downsized ring, and demonstrated that MV area during exercise is associated with diastolic tethering and LV geometrical and functional changes after surgery.[40, 41]

Table 2. Predictors for recurrence of MR after mitral valve repair by restrictive mitral annuloplasty, assessed by transthoracic echocardiography.[36, 40, 59, 81]

Valvular parameters
MR grade ≥3.5
Central or complex regurgitant jet
Tenting area ≥2.5 cm^2
Coaptation distance (= tenting height) ≥10 mm
Posterior leaflet angle ≥45º
Posterior leaflet tethering distance ≥40 mm
Mitral annulus diameter ≥37 mm*
Ventricular parameters
LV end-diastolic diameter ≥65 mm
LV end-systolic diameter ≥51 mm
LV end-systolic volume ≥145 ml
Presence of a basal aneurysm/dyskinesis
Systolic sphericity index ≥0.7
Myocardial performance index ≥0.9
Wall motion score index ≥1.5
Interpapillary muscle distance >20 mm
Diastolic dysfunction (restrictive filling pattern)

*Assessed by transoesophageal echocardiography. LV = left ventricle, MR = mitral regurgitation.

Edge-to-edge procedure

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Rationale and indication

The idea for using the edge-to-edge procedure in addition to implantation of an RMA ring in patients with secondary MR is that it will enhance durability of MV repair and prevent MR recurrence. The edge-to-edge technique involves suturing the edges of the MV leaflets together at the site of regurgitation, specifically addressing the site of the regurgitant jet. This ensures early valve closure and abolishes occurrence of the 'loitering effect' (delayed mitral leaflet coaptation in early systole, due to mitral annulus dilatation and circularization, and posterior papillary muscle displacement).[42] Moreover, anchoring the leaflets together might exert an upward tension on the chordae tendinae and therefore on the papillary muscles and the adjacent LV wall (a kind of 'reins' effect), potentially counteracting progression of LV remodelling.

The edge-to-edge procedure can be considered in patients with both ischaemic and non-ischaemic MR, who are at increased risk of MR recurrence after repair (**Table 2**).[36–39] Tenting height (TH; also known as coaptation depth) is defined as the distance from the annular plane of the MV to the leaflet coaptation point and represents the degree of mitral leaflet tethering, independent of LV function and shape. In patients with annular dilatation and moderate leaflet tethering (TH <10 mm), isolated RMA with a complete rigid or semi-rigid ring can be performed. However, when tethering is more pronounced (TH >10 mm), addition of the edge-to-edge technique to RMA is preferred.

Surgical technique

To perform the edge-to-edge procedure, the location of the regurgitant jet should be identified on preoperative echocardiography, to choose the site of the approximating stitch. In case of a central jet (between A2 and P2), a central edge-to-edge repair is performed leading to a double-orifice MV configuration (**Figure 3**). When the regurgitant jet is located at the posterior commissure, as in some cases of ischaemic MR, a commissural edge-to-edge suture is applied, resulting in a single orifice MV with a relatively smaller area. The length of the suture is always kept as short as possible to minimize the risk of postoperative MV stenosis: in most patients between a few millimetres and 1 cm. A complete rigid or semi-rigid prosthetic ring is invariably implanted and is usually 1 or 2 sizes smaller than the anterior leaflet surface.

Results

Outcomes of the edge-to-edge procedure have been investigated in several retrospective observational studies.[43–47] The earliest reports were disappointing; however, these studies described the edge-to-edge procedure without concomitant annuloplasty or combined with a flexible band, which could not prevent progression of annular dilatation.[43–45] In more recent studies,[46, 47] we described outcomes of patients with moderately severe to severe ischaemic and non-ischaemic MR and LV ejection fraction ≤35%, who underwent either a combination of RMA with edge-to-edge procedure (in case of a TH ≥10 mm) or RMA alone (in case of a TH <10 mm). In-hospital mortality was not significantly different between both groups (2.5% after RMA alone vs 3% after RMA with edge-to-edge procedure, p = 1.0).[47] Cumulative incidence of recurrent MR ≥ grade 3 was significantly lower after the combined procedure compared with RMA alone, both at 18 months (5% vs 23%, respectively, p = 0.04)[46] and 10 years after surgery (10% vs 31%, p = 0.01).[47] In both groups, LV end-diastolic dimensions decreased (67 to 58 mm after RMA and 68 to 62 mm after RMA with edge-to-edge procedure) and NYHA functional class improved after surgery.[46, 47] Although addition of the edge-to-edge technique to RMA significantly decreased the rate of recurrent MR, the improved repair durability did not translate into better LV reverse remodelling or improved long-term survival (55% after RMA alone compared to 42% after RMA with edge-to-edge procedure at 10-year follow-up, p = 0.2).[47]

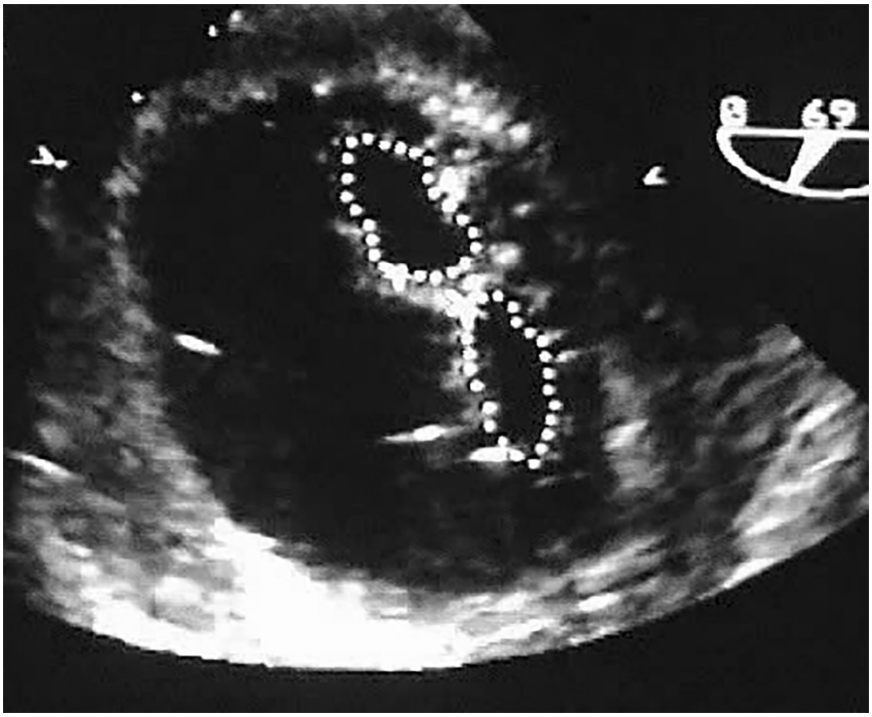

Figure 3. Echocardiographic image of the edge-to-edge procedure.

Limitations and pitfalls of the technique

The edge-to-edge procedure restricts the MV orifice area, which may potentially induce a stenosis. Although a clinically relevant MV stenosis has not been observed in any of the patients, experience and careful choice of the annuloplasty ring size are mandatory in order to avoid significant MV stenosis. The edge-to-edge technique should be avoided in rare instances where leaflet tethering is associated with only mild annular dilatation. Finally, unsatisfactory results can be expected, even with the edge-to-edge technique, in the case of extreme mitral leaflet tethering or extremely advanced LV remodelling.

Subvalvular procedures

Subvalvular procedures, which are generally used as an adjunct to annuloplasty, aim at restoring the configuration of the subvalvular apparatus and subsequently reduce tethering forces on the MV. In addition, these techniques provide a direct change in LV geometry. Both contribute to the durability of MV repair. Subvalvular procedures include various techniques with different concepts[48] and each procedure should be selected considering the direction of MV tethering (apical, outward or posterior).[49] Two of these techniques will be discussed.

Subvalvular procedures: RING + STRING

Frank Langer, Hans-Joachim Schäfers, Homburg/Saar, Germany

Rationale and indication

The RING + STRING technique combines implantation of an RMA ring (RING) with papillary muscle repositioning (STRING). This approach addresses annular dilatation as well as subvalvular systolic leaflet tethering and LV geometry — serving as an internal LV restraint.

Indication for papillary muscle repositioning in our practice is dictated by the degree of LV remodelling, for which TH is one of the more easily determined quantitative parameters.[36] If TH exceeds 10 mm, almost all patients develop recurrent MR with absence of reverse remodelling.[50] Consequently, we add papillary muscle repositioning to mitral annuloplasty in patients with secondary MR ≥ grade 3 and TH ≥10 mm.[51]

Surgical technique

Standard MV repair (RING) is performed with a moderately undersized ring (by 1 to 2 sizes in relation to the intertrigonal distance). Thereafter, a horizontal aortotomy is performed and a

double-armed Teflon pledgeted 3-0 polytetrafluoroethylene (PTFE) suture (STRING) is passed through the head of the papillary muscle and then passed from the LV cavity through the aorto-mitral continuity underneath the commissure between the non-coronary and left coronary aortic cusps and exteriorized. In patients with ischaemic MR due to local LV remodelling, a string for the posterior papillary muscle often suffices. In patients with ischaemic MR due to global LV remodelling and in patients with non-ischaemic MR we use 2 strings, one for each papillary muscle. During termination of cardiopulmonary bypass, the STRING-suture is tied under transoesophageal echocardiography guidance in the loaded beating heart. Tension on the suture is titrated under direct echocardiographic control in 2-dimensional-mode, achieving the most physiological shape of the anterior mitral leaflet along its entire body and bringing the coaptation point as close to the annular plane as possible (**Figure 4**).

Results

Studies describing outcomes regarding the RING + STRING procedure are limited.[51, 52] In our institution, 224 patients with ischaemic (n = 148) or non-ischaemic (n = 76) MR and TH ≥10 mm have undergone papillary muscle repositioning in addition to a moderately undersized RMA. The in-hospital mortality was 8%. During follow-up (median 50 months), 11% of patients developed recurrent MR ≥ grade 3. MV reoperation was performed in 15 patients (rerepair in 6 and MV replacement in 9). Decreased LV end-diastolic diameter was observed in 60% of patients (mean -7 mm change in LV end-diastolic diameter from baseline) and NYHA functional class significantly improved. Overall freedom from death, LVAD or heart transplantation was 57% at 5 years after surgery.

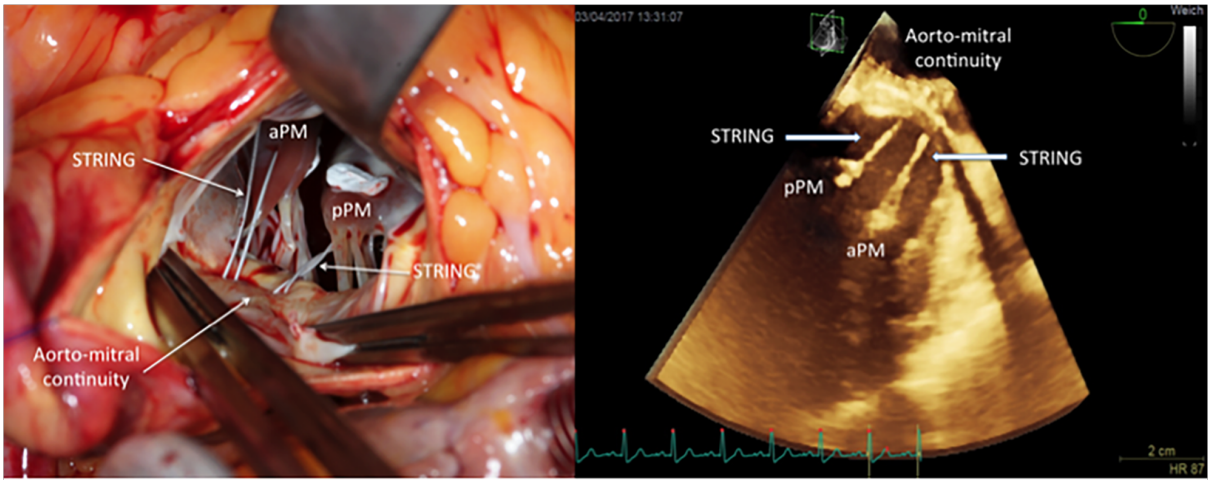

Figure 4. Intraoperative and echocardiographic image of the RING + STRING procedure.
Left: Intraoperative view via horizontal aortotomy: 2 PTFE sutures ('STRING') anchored in heads of both papillary muscles (aPM = anterior papillary muscle; pPM = posterior papillary muscle) and exteriorized through the aorto-mitral continuity. Right: 3-dimensional-transesophageal echocardiography: 2 PTFE sutures ('STRING') anchored in heads of both papillary muscles fixed at the aorto-mitral continuity.

Limitations and pitfalls of the technique

Ring dehiscence may occur after RMA — even after moderate downsizing. Since February 2008 we have eliminated this clinical problem by modifying our suturing technique. After the annular mattress sutures were tied, they were then passed around the annuloplasty ring once more, taking additional bites of atrial tissue and tied again (double-suture technique). Furthermore, in a limited proportion we have observed residual/recurrent tethering, most likely resulting from inadequate tension on the PTFE sutures. Finally, LV reverse remodelling could not be achieved in all patients; further research should be directed towards identifying patients who will not have recovery of LV function.

Subvalvular procedures: Papillary muscle approximation

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Rationale and indication

Papillary muscle approximation (PMA) aims at restoring configuration of the subvalvular apparatus and subsequently reducing tethering forces on the MV. This obviates the need for a downsized annuloplasty ring, and consequently dispels the potential risk of inducing functional mitral stenosis.[53]

We typically add PMA and anterior suspension for patients with moderate-to-severe (≥ grade 2) secondary MR and TH ≥10 mm or diastolic inter-papillary muscle distance ≥30 mm.[54]

Surgical technique

The extent of PMA is determined by the degree of LV remodelling (presence of scar). Incomplete PMA is performed by partial approximation from the tips to the mid-parts of the papillary muscles (using pledgeted mattress sutures of 3-0 polypropylene), through the mitral or aortic valve (**Figure 5**). In the presence of a transmural scar of the anterior LV wall, we perform a complete side-by-side PMA through an anterior LV incision (**Figure 5**). In all patients, concomitant MV annuloplasty with a true- or undersized semi-rigid or rigid ring is performed.[55]

Results

The efficacy of PMA has been investigated in several observational studies and 1 RCT.[55–59] The RCT compared RMA + PMA (n = 48) to RMA alone (n = 48) for patients with severe ischaemic MR.[59] This trial demonstrated no difference in 30-day mortality (6.2% after RMA + PMA compared with 8.3% after RMA alone). Recurrence of MR ≥ grade 3 at 5-year follow-up was

significantly higher in the RMA alone group (56%) compared with the combined procedure (27%; p = 0.013). Furthermore, patients with RMA + PMA showed more LV reverse remodelling (-5.8 mm change in LV end-diastolic diameter from baseline to 5 years follow-up, vs -0.2mm after RMA alone, p <0.001). There was no significant difference in mortality at 5 years (23% after RMA + PMA vs 29% after RMA alone, p = 0.496), but a trend towards better freedom from major adverse cardiac and cerebrovascular events (MACCE) was observed after RMA + PMA [HR 0.66 (0.42 – 1.04), p = 0.073].

The vast majority of studies regarding subvalvular procedures have been conducted in patients with ischaemic MR. However, a propensity matched study including both patients with ischaemic and non-ischaemic MR demonstrated more LV reverse remodelling after RMA + PMA compared with RMA alone.[60] Therefore, subvalvular techniques may be considered in patients with non-ischaemic MR, although more research is needed to establish the beneficial effect in this subgroup of patients.

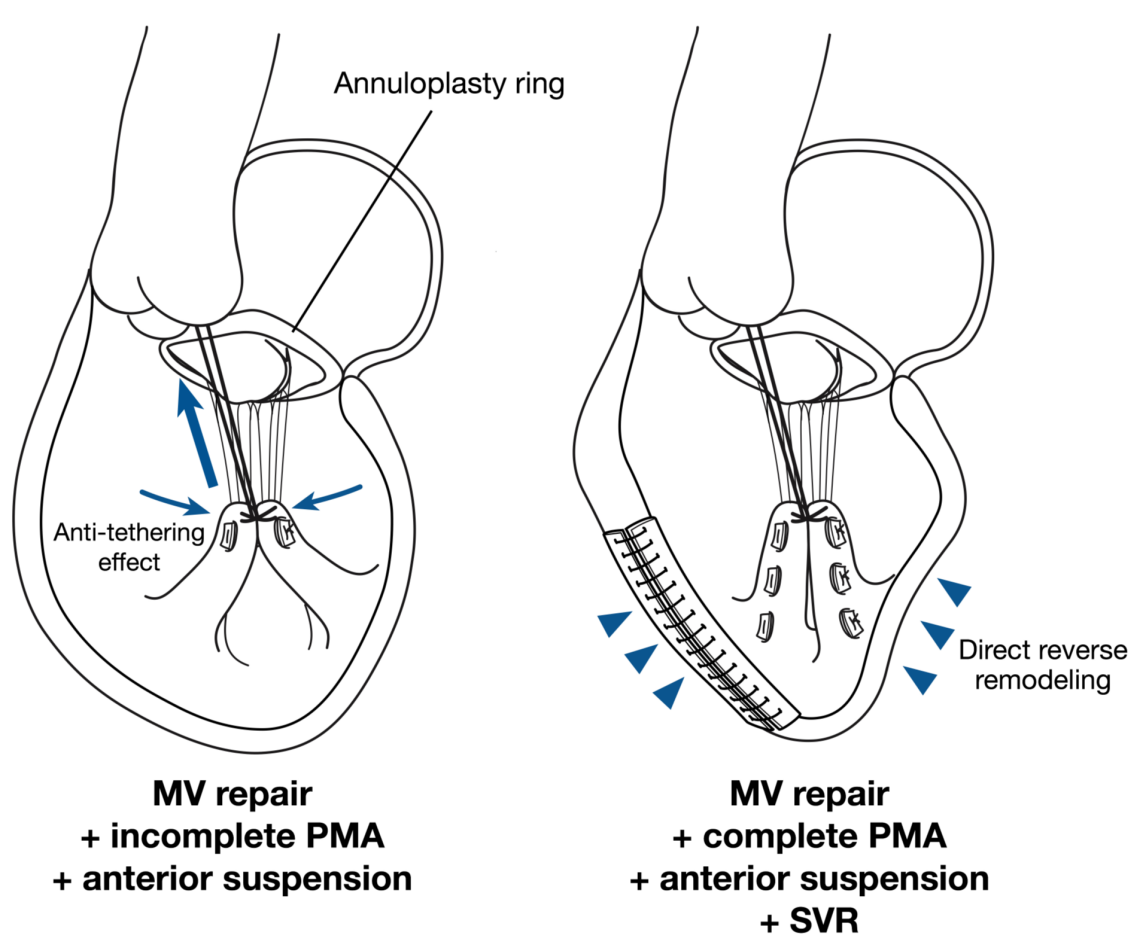

Figure 5. Schematic image of papillary muscle approximation and concomitant procedures.
MV = mitral valve, PMA = papillary muscle approximation, SVR = surgical ventricular reconstruction.

Limitations and pitfalls

PMA in addition to RMA, addressing the specific direction of MV tethering (apical, outward or posterior), reduces the risk of recurrent MR compared to RMA alone. However, in a subgroup of patients, elimination of MV tethering by subvalvular procedures is not sufficient to ensure durability of repair.

Mitral valve replacement

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Rationale and indication

The rationale for replacing rather than repairing the MV in patients with secondary MR stems from the high rates of MR recurrence observed after MV repair.[38] MV replacement may improve outcomes by providing a more predictable and durable correction of MR and can be considered in patients with severe ischaemic MR and echocardiographic parameters that are associated with an increased risk of MV repair failure.[12, 13] Furthermore, mortality rates for MV replacement have significantly improved from 10–20% in older series to 4–5% in contemporary series utilizing complete chordal sparing technique.[61] Therefore, the common belief that MV replacement is associated with a higher operative mortality than MV repair is not true today.[28, 29, 62–64]

Results

The strongest evidence to date supporting MV replacement for patients with severe ischaemic MR comes from the multicentre RCT sponsored by the CTSN, where MV repair using an undersized rigid complete annuloplasty ring (and additional subvalvular procedures performed according to surgeon's discretion) was compared with MV replacement with complete chordal sparing.[28, 29] Recurrence of moderate or severe MR was significantly greater in the repair than in the replacement group (33% vs 2% at 1 year; 59% vs 3.8% at 2 years). The primary endpoint of LV reverse remodelling was similar between the groups at both the first- (indexed LVESV -6.6 ml/m^2 after repair vs -6.8 ml/m^2 after replacement, respectively) and second year after surgery (-9.0 vs -6.5ml/$m^{2,}$ respectively). Mortality at 30 days, 1 year and 2 years was statistically equivalent between both groups (1.6% after repair vs 4% after replacement; 14% vs 18%; 19% vs 23%), as was MACCE. At 1 year, no difference in clinical outcomes was seen, but after 2 years, patients who underwent repair had more heart failure events (24 per 100 patients years vs 15.5 per 100 patients years, p = 0.05) as well as a significantly higher rate of readmissions for cardiovascular causes (48 vs 32 per 100 patient years, p = 0.01). In addition,

there was a trend for greater improvement in quality of life (p = 0.07) as measured by the Minnesota Living with Heart Failure Questionnaire of patients who had a MV replacement. Interestingly, a subgroup analysis demonstrated that patients who underwent MV repair and did not develop recurrent MR had a greater degree of LV reverse remodelling (23% decrease in indexed LVESV) 1 year after surgery than patients who underwent MV replacement (8% decrease in indexed LVESV).[28, 29]

Limitations and pitfalls

MV replacement for severe ischaemic MR has the limitations and pitfalls of any MV replacement, including the risk of infection, thromboembolism and structural valve deterioration over time. Given the observation that patients without recurrent MR after MV repair have more LV reverse remodelling than patients after MV replacement, it is imperative that we learn how to predict the subgroup of patients who can have a durable MV repair.

MitraClip

Alec Vahanian, Paris, France; Jean-Francois Obadia, Lyon, France

Rationale and indication

The rationale for the development of transcatheter techniques in patients with severe secondary MR comes from the fact that secondary MR carries a poor prognosis, patients are often older with several comorbidities, and surgery may be high-risk or even contraindicated; in addition, the benefit of surgery with regard to survival is largely unproven.

The MitraClip technique represents the largest experience available in the domain of transcatheter MV interventions. This technique has been used for more than 10 years, treating >80.000 patients worldwide, of which two thirds had secondary MR. MitraClip replicates the surgical edge-to-edge technique, creating a 'double-orifice' MV.[65]

Recommendations for the use of MitraClip in the current guidelines[2, 9] are of low-level evidence (**Table 1**) and based on 1 RCT (EVEREST II), including a mix of patients with organic and secondary MR, and a number of registries, including mostly, but not exclusively, patients with secondary MR.[66–73] Recently, 2 RCTs have been performed regarding the use of MitraClip in patients with secondary MR.[74, 75]

Results

Registries on outcomes regarding MitraClip for the treatment of secondary MR have inherent limitations. Therefore, we shall focus on 2 RCTs (the MITRA-FR and COAPT trial), which were recently reported and bring important, even if apparently contradictory, information.[74, 75]

Both RCTs only included patients with MR due to ischaemic or non-ischaemic cardiomyopathy and compared optimal GDMT with GDMT + MitraClip implantation. Outcomes were assessed at 1-year follow-up in the MITRA-FR and at 2-year follow-up in the COAPT trial. There are some differences in baseline characteristics between the patients in the 2 trials. First, patients in the MITRA-FR trial were at a more advanced stage of disease: all had a previous heart failure hospitalization and the left ventricles were larger. Furthermore, the initial degree of MR was lower in the MITRA-FR (EROA 31 mm^2) than in the COAPT trial (EROA 41 mm^2), due to differences in thresholds for MR severity between European and US guidelines. Finally, in the COAPT trial, medical therapy was optimized before randomization by a central selection committee (which has methodological advantages but may limit the applicability of the findings), whereas in the MITRA-FR trial this evaluation was based on the local Heart Team decision (which may be suboptimal but represents more 'real-life' practice). Both RCTs confirmed low procedural risk; urgent surgery was not needed in MITRA-FR and in 0.3% in the COAPT trial; 30-day mortality was 3.3% and 2.3%, respectively. Procedural success was high in both studies (91% in MITRA-FR and 95% in the COAPT) and residual MR ≥ grade 2 at discharge was observed in 24% of patients in MITRA-FR and 18% in COAPT. After 1 year, approximately 30% of patients had MR ≥ grade 2 in COAPT compared with approximately 50% in MITRA-FR, which has more missing data. However, it should be kept in mind that the grading of MR was different between the 2 trials and none of the RCTs provided precise figures concerning 'recurrence of MR', which is a concern in surgical publications. In COAPT, LV volumes slightly decreased between the baseline and 2 years follow-up in the intervention group (-3.7 ml), compared with an increase in the control group (+17.1 ml). LV reverse remodelling was not observed in MITRA-FR. Improvement in clinical outcomes was the primary endpoint of both trials: death or heart failure rehospitalizations at 12 months in the MITRA-FR and all heart failure hospitalizations at 24 months in COAPT. There were no differences between groups in MITRA-FR, whereas MitraClip reduced the rate of heart failure hospitalizations, and improved survival, quality of life and functional capacity in the COAPT trial.

The striking differences between the outcomes in the 2 trials are difficult to explain. The most likely explanation is that patients in the MITRA-FR trial were treated at a more advanced stage of LV disease with less MR, where the role of LV dysfunction predominates over the valve dysfunction[76]: COAPT patients had disproportionate MR in relation to LV dysfunction and

derived benefit from valve intervention; MITRA-FR patients had proportionate MR and did not benefit from valve intervention.

Limitations and pitfalls of the technique

Development of MV stenosis is a potential complication of MitraClip implantation. Although mitral stenosis was not observed in either RCT, careful haemodynamic assessment should be performed to avoid such complication. The edge-to-edge transcatheter technique shares the limitations of the isolated surgical technique where the combination with annuloplasty is associated with better outcomes.[65] Currently, other transcatheter techniques such as annuloplasty (as stand-alone procedure or combined with the edge-to-edge technique) and transcatheter MV replacement are at an early stage of development but may be useful in the future.

Left ventricular assist device

Matthias Siepe, Freiburg, Germany

Rationale and indication

The existing evidence on patients with secondary MR and severe LV dysfunction highlights an overall very poor prognosis. Choosing the optimal treatment strategy for these patients is difficult, as reflected by this Great Debate article. MV procedures may not improve outcome, since the underlying disease is not addressed, and ongoing LV remodelling may result in further deterioration of LV function and recurrence of MR. Transcatheter procedures avoid the perioperative risks associated with surgery. However, the recently published MITRA-FR and COAPT trials presented contrasting outcomes regarding efficacy of the MitraClip compared with GDMT.[74, 75] For patients with severe secondary MR and more severe LV dysfunction — like those included in the MITRA-FR trial — each Heart Team should consider allocating patients to LVAD implantation as a valid alternative.

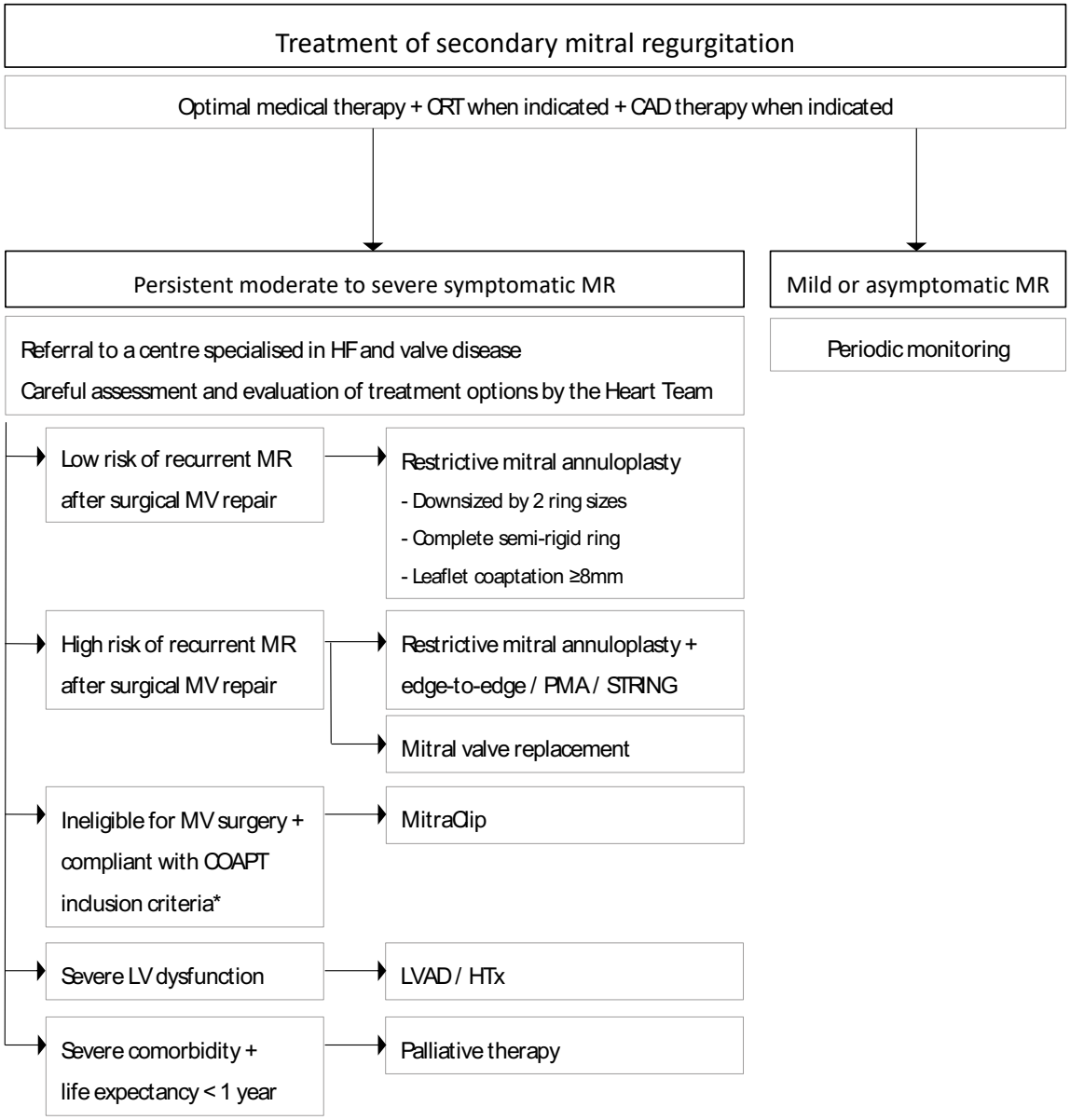
Results

Survival after LVAD implantation has steadily improved over the years, due to improvements in LVAD devices, patient selection, perioperative management and outpatient treatment. There is convincing evidence that in severe end-stage heart failure, the use of ventricular assist devices leads to remarkable improvement of life expectancy compared with GDMT.[77, 78] Nowadays, LVAD therapy has a 1-year survival of approximately 75%.[79] Concomitant MV repair is sometimes considered in patients with severe MR undergoing LVAD implantation.[80] During

LVAD support, MR seems to be irrelevant due to the continuous suction of the device in the LV, which leads to unloading of the LA and pulmonary veins, resulting in a permanently open MV. MR might become relevant again when weaning from the device or a pulsatile mode of the device is anticipated. However, since the likelihood of either of these circumstances is rather low, almost all centres prefer not to address the MR in patients undergoing LVAD implantation.

Limitations and pitfalls

LVAD implantation in patients with secondary MR might be an acceptable solution for those secondary MR patients with the worst left ventricles, but carries the risks of any LVAD implantation, i.e. thrombo-embolic events, anticoagulation-related haemorrhage and infection. Furthermore, patients with severe right ventricular dysfunction are not eligible for LVAD therapy. Therefore, LVAD implantation should be considered before right ventricular function deteriorates.



* Inclusion criteria of the COAPT trial[74]: e.g. symptomatic moderate-to-severe (grade 3+) or severe (grade 4+) MR according to the AHA/ACC guidelines definition, NYHA class II- ambulatory IV, LV ejection fraction ≥20% and ≤50%, LV end-systolic dimension ≤70mm, one hospitalization for heart failure in the 12 months prior to enrollment and/or a corrected BNP ≥300 pg/ml or a corrected NT-proBNP ≥1500 pg/ml and absence of severe tricuspid regurgitation or right ventricular failure

CAD = coronary artery disease, CRT = cardiac resynchronisation therapy, HF = heart failure, HTx = heart transplantation, LV = left ventricle, LVAD = left ventricular assist device, MR = mitral regurgitation, MV = mitral valve, PMA = papillary muscle approximation

Figure 6. Flowchart regarding the treatment of secondary mitral regurgitation.

Conclusion and future implications

The optimal treatment strategy for patients with secondary MR is the subject of ongoing debate. The cornerstone in the management of these patients remains optimal guideline-directed pharmacological and device therapy. Care for patients with persistence of secondary MR despite optimal medical therapy should be concentrated in specialized centres with expertise in heart failure and valve disease.

For patients with severe comorbidity — limiting life expectancy to <1 year — palliative therapy is warranted. For all other patients, the Heart Team — consisting of heart failure specialists, interventional cardiologists, arrhythmia cardiologists and cardiac surgeons — should carefully balance the different available treatment options.[2, 7] A flowchart regarding these treatment options is shown in Figure 6.

The benefit of percutaneous MV repair using MitraClip has recently been investigated in 2 RCTs. Results of these trials demonstrated that patients in whom heart failure is predominantly related to valvular dysfunction with relatively preserved LV function — included in the COAPT trial — derived benefit from MitraClip implantation.[74, 75] Therefore, it seems reasonable to try a transcatheter procedure in the highly selected subgroup of patients with secondary MR who fall within the inclusion criteria of this trial (as specified in Figure 6).[75]

Several surgical MV procedures have evolved over the years. Mitral valve surgery has the advantage that not only the MV can be addressed, but concomitant procedures can be performed as well, e.g. CABG, tricuspid valve repair and arrhythmia surgery. However, thus far, a survival benefit could not be observed in any of the surgical trials.

Mitral valve repair by RMA has demonstrated beneficial clinical and echocardiographic results in the majority of patients in several studies.[18, 21–23, 27] However, even in the most successful series a subgroup of patients does not show LV reverse remodelling and/or develops recurrent MR.[21, 33, 81] Since recurrence of MR is associated with significantly higher mortality[81], additional valvular or subvalvular techniques may be considered in patients with a high-risk of MV repair failure. These patients can be identified by sophisticated echocardiographic parameters (Table 2),[36–39] but a practical guide remains the tenting height. If TH exceeds 10mm, additional procedures — edge-to-edge repair, RING + STRING or PMA — can improve the outcome in terms of freedom from MR recurrence and LV reverse remodelling.

Alternatively, MV replacement can be considered to avoid MR recurrence. Mitral valve replacement provides a durable correction of MR and the CTSN trial found a reduction of heart failure events and cardiovascular hospital readmissions compared with MV repair. However,

the absence of recurrent MR after MV replacement did not translate into better LV reverse remodelling or survival.[28, 29]

Finally, in the subgroup of patients with secondary MR in whom LV dysfunction is too advanced and who most likely will not benefit from any MV procedure, the Heart Team should consider heart transplantation or LVAD therapy.

Patients with secondary MR comprise a highly heterogeneous population and should be treated in specialized centres with expertise in heart failure and valve disease. Dissatisfying outcomes are mainly associated with MR recurrence and/or absence of LV reverse remodelling—which are interrelated in a complex way. Recurrent MR may lead to absence of LV reverse remodelling and adverse clinical outcome, while the absence of LV reverse remodelling may lead to recurrence of MR and again adverse clinical outcome. Since merely resolving MR — by MV replacement — does not offer a definitive solution, the extent of LV dysfunction, rather than abolishment of MR, seems to ultimately determine the fate of patients with secondary MR — or at least for some of them. Most likely a subgroup of patients is already at a stage of LV disease where reverse remodelling and consequently better clinical outcome are no longer attainable at the time of intervention. This specific subgroup of patients will not benefit from any MV procedure, but requires an intervention addressing the underlying ventricular component. We should appreciate that the same limitations will apply to outcomes after percutaneous MV replacement — by some offered as a promising future therapy for secondary MR.

For now, the main challenge for cardiologists and cardiothoracic surgeons remains identifying the individual patients who are most likely to benefit from a MV procedure, and to select the appropriate procedure for each of them. The currently available imaging techniques primarily focus on MV configuration and LV parameters: size, geometry and function. Using these techniques, we can quite adequately predict the probability of recurrent MR after MV interventions.[36–39] However, prediction of the ability to reverse LV remodelling — which seems crucial for recovery after MV interventions — remains an area largely uncovered. Our focus should therefore be to improve imaging techniques assessing the underlying LV disease and its expected functional recovery after MV interventions, and to further improve the different percutaneous and surgical procedures, so that we are able to provide patients with secondary MR a timely and truly tailor-made treatment which optimizes their outcomes.

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Chapter 3

Surgery for severe ischaemic mitral regurgitation

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To the editor

Goldstein et al. describe the 2-year results of their trial comparing mitral valve repair with mitral-valve replacement for severe ischaemic mitral regurgitation. Translation of these findings into meaningful conclusions for everyday clinical practice requires an in-depth look at the data presented.

In this trial, patients who had a successful repair (without clinically significant recurrent regurgitation) had the potential for reverse remodelling, with a 30% reduction of the end-systolic volume index, whereas reverse remodelling was absent after valve replacement. This finding underlines the need to identify patients who have a good chance of successful repair and treat them accordingly.

Cardiac surgeons should observe that the absence of mitral regurgitation in the operating theatre after repair does not indicate that the procedure was successful. The 30% incidence of moderate regurgitation only 30 days after surgery cannot be explained by disease progression, but it should be viewed as residual rather than recurrent regurgitation related to failed repair.[1] As a previous study[2] has shown, long-term success also requires sufficient leaflet coaptation of at least 8 mm. Unfortunately, this criterion was not mandated in this trial.

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Chapter 4

Impact of recurrent mitral regurgitation after mitral valve repair for functional mitral regurgitation: Long-term analysis of competing outcomes

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Abstract

Aims: Recurrent mitral regurgitation (MR) has been reported after mitral valve repair for functional MR. However, the impact of recurrent MR on long-term survival remains poorly defined. In the present study, mortality-adjusted recurrent MR rates, the clinical impact of recurrent MR and its determinants were studied in patients after mitral valve repair with revascularization for functional MR in the setting of ischaemic heart disease.

Methods and results: Long-term clinical and echocardiographic outcome was evaluated in 261 consecutive patients after restrictive mitral annuloplasty and revascularization for moderate to severe functional MR, between 2000 and 2014. The cumulative incidence of recurrent MR ≥ grade 2, assessed by competing risk analysis, was 9.6 ± 1.8% at 1-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up. Cumulative survival was 85.8% [95% confidence interval (CI) 81.0 – 90.0] at 1-year, 67.3% [95% CI 61.1 – 72.6%] at 5-year, and 46.1% [95% CI 39.4 – 52.6%] at 10-year follow-up. Age, preoperative New York Heart Association Class III or IV, a history of renal failure, and recurrence of MR expressed as a time-dependent variable (HR 3.28 [1.87 – 5.75], p <0.001), were independently associated with an increased mortality risk. Female gender, a history of ST-elevation myocardial infarction, a preoperative QRS duration ≥120 ms, a higher preoperative MR grade, and a higher indexed left ventricular end-systolic volume were in-dependently associated with an increased likelihood of recurrent MR.

Conclusion: Mitral valve repair for functional ischaemic MR resulted in a low incidence of recurrent MR with favourable clinical outcome up to 10 years after surgery. Presence of recurrent MR at any moment after surgery proved to be independently associated with an increased risk for mortality.

Introduction

Functional mitral regurgitation (MR) is a common phenomenon in patients with ischaemic heart disease and results from a combination of increased mitral leaflet tethering and decreased closing forces, due to regional or global left ventricular (LV) remodelling.[1] Presence of functional MR induces volume overload, resulting in further LV remodelling and worsening MR. Consequently, functional MR is a relevant marker of adverse clinical outcome.[2,3]

The treatment of patients with functional MR focuses on both the mitral valve (by curing MR) and the left ventricle (by initiating and sustaining LV reverse remodelling). The most effective surgical strategy to address the mitral valve — either by mitral valve repair or by mitral valve replacement — has been studied in many (predominantly observational) studies, but remains a matter of ongoing debate.[4,5] Arguments in favour of mitral valve repair — generally by restrictive mitral annuloplasty (RMA) — are based on the presumed lower perioperative morbidity and mortality associated with mitral valve repair compared to replacement.[6] On the other hand, high recurrent MR rates reported after mitral valve repair have led to the believe that mitral valve replacement might result in better clinical outcome since it provides a more durable correction of MR.[7–10]

Recently, a randomized controlled trial was conducted by the Cardio-Thoracic Surgery network (CTSN), comparing mitral valve repair and mitral valve replacement for patients with severe functional ischaemic MR.[11,12] This trial did not demonstrate relevant differences with regard to LV reverse remodelling or survival between both groups, despite a clearly higher recurrent MR rate after mitral valve repair (33% at 1-year and 59% at 2-year follow-up) compared to mitral valve replacement (2% at 1-year and 4% at 2-year follow-up). These results have raised the question: Does recurrent MR, in terms of clinical outcome, matter at all?

Although recurrent MR was found to be associated with absence of LV reverse remodelling and adverse clinical outcome in several observational studies,[7–10] the effect of recurrent MR on long-term survival remains poorly defined. Furthermore, previous studies were not able to account for the attrition of patients due to death during follow-up. Given the high mortality in these patients, the true incidence of recurrent MR and its clinical impact may not be fully appreciated.

The aim of the present study was to evaluate long-term outcomes in patients with functional MR in the setting of ischaemic heart disease, who underwent a structured approach of mitral valve repair with revascularization, focusing on mortality-adjusted recurrent MR rates (by competing risk analysis), the clinical impact of recurrent MR and its determinants.

Methods

Study population and study design

Consecutive patients with coronary artery disease scheduled to undergo coronary artery bypass grafting (CABG) and moderate to severe chronic ischaemic MR (grade 3 or 4) due to restrictive systolic leaflet motion (Carpentier IIIb), who underwent mitral valve repair at Leiden University Medical Center between 2000 and 2014, were included. Severity of MR was assessed by echocardiography at rest, or — in patients scheduled for CABG with fluctuating MR or MR grade 2 — during bicycle exercise or intra-operative provocative testing, as previously described.[13–15] Patients with functional MR due to non-ischaemic-dilated cardiomyopathy, patients with organic mitral valve abnormalities or aortic valve disease and patients requiring LV reconstruction surgery for an LV aneurysm were excluded.

Baseline and surgical characteristics, echocardiographic data, and clinical outcome were evaluated for all patients. The study complies with the Declaration of Helsinki, the institutional medical ethics committee approved the protocol and written informed consent was obtained from all participating patients.

Surgical technique

All surgical procedures were performed through midline sternotomy under normothermic cardiopulmonary bypass with intermittent antegrade warm-blood cardioplegia. Conventional multivessel CABG was performed, aiming at complete revascularization. The mitral valve was exposed through a transseptal approach and mitral valve repair was performed with a complete semi-rigid ring (Carpentier Edwards Physio Ring, Edwards Lifesciences, Irvine, CA, USA). Ring size was carefully determined by measuring the anterior leaflet height and then downsizing by two ring sizes (i.e. size 26 when measuring 30). No additional procedures were performed on the mitral valve leaflets, nor on the subvalvular apparatus or the left ventricle itself. Concomitant tricuspid annuloplasty was performed with a Carpentier Edwards Classic or MC3 ring in patients with tricuspid regurgitation ≥ grade 2 or — from the year 2003 onward — in presence of a tricuspid annular diameter >40 mm.

Intra-operative transoesophageal echocardiographic assessment of LV and mitral valve function was performed in all patients. Mitral valve repair was considered successful in case no or mild MR and a leaflet coaptation height of at least 8 mm were observed. If these criteria were not met, further downsizing was performed.

Echocardiography

Two-dimensional and Doppler transthoracic echocardiography was performed preoperatively and before discharge in all patients. Mitral regurgitation severity was semi-quantitatively assessed on a scale from 1 to 4 by colour-flow Doppler in conventional parasternal long-axis and apical two-, three-, and four-chamber images.[16] Left atrial and LV diameters were determined from parasternal long-axis acquisitions and LV volumes were measured in apical two- and four-chamber images and indexed to body surface area (BSA).[17] Left ventricular ejection fraction (LVEF) was calculated by the modified biplane Simpson's method.[17] Transtricuspid pressure gradient was estimated using the modified Bernoulli equation on the transtricuspid continuous-wave signal.[18] Subsequent echocardiographic follow-up was performed in our institution or in the patient's home institution.

Study endpoints and follow-up

Primary endpoint of this study was recurrence of MR. The first Doppler echocardiography demonstrating MR ≥ grade 2 after surgery was considered 'MR recurrence'. Secondary endpoints were all-cause mortality, reinterventions (mitral valve reinterventions, heart transplantation, and implantation of an LV assist device) and hospital readmissions for congestive heart failure (requiring treatment with parenteral diuretics or inotropes).

After surgery, patients were followed by their personal physician at our institution or in the patient's home institution. All available echocardiographic reports were obtained to assess recurrence of MR. Information regarding clinical events was obtained by direct patient interview and patients' medical records. All endpoints were assessed from surgery until 10-year follow-up or until 1 June 2017.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median with interquartile ranges (IQR) and compared using the paired and unpaired Student's t-test. Categorical variables are described as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. Recurrence of MR and death are not independent endpoints, hence competing risk analysis was performed to assess the cumulative incidence of recurrent MR. Univariable and multivariable Fine and Gray models were used to assess preoperative variables associated with recurrence of MR.[19] The Kaplan–Meier method was used to estimate absolute mortality risk. Univariable and multivariable Cox proportional hazards regression analyses were performed to analyse variables associated with all-cause mortality; MR recurrence was

analysed as time-dependent variable. For the comparison of patients with and without recurrent MR we used recurrent MR as time-dependent covariate to avoid immortal time bias. A level of p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistical software version 20.0 (IBM Corp., Armonk, NY, USA) or Stata version 14 (StataCorp., College Station, TX, USA: StataCorp LP).

Table 1. Baseline characteristics (n = 261).

	Whole cohort (n = 261)	Recurrent MR (n = 67)	No recurrent MR (n = 194)	p-value
Clinical data				
Age (years)	69 ± 9	69 ± 8	69 ± 9	0.948
Female	81 (31%)	28 (42%)	53 (27%)	0.027
BSA (m^2)	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.006
NYHA class	2.7 ± 0.8	2.8 ± 0.9	2.6 ± 0.8	0.165
CCS class	1.8 ± 1.3	1.9 ± 1.3	1.8 ± 1.2	0.535
Diabetes	64 (25%)	14 (21%)	50 (26%)	0.424
Renal failure	11 (4%)	6 (9%)	5 (3%)	0.036
COPD	25 (10%)	7 (10%)	18 (9%)	0.779
Hypertension	88 (34%)	24 (36%)	64 (33%)	0.673
Stroke / TIA	29 (11%)	6 (9%)	23 (12%)	0.515
STEMI	180 (69%)	54 (81%)	126 (65%)	0.017
Atrial fibrillation	39 (15%)	6 (10%)	33 (17%)	0.100
QRS duration (ms)	122 ± 33	128 ± 34	120 ± 33	0.075
Previous cardiac surgery	49 (19%)	16 (24%)	33 (17%)	0.214
Pulmonary hypertension	13 (5%)	6 (9%)	7 (4%)	0.083
ICD	20 (8%)	6 (9%)	14 (7%)	0.645
CRT	6 (2%)	1 (1%)	5 (3%)	0.609
Log EuroSCORE I	12.9 ± 12.3	17 ±15	11 ± 11	0.001
Echocardiographic data				
MR grade	3.0 ± 0.7	3.3 ± 0.6	2.9 ± 0.7	0.001
Grade 2	36 (14%)	4 (6%)	32 (16%)	
Grade 3	134 (51%)	32 (48%)	102 (53%)	
Grade 4	91 (35%)	31 (46%)	60 (31%)	
LA dimension (mm)	46 ± 7	46 ± 8	45 ± 7	0.372
LV end-diastolic dimension (mm)	61 ± 8	64 ± 9	60 ± 8	0.002
Indexed to BSA (mm/m^2)	32 ± 5	35 ± 5	32 ± 4	<0.001
LV end-systolic dimension (mm)	50 ± 10	53 ± 10	48 ± 9	<0.001
Indexed to BSA (mm/m^2)	26 ± 6	29 ± 6	25 ± 5	<0.001
LV ejection fraction (%)	37 ± 9	35 ± 8	38 ± 9	0.077
LV end-diastolic volume (ml)	168 ± 59	192 ± 64	159 ± 55	<0.001
Indexed to BSA (ml/m^2)	88 ± 29	103 ± 31	82 ± 26	<0.001
LV end-systolic volume (ml)	108 ± 47	126 ± 48	102 ± 45	<0.001
Indexed to BSA (mm/m^2)	56 ± 24	68 ± 25	53 ± 22	<0.001
Transtricuspid PG (mmHg)	30 ± 11	30 ± 10	31 ± 11	0.975

BSA = body surface area, CCS = Canadian Cardiovascular Society, COPD = Chronic obstructive pulmonary disease, CRT = cardiac resynchronization therapy, ICD = implantable cardioverter-defibrillator, MR = mitral regurgitation, LA = left atrium, LV = left ventricle, PG = pressure gradient, NYHA = New York Heart Association, STEMI = ST-elevation myocardial infarction, TIA = transient ischaemic attack.

Results

Study population

Two hundred and sixty-one patients, who underwent RMA for moderate to severe functional ischaemic MR between 2000 and 2014, were included. Baseline patient characteristics are summarized in Table 1. Mean age was 69 ± 9 years. All patients had coronary artery disease and 69% had a previous ST-elevation myocardial infarction (STEMI); 63% of patients were in New York Heart Association (NYHA) Class III or IV. Preoperative echocardiographic assessment demonstrated MR grade 3 in 51% of patients and grade 4 in 35%. In 36 patients scheduled for CABG with fluctuating MR or MR grade 2, MR increased to grade 3 or 4 during bicycle exercise testing (n = 8) or intra-operative provocative testing (n = 28). Mean LV end-systolic volume indexed to BSA (LVESVI) was 56 ± 24 mL/m^2 and mean LVEF was 37 ± 9%.

Surgical data are summarized in Table 2. Mitral valve repair could be achieved in all patients (mean implanted ring size 26 ± 2). Intra-operative transoesophageal echocardiography demonstrated a competent mitral valve in all patients (no MR in 95%, trace or grade 1 MR in 5% of patients) with a mean leaflet coaptation height of 8 ± 1 mm.

Table 2. Surgical data (n = 261).

	Whole cohort (n = 261)	Recurrent MR (n = 67)	No recurrent MR (n = 194)	p-value
Mitral annular diameter	30 ± 2	30 ± 2	30 ± 2	0.407
Mitral annuloplasty ring size	26 ± 2	27 ± 2	26 ± 2	0.486
24	66 (25%)	18 (27%)	47 (24%)	
26	95 (36%)	18 (27%)	78 (40%)	
28	83 (32%)	27 (40%)	56 (29%)	
30	15 (6%)	3 (5%)	12 (6%)	
32	2 (1%)	1 (1%)	1 (1%)	
Coronary artery bypass grafting	226 (87%)	56 (84%)	170 (88%)	0.402
No. of distal anastomosis	3.0 ± 1.3	3.0 ± 1.2	3.0 ± 1.4	0.773
Tricuspid valve annuloplasty	84 (32%)	20 (30%)	64 (33%)	0.635
AF ablation	33 (13%)	25 (13%)	8 (12%)	0.841
CPB time	191 ± 64	191 ± 58	192 ± 67	0.971
Aortic cross-clamp time	134 ± 46	126 ± 42	136 ± 47	0.207

AF = atrial fibrillation, CPB = cardiopulmonary bypass, MR = mitral regurgitation.

Recurrence of mitral regurgitation

Echocardiographic follow-up was performed in >80% of alive patients for each defined time interval between surgery and 10 years after surgery (Figure 1). After surgery, recurrence of MR ≥ grade 2 was diagnosed in 67 patients, at a median of 1.7 years [IQR 0.5 – 4.7] post-operatively. Recurrent MR was observed at discharge in 10 patients (MR grade 2 in eight patients and grade

3 in two patients), whereas recurrence of MR developed after discharge in 57 patients. The cumulative incidence of recurrent MR was 9.6 ± 1.8% at 1-year, 14.3 ± 2.2% at 2-year, 16.6 ± 2.3% at 3-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up (**Figure 2**).

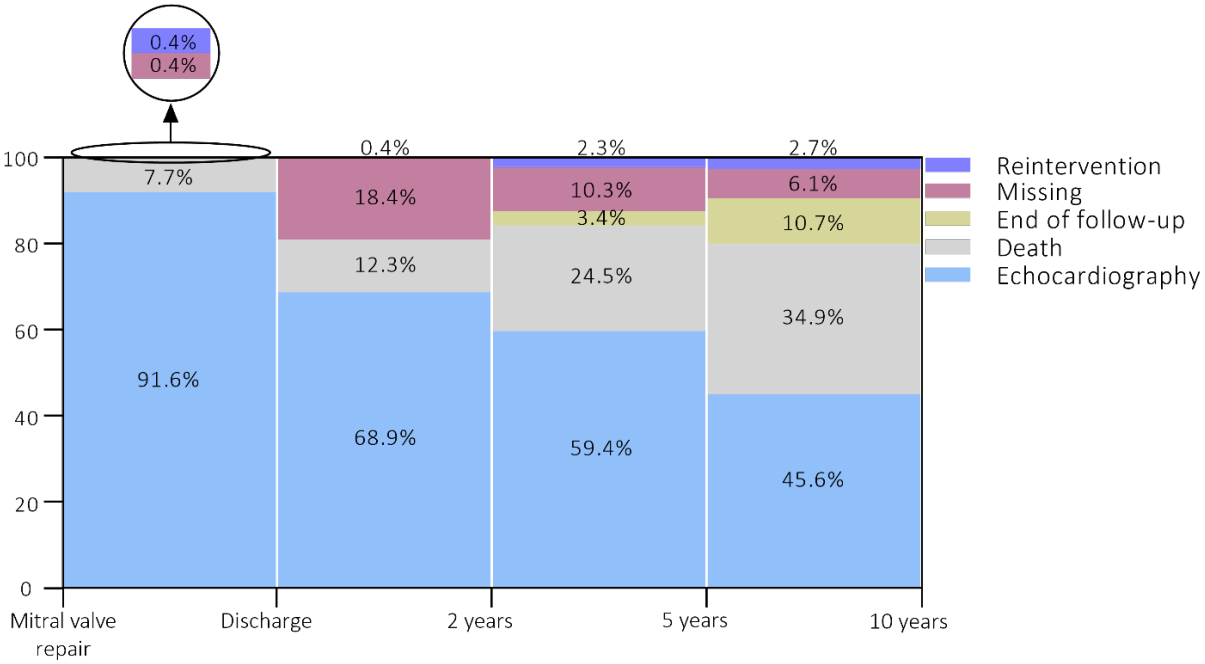


Figure 1. Echocardiographic follow-up.

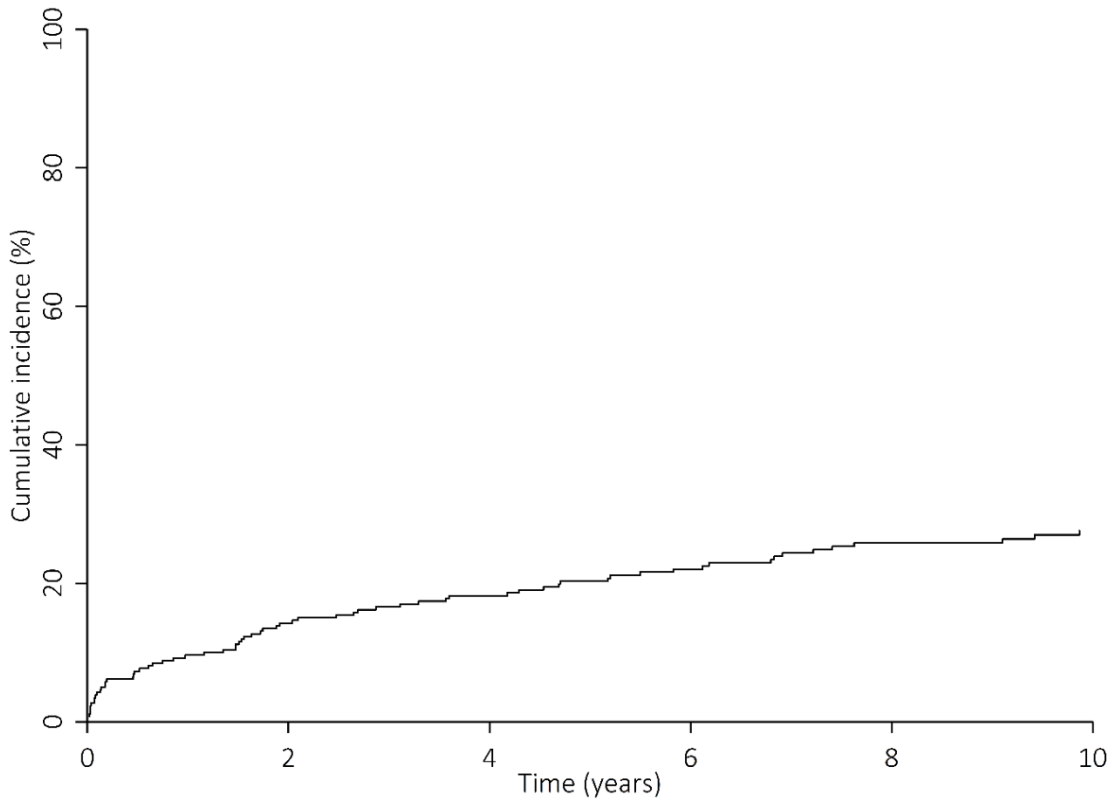


Figure 2. Cumulative incidence of recurrent mitral regurgitation by competing risk analysis.

Clinical outcome

Clinical follow-up was complete and median follow-up duration was 6.8 years [IQR 3.0 – 10.0]. During follow-up, 10 patients (3.8%) underwent a reintervention. In eight patients, the reintervention was performed for recurrent MR, due to ring dehiscence (n = 2), endocarditis (n = 2), and progressive mitral leaflet tethering (n = 4). The mitral annuloplasty ring was removed because of mitral valve stenosis in one patient. Finally, one patient with progressive heart failure underwent LV assist device implantation. Eighty-three hospital survivors (34%) were rehospitalized for congestive heart failure; these patients experienced 156 readmissions (9.8 per 100 patient years). A total of 127 patients died (including 20 in-hospital deaths) Cumulative survival was 85.8% [95% confidence interval (CI) 81.0 – 90.0] at 1-year, 80.1% [95% CI 74.7 – 84.4%] at 2-year, 67.3% [95% CI 61.1 – 72.6%] at 5-year, and 46.1% [95% CI 39.4 – 52.6%] at 10-year follow-up (**Figure 3**).

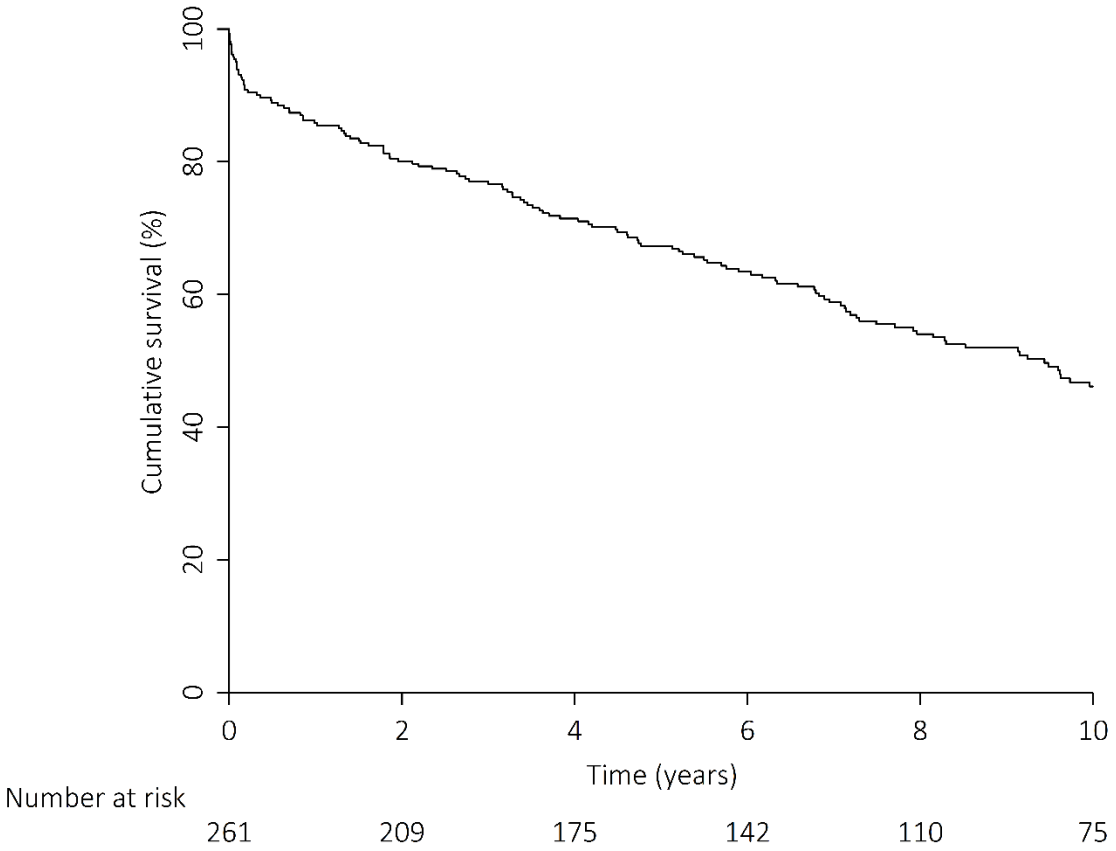


Figure 3. Survival after mitral valve repair.

Predictors for mortality and significance of recurrent mitral regurgitation

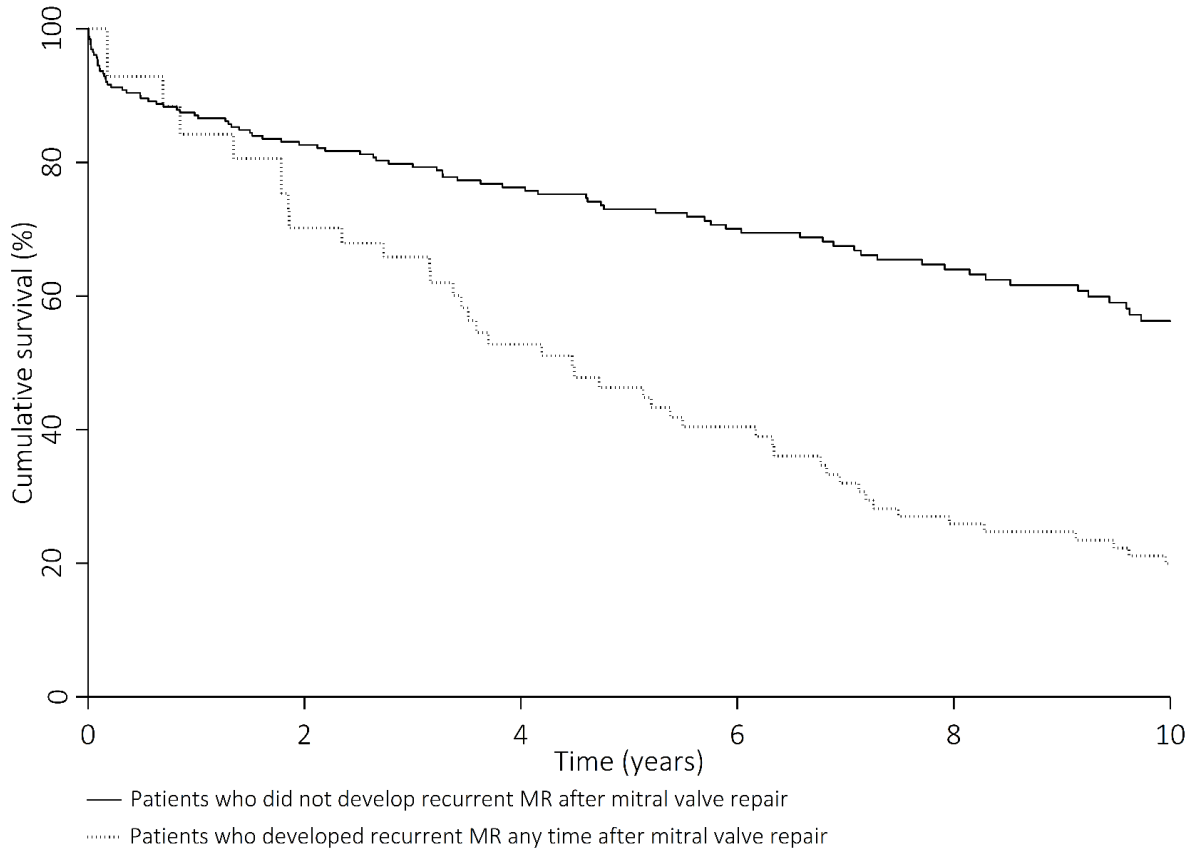
Predictors for all-cause mortality are presented in Table 3. After correction for potential confounders, the following variables were associated with an increased mortality risk: age (HR 1.05 [1.02 – 1.08], p = 0.002), preoperative NYHA Class III or IV (HR 2.08 [1.56 – 3.74], p = 0.015), a history of renal failure (HR 3.35 [1.46 – 7.71], p = 0.004), and recurrence of MR expressed as a time-dependent variable (HR 3.28 [1.87 – 5.75], p <0.001). The clinical impact of recurrent MR on survival is displayed in the Take home figure.

Reinterventions were performed in eight patients (11.9%) with recurrent MR compared with two patients (1.2%) without recurrent MR (p = 0.001). Furthermore, recurrent MR was associated with an increased risk for readmissions for congestive heart failure (HR 2.19 [1.40 – 3.44], p = 0.001); 51% of patients with recurrent MR were readmitted for congestive heart failure (16.8 rehospitalizations per 100 patient years) compared to 30% of patients without recurrent MR (7.2 rehospitalizations per 100 patient years).

Table 3. Predictors for all-cause mortality after surgery (n=261).

	Univariable		Multivariable	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Preoperative clinical data				
Age	1.04 [1.02 – 1.06]	<0.001	1.05 [1.02 – 1.08]	0.002
Female gender	0.97 [0.66 – 1.41]	0.866		
NYHA class III – IV	1.75 [1.13 – 2.71]	0.013	2.08 [1.56 – 3.74]	0.015
Diabetes Mellitus	1.12 [0.75 – 1.67]	0.578		
Renal failure	2.23 [1.13 – 4.40]	0.021	3.35 [1.46 – 7.71]	0.004
STEMI	1.25 [0.84 – 1.85]	0.279		
Atrial fibrillation	1.14 [0.69 – 1.89]	0.610		
Previous cardiac surgery	1.50 [1.00 – 2.27]	0.056	1.48 [0.77 – 2.83]	0.235
QRS duration ≥ 120ms	1.57 [1.10 – 2.26]	0.014	1.30 [0.74 – 2.27]	0.355
CRT	1.96 [0.72 – 5.30]	0.187		
Preoperative echocardiographic data				
MR grade	1.23 [0.96 – 1.58]	0.107		
LV ejection fraction ≥ 30%	1.27 [0.81 – 1.98]	0.293		
LV end-systolic volume indexed to BSA (ml/m^2)	1.01 [1.00 – 1.02]	0.008	1.01 [1.00 – 1.02]	0.070
Operative data				
Mitral annuloplasty ring size	1.00 [0.90 – 1.10]	0.979		
Concomitant CABG	0.83 [0.51 – 1.36]	0.460		
Concomitant TVP	0.96 [0.65 – 1.42]	0.852		
Concomitant AF ablation	0.81 [0.45 – 1.42]	0.448		
CPB time	1.00 [1.00 – 1.01]	0.017	1.00 [1.00 – 1.01]	0.327
Follow-up data				
MR recurrence*	3.15 [2.13 – 4.65]	<0.001	3.28 [1.87 – 5.75]	<0.001

*MR recurrence was analysed as a time-dependent variable. CABG = coronary artery bypass grafting, CI = confidence interval, HR = hazard ratio, TVP = tricuspid valve annuloplasty, other abbreviations as in Table 1.



Take home figure. Two hundred sixty-one patients underwent mitral valve repair for ischaemic functional MR. Recurrence of MR was observed in 67 patients, whereas recurrent MR was absent in 194 patients. Time-dependent Cox regression analysis shows that patients without recurrent MR (solid line) have significantly better survival compared to patients who develop recurrent MR at any time after mitral valve repair (dotted line).

Predictors for recurrent mitral regurgitation

Given that recurrent MR was associated with adverse clinical outcome, we aimed to identify preoperative predictors for MR recurrence. Comparison of clinical characteristics of patients with and without recurrent MR (Table 1) demonstrated that patients with recurrent MR were more often female, had a higher EuroSCORE and more were more likely to have a history of renal failure or STEMI. Comparison of preoperative echocardiographic characteristics showed a higher preoperative MR grade and larger LV dimensions and volumes in patients with recurrent MR compared to patients without recurrent MR (Table 1). Surgical data were not clearly different between both groups (Table 2).

Multivariable regression analysis (according to Fine and Gray's subdistribution hazards model) demonstrated that female gender (subdistribution hazard ratio (sHR) 2.11 [1.12 – 3.99], p = 0.022), a history of STEMI (sHR 2.43 [1.19 – 4.92], p = 0.014), a preoperative QRS duration ≥120 ms (sHR 2.16 [1.14 – 4.09], p = 0.019), a higher preoperative MR grade (sHR 1.59 [1.03 – 2.47], p = 0.037), and a higher LVESVI (sHR 1.02 [1.01 – 1.03], p = 0.001) were all independently associated with an increased likelihood of recurrent MR (Table 4).

Table 4. Predictors of MR recurrence (n=261).

	Univariable		Multivariable	
	sHR [95% CI]	p-value	sHR [95% CI]	p-value
Preoperative clinical data				
Age	1.00 [0.97 – 1.03]	0.988		
Female gender	1.84 [1.13 – 3.01]	0.015	2.11 [1.12 – 3.99]	0.022
NYHA class III/IV	1.09 [0.64 – 1.87]	0.754		
Renal failure	2.62 [1.17 – 5.87]	0.020	1.79 [0.79 – 4.04]	0.161
STEMI	1.99 [1.09 – 3.62]	0.025	2.43 [1.19 – 4.96]	0.014
Atrial fibrillation	0.52 [0.23 – 1.20]	0.124		
Pulmonary hypertension	2.56 [1.05 – 6.24]	0.039	1.84 [0.69 – 4.92]	0.223
QRS duration ≥120ms	2.30 [1.38 – 3.82]	0.001	2.16 [1.14 – 4.09]	0.019
CRT	0.62 [0.08 – 4.64]	0.640		
Preoperative echocardiographic data				
MR grade	1.98 [1.40 – 2.82]	<0.001	1.59 [1.03 – 2.47]	0.037
LV ejection fraction ≥30%	1.49 [0.84 – 2.65]	0.175		
LV end-systolic volume indexed to BSA (ml/m^2)	1.02 [1.01 – 1.03]	<0.001	1.02 [1.01 – 1.03]	0.001
Operative data				
Mitral annuloplasty ring size	1.05 [0.92 – 1.21]	0.460		
Concomitant CABG	0.74 [0.38 – 1.44]	0.379		
CPB time	1.00 [1.00 – 1.00]	0.933		

CI, confidence interval; sHR, subdistribution hazard ratio; other abbreviations as in Table 1 and 2.

Discussion

In the present study, long-term clinical and echocardiographic outcome — specifically focusing on the incidence, clinical impact and determinants of recurrent MR — was evaluated in patients who underwent mitral valve repair for functional ischaemic MR. Main findings of this study are: 1) The overall cumulative incidence of recurrent MR was 9.6 ± 1.8% at 1-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up; 2) Recurrence of MR during follow-up significantly increased the risk for reoperations, hospital readmissions, and mortality; 3) Female gender, a history of STEMI, preoperative QRS duration ≥ 120 ms, higher preoperative MR grade, and higher preoperative LVESVI were independently associated with an increased likelihood of recurrent MR following mitral valve repair.

Incidence of recurrent mitral regurgitation

Functional MR is a common phenomenon in patients with coronary artery disease and is independently associated with adverse clinical outcome. Mitral valve repair — by implantation of an RMA ring — aims to restore mitral valve competence and initiate LV reverse remodelling, in order to improve clinical outcome in these patients. Although several studies demonstrated that RMA can ensure a durable correction of MR,[20–24] others reported considerable incidences of recurrent MR.[7–10] However, follow-up duration was limited and different surgical techniques were used in these studies. More importantly, none of these studies accounted for the competing risk of death, which may mask the true incidence of recurrent MR.

In the present study, recurrence of MR was assessed up to 10 years after mitral valve repair and we uniquely accounted for death as a competing event. The cumulative incidence of recurrent MR observed in the current study — 10% at 1-year, 14% at 2-year, 20% at 5-year, and 28% at 10-year follow-up — is lower than that observed in many observational studies[7–10] and far lower than the incidence recently reported by the CTSN investigators (33% at 1-year and 59% at 2-year follow-up).[11,12] Although the observed difference may partly be explained by the fact that preoperative MR grade was higher in the CTSN trial (including only patients with severe MR) compared to the present study (including patients with moderate to severe MR), preoperative LVESVI and LVEF were comparable (61 ± 26 mL/m^2 and 42 ± 12% in the CTSN trial, vs. 56 ± 24 mL/m^2 and 37 ± 9% in the present study). The low incidence of recurrent MR observed in the present study, might therefore rather be explained by the structured surgical approach to patients with functional ischaemic MR in our institution. This approach consists of implantation of a semi-rigid annuloplasty ring, stringently downsized by two ring sizes, and aiming at a coaptation length of at least 8 mm. In contrast, in other studies uniformity in ring type and sizing is often lacking and leaflet coaptation at the end of surgery is not routinely

assessed. Furthermore, durability of mitral valve repair may be related to the experience of the surgeon performing the procedure.[4,5] Recurrent MR was observed in 4% of hospital survivors at discharge in the current study, whereas the CTSN trial reported a recurrent MR rate of 30% within 30 days after surgery.[12] Such a high incidence cannot be explained by disease progression and should be considered residual MR due to suboptimal repair rather than recurrent MR.

Clinical outcome and significance of recurrent mitral regurgitation

Follow-up duration in the present study is longer than in any previous report. The observed survival rates — 86% at 1-year, 80% at 2-year, 67% at 5-year, and 46% at 10-year follow-up — are better than short-term survival rates in some previous reports[8,25,26] and comparable to those reported by others.[20–24] We identified four preoperative predictors for adverse long-term survival: age, preoperative NYHA functional Class III or IV, a history of renal failure, and recurrence of MR. Several previous studies have shown that recurrence of MR is associated with absence of LV reverse remodelling and poor clinical outcome.[7–10] However, to the best of our knowledge, this study is the first to demonstrate that recurrence of MR occurring at any moment during the course of follow-up is independently associated with poor long-term clinical outcome, including an increased risk of reoperation, heart failure readmissions, and a three times higher risk of death [HR 3.28 (1.87 – 5.75), p <0.001].

Preoperative predictors for recurrence of mitral regurgitation

Since recurrence of MR independently affects subsequent clinical outcome, preoperative patient selection — based on the likelihood to develop recurrent MR — is crucial to optimize outcome after mitral valve repair. In the current study, female gender, a history of STEMI, preoperative QRS duration ≥ 120 ms, higher preoperative MR grade, and higher preoperative LVESVI were associated with an increased risk for recurrent MR. In line with earlier reports, these parameters can almost all be related to LV remodelling, underlining once again that the extent of remodelling of the LV plays a key role in determining the success of mitral valve repair.[7,10,27–29] These findings can be used in the decision-making process on the optimal treatment of patients with functional ischaemic MR, which should be performed on a case-by-case basis by the Heart Team, as proposed by the current ESC/EACTS guidelines.[4,5]

Clinical implications

The optimal surgical strategy to treat patients with functional MR in the setting of ischaemic heart disease—either by mitral valve repair or by mitral valve replacement — remains a topic of debate. The high incidences of recurrent MR reported after mitral valve repair increasingly lead to the believe that mitral valve replacement might be the better option.

Results of the present study convey two important messages: first, it demonstrates that a structured surgical approach to mitral valve repair results in a low incidence of recurrent MR and favourable clinical outcome up to 10 years after surgery. These findings stress the importance of using a complete semi-rigid annuloplasty ring, proper downsizing and obtaining a supra-physiologic coaptation length. Second, in the subgroup of patients developing recurrent MR after surgery, the risk for poor clinical outcome was significantly increased. These findings may lead to the conclusion that mitral valve replacement should be preferred over mitral valve repair. However, several studies have demonstrated that patients after a successful mitral valve repair (without recurrent MR) have potential for LV reverse remodelling.[20–24] Even the CTSN trial shows a 30% decrease in indexed LV end-systolic volume in patients after successful mitral valve repair, whereas a volume reduction of only 10% was observed in patients after mitral valve replacement.[11,12] Based on these results a durable mitral valve repair seems to be better than a mitral valve replacement. Therefore, the key focus for future studies should be aimed at identifying preoperative parameters to select patients with potential for a durable mitral valve repair. Mitral valve replacement or mitral valve repair with additional subvalvular techniques should be considered only in patients without such potential.

Study limitations

The present study is an observational, retrospective study and may therefore bear associated biases. After the discharge echocardiogram, follow-up was performed either at our institution or in the patient's home institution. Since the quality of echocardiograms performed elsewhere could not be individually confirmed, the possibility exists that some of the patients with follow-up outside our institution had MR recurrence, which was not detected. Furthermore, patients with missing echocardiographic follow-up data could have developed recurrent MR. However, echocardiographic follow-up from surgery up to 10 years after surgery was complete in >80% of alive patients. The contribution of coronary revascularization and mitral valve repair to LV reverse remodelling and thus MR recurrence and outcome cannot be assessed separately. Data on myocardial viability or the extent of scar tissue was very limited in our study population, and therefore, its importance could not be taken into consideration. However, all patients underwent complete revascularization to maximize the potential for LV recovery. Finally, due

to the long-term follow-up (inclusion of patients started in 2000), technical challenges resulted in the limited use of qualitative and semi-quantitative parameters for assessment of MR severity, whereas in the most recent recommendations the use of quantitative parameters is recommended.[28]

Conclusion

In the present study, a structured approach of mitral valve repair for functional MR due to ischaemic heart disease resulted in a low incidence of recurrent MR and favourable clinical outcome up to 10 years after surgery. Presence of recurrent MR at any moment after surgery proved to be independently associated with an increased risk for reinterventions, readmissions for congestive heart failure, and mortality. These findings indicate that mitral valve repair is a suitable treatment option for the vast majority of patients with functional MR. Given the clear clinical impact of recurrent MR, future studies should aim at preoperative identification of patients with a high likelihood of developing recurrent MR.

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Chapter 5

Prognostic value of left ventricular reverse remodelling and recurrent mitral regurgitation after personalised surgical treatment of patients with non-ischaemic cardiomyopathy and functional mitral regurgitation

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Abstract

Objectives: The aim of this study was to determine the prevalence of left ventricular reverse remodelling (LVRR) and recurrent mitral regurgitation (MR) at mid-term follow-up (1–2 years after surgery) in patients after personalised surgical treatment of heart failure and functional MR due to non-ischaemic cardiomyopathy and to assess their prognostic impact on long-term clinical outcomes.

Methods: Consecutive patients with refractory heart failure and non-ischaemic MR, who underwent mitral valve surgery with or without additional procedures, were identified. Patients with complete preoperative and mid-term echocardiographic data were included. LVRR (≥15% decrease in indexed left ventricular end-systolic volume) and recurrent MR (≥ grade 2) were echocardiographically assessed at midterm follow-up, and the primary end point was a composite of all-cause mortality and heart transplantation (HTx-free survival).

Results: The prevalence of LVRR was 38%, and the prevalence of recurrent MR was 20% at mid-term follow-up. The absence of LVRR and the presence of recurrent MR — which were highly correlated — were significantly associated with worse HTx-free survival. HTx-free survival 1 and 3 years after mid-term follow-up were 100% and 88 ± 6% in patients with LVRR (n = 29), 82 ± 7% and 68 ± 8% in patients without LVRR and without recurrent MR (n = 34), and 49 ± 14% and 33 ± 13% in patients without LVRR and with recurrent MR (n = 14).

Conclusions: Patients with LVRR at mid-term follow-up showed favourable HTx-free survival, whereas HTx-free survival was significantly worse in patients without LVRR and without recurrent MR and extremely poor in patients without LVRR and with recurrent MR. Close echocardiographic monitoring is warranted for timely identification of this latter subgroup of patients, in order to re-evaluate additional treatment options and improve their prognosis.

Introduction

Functional mitral regurgitation (MR) is frequently observed in patients with non-ischaemic cardiomyopathy and is associated with poor prognosis.[1,2] Functional MR results from a combination of papillary muscle displacement, systolic leaflet tethering, annular dilatation and decreased closing forces due to left ventricular (LV) remodelling. Subsequently, functional MR causes volume overload which induces a vicious cycle of progressive LV remodelling and worsening MR.[3]

In patients with moderate-to-severe or severe non-ischaemic MR who remain symptomatic despite optimal guideline-directed medical therapy, consisting of a combination of pharmacological treatment and device therapy [use of an internal cardiac defibrillator and/or cardiac resynchronization therapy (CRT)], surgical treatment options may be considered.[4-6] These options include heart transplantation (HTx), implantation of an LV assist device or mitral valve repair. The optimal treatment strategy for these patients is still a point of debate, as reflected by the current guidelines.[5,6] Therefore, these patients require a personalised treatment plan by a dedicated Heart Team.

Mitral valve repair in non-ischaemic cardiomyopathy, by implantation of a restrictive mitral annuloplasty (RMA) ring, aims at restoring mitral valve competence and initiating LV reverse remodelling (LVRR). Several studies have shown that RMA results in improved New York Heart Association (NYHA) functional class, better quality of life and LVRR.[7-10] Furthermore, results from the Acorn trial showed more extensive decrease of LV volumes after RMA with concomitant implantation of a cardiac support device (CSD), compared with RMA alone.[11,12] On the other hand, considerable incidences of recurrent MR have been reported after RMA[10,13,14], which has led to reluctance to perform mitral valve repair with or without concomitant ventricular procedures in patients with non-ischaemic MR. However, the impact of both LVRR and recurrent MR on long-term clinical outcome remains unknown.

The objective of this study was to determine the prevalence of LVRR and recurrent MR at mid-term follow-up (between 1 and 2 years after surgery) in patients who underwent personalised surgical treatment for heart failure and functional MR due to non-ischaemic cardiomyopathy, assess their prognostic impact on long-term clinical outcome and identify baseline predictors of both LVRR and recurrent MR.

Patients and Methods

Study population and study design

Consecutive patients with refractory heart failure with reduced ejection fraction and moderate-to-severe or severe functional MR due to non-ischaemic cardiomyopathy, who underwent mitral valve surgery at Leiden University Medical Centre between 2003 and 2014, were retrospectively identified. Baseline and surgical characteristics, echocardiographic data and clinical outcomes were evaluated for all patients. For the purpose of this study, only patients with complete preoperative and mid-term echocardiographic data were included.

This study complied with the Declaration of Helsinki, the institutional medical ethics committee approved the protocol, and written informed consent was obtained from all patients.

Surgical indications and procedure

All surgical procedures were performed via midline sternotomy with normothermic cardiopulmonary bypass and intermittent antegrade warm blood cardioplegia. The mitral valve was exposed through a vertical transseptal approach along the right border of the foramen ovale. Mitral valve repair was performed using RMA. The ring size (Carpentier–Edwards Physio ring; Edwards Lifesciences, Irving, CA, USA) was determined after careful measurement of the anterior leaflet height and then downsized by 2 ring sizes (i.e. size 26 when measuring 30). Mitral valve repair was considered successful if there was no/trivial residual MR and a minimum coaptation length of 8mm on intraoperative echocardiography. Concomitant implantation of a CorCap (Acorn Cardiovascular, St. Paul, MN, USA) CSD was performed in patients with advanced LV remodelling, i.e. preoperative LV end-diastolic diameter (LVEDD) ≥65 mm or indexed LVEDD ≥30 mm/m^2. The CSD was implanted on the beating heart with suture fixation of the device to the dorsal base of the heart along the atrioventricular groove. At the end of the surgical procedure, the CSD was tailored to meet the preoperative LV dimensions measured on transoesophageal echocardiography. Tricuspid valve repair was performed with a Carpentier–Edwards MC3 annuloplasty ring in patients with tricuspid regurgitation ≥ grade 3 and/or a tricuspid annular diameter >40 mm (or ≥21 mm/m^2 body surface area). In patients without CRT, an epicardial LV lead was implanted at the anterolateral LV wall to facilitate future resynchronization therapy. In patients with persistent atrial fibrillation, radiofrequency ablation was performed.

Echocardiographic assessment

Two-dimensional and Doppler transthoracic echocardiograms were performed preoperatively, before discharge and at midterm follow-up (between 1 and 2 years after surgery). All echocardiographic images were digitally stored and analysed offline by 2 independent investigators.

Mitral and tricuspid regurgitation severity were graded semiquantitatively from colour-flow Doppler[15] in the conventional parasternal long-axis and apical 4-chamber images early in this series and using the integrative approach in more recent years.[16] Left-sided cardiac chamber dimensions were determined from parasternal long-axis acquisitions.[17] LV volumes were measured in apical 2- and 4-chamber images and indexed to body surface area. LV ejection fraction (LVEF) was calculated by the modified biplane Simpson's method.[17] Systolic pulmonary artery pressure was estimated using the modified Bernoulli equation on the transtricuspid continuous-wave signal by adding the estimated right atrial pressure.[18]

Subsequent echocardiographic follow-up was performed in our institution or in the patient's home institution. Follow-up echocardiographic data regarding MR severity were assessed as collected.

LVRR was defined as at least 15% reduction of preoperative indexed LV end-systolic volume (LVESVI) at mid-term follow-up. Recurrent MR was defined as MR ≥ grade 2 and was assessed using the mid-term echocardiogram and from then up to 10-year follow-up or until 1 April 2017.

Clinical outcome

The primary end point of this study was a composite of all-cause mortality and HTx. Secondary end points were defined as mitral valve reintervention and hospital readmission for congestive heart failure (requiring treatment with parenteral diuretics or inotropes).

All end points were assessed by mid-term echocardiography until the 10-year follow-up or 1 April 2017. Information regarding the clinical end points was obtained by direct patient interview, use of a cardiovascular event questionnaire and the medical records of the patients.

Statistical analyses

Statistical analysis was performed using SPSS statistical software version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation and compared using the paired and unpaired Student's t-tests, when appropriate. Categorical variables are described as frequencies and percentages and compared using the X^2 or Fisher's

exact test. The Kaplan–Meier method was used to estimate cumulative time-to-event risks. Univariable and multivariable Cox proportional hazards regression analyses were performed to assess variables associated with HTx-free survival (freedom from all-cause mortality and HTx) after mid-term echocardiographic follow-up. Finally, univariable logistic regression analysis was performed to determine preoperative predictors of LVRR and recurrent MR, and variables with p-value <0.1 were entered in a multivariable logistic regression model. For all tests, a p-value of <0.05 was considered significant.

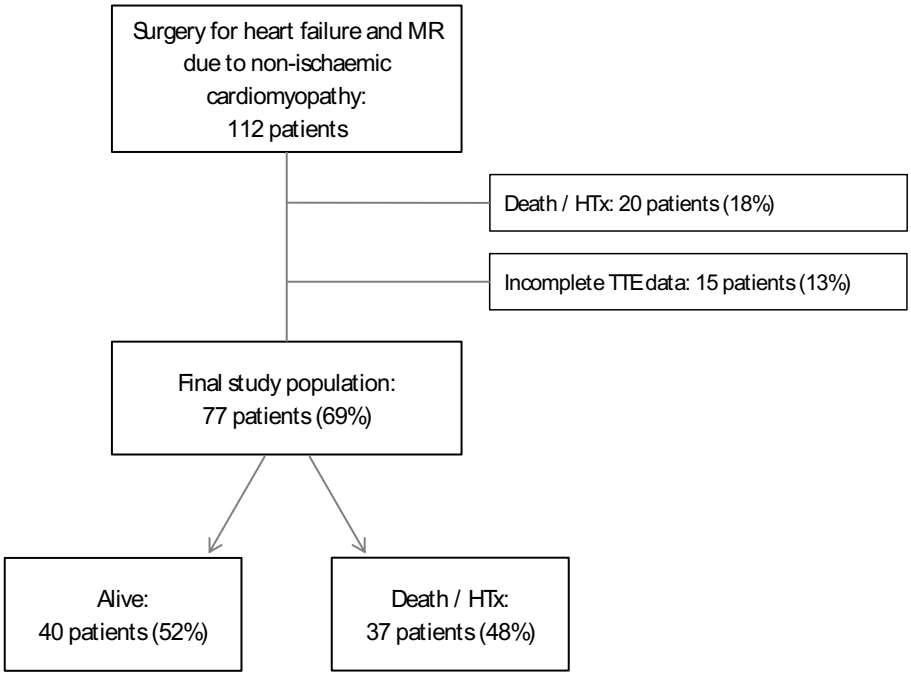

Figure 1. Flowchart of the study population.
HTx = heart transplantation, MR = mitral regurgitation, TTE = transthoracic echocardiography.

Results

Study population

A total of 112 patients with heart failure and moderate-to-severe or severe MR due to non-ischaemic cardiomyopathy underwent mitral valve surgery between 2003 and 2014. Complete preoperative and mid-term echocardiographic data were available for 77 of 112 patients (Figure 1). Baseline and surgical characteristics of these 77 patients are summarized in Table 1. Mean age was 62 ± 11 years and 51% were female. All patients were on optimal guideline-directed medical therapy, and indications for surgery were established by a dedicated Heart Team. Mean NYHA functional class was 3.0 ± 0.5 with 95% of patients in NYHA class III or IV. Preoperative echocardiographic assessment demonstrated a mean MR grade of 3.4 ± 0.6 and advanced LV remodelling (LVESVI 79 ± 29 ml/m^2) with reduced LVEF (28 ± 8%; Table 2). All patients underwent RMA surgery, with an implanted ring size of 24 or 26 in 75% of patients. Intraoperative echocardiography showed a competent mitral valve in all patients with a mean coaptation length of 8 ± 1 mm. A CSD was implanted in 68% of patients, concomitant tricuspid annuloplasty was performed in 84% of patients, and 31% of patients underwent ablation for atrial fibrillation. After surgery, patients continued to receive guideline directed medical therapy in a structured outpatient follow-up programme; 64% of patients had CRT and 68% had an internal cardiac defibrillator.

Outcomes at mid-term follow-up

Overall echocardiographic and functional outcome

Echocardiographic assessment at mid-term follow-up (mean 16 ± 7 months after surgery) demonstrated an overall decrease in LV volumes with a concomitant improvement in LVEF. Furthermore, mean MR grade significantly decreased from 3.4 ± 0.6 preoperatively to 1.1 ± 1.0 ($p < 0.001$, Table 2). Mean NYHA functional class had significantly improved from 3.0 ± 0.5 preoperatively to 2.1 ± 0.8 at mid-term follow-up ($p < 0.001$).

Prevalence of reverse remodelling and recurrent mitral regurgitation

LVRR was observed in 29 of 77 (38%) patients. In patients with LVRR, LVESVI decreased from 82 ± 22 ml/m2 preoperatively to 46 ± 16 ml/m^2 at mid-term follow-up ($p < 0.001$) with improved LVEF (27 ± 7 vs 38 ± 8%, $p < 0.001$; Table 3). In contrast, in patients without LVRR, ongoing LV remodelling was observed after surgery (LVESVI 77 ± 33 ml/m^2 preoperatively, increasing to 87 ± 35 ml/m^2 at mid-term follow-up, $p < 0.001$) with reduced LVEF (28 ± 8 vs 26 ± 9%, $p = 0.029$). Recurrent MR ≥ grade 2 was observed in 15 (20%) patients at mid-term follow-up. Recurrent

MR had developed between discharge and the mid-term echocardiography in all of these patients, except for 2 patients with residual MR grade 2 at discharge.

LVRR and recurrent MR were highly correlated: recurrent MR ≥ grade 2 was present in 14 of 48 (29%) patients without LVRR, whereas it was present in only 1 of 29 (3%) patients with LVRR ($p = 0.006$).

Table 1. Baseline characteristics and surgical data of the study population (n = 77).

Baseline characteristics	
Age (years)	62 ± 11
Female gender (n, %)	39 (51%)
NYHA class III/IV (n, %)	62 (82%) / 10 (13%)
Hypertension (n, %)	23 (30%)
Pulmonary hypertension (n, %)	16 (21%)
VT (n, %)	18 (23%)
AF (n, %)	32 (42%)
Left bundle branch block (n, %)	35 (46%)
Cardiac resynchronization therapy (n, %)	13 (17%)
Internal cardiac defibrillator (n, %)	22 (29%)
Peripheral artery disease (n, %)	2 (2.6%)
Cerebrovascular events (n, %)	2 (2.6%)
Diabetes (n, %)	18 (23%)
Chronic pulmonary disease (n, %)	16 (21%)
Creatinine (µmol/L)	104 ± 40
Log EuroSCORE I	10 ± 7
Surgical data	
Previous cardiac surgery (n, %)	0
Urgent surgery (n, %)	20 (26%)
MV annulus diameter	30 ± 3
MV ring size	26 ± 2
CSD implantation (n, %)	52 (68%)
Tricuspid valve repair (n, %)	65 (84%)
Intra-aortic balloon pump (n, %)	11 (14%)
Cardiac resynchronization therapy (n, %)	36 (47%)
Internal cardiac defibrillator (n, %)	30 (39%)
AF ablation (n, %)	24 (31%)
VT ablation (n, %)	4 (5.2%)
Cardiopulmonary bypass time (min)	141 ± 38
Cross-clamp time (min)	79 ± 22

AF = atrial fibrillation, CSD = cardiac support device, MV = mitral valve, VT = ventricular tachyarrhythmia

Table 2. Comparison of preoperative and mid-term echocardiographic data (n=77).

	Preoperative	Mid-term	p-value
MR grade	3.4 ± 0.6	1.1±1.0	<0.001
0	-	22 (29%)	
1	-	40 (52%)	
2	-	9 (12%)	
3	41 (53%)	4 (5%)	
4	36 (47%)	2 (3%)	
LVEDD (mm)	69 ± 8	65 ± 10	<0.001
LVESD (mm)	60 ± 9	57 ± 12	0.002
LAD (mm)	48 ± 7	44 ± 8	<0.001
LVEF (%)	28 ± 8	30 ± 10	0.037
LVEDV (ml)	207 ± 67	188 ± 74	0.004
LVESV (ml)	152 ± 59	137 ± 69	0.019
LVEDVI (ml/m^2)	108 ± 33	98 ± 38	0.004
LVESVI (ml/m^2)	79 ± 29	72 ± 35	0.020
sPAP (mmHg)	43 ± 10	37 ± 12	0.007

LAD = left atrial diameter, LVEDD = LV end-diastolic diameter, LVEDV = LV end-diastolic volume, LVEDVI = LV end-diastolic volume indexed to body surface area, LVEF = LV ejection fraction, LVESD = LV end-systolic diameter, LVESV = LV end-systolic volume, LVESVI = LV end-systolic volume indexed to body surface area, MR = mitral regurgitation

Outcomes at long-term follow-up

Overall echocardiographic and clinical outcome

Mean follow-up duration after the mid-term echocardiogram was 57 ± 39 months. During this interval, recurrence of MR ≥ grade 2 was observed in another 7 patients, resulting in an overall incidence of 29%. New recurrent MR did not develop in patients with LVRR at the mid-term echocardiogram, whereas it developed in 7 of 34 (21%) patients without LVRR. During follow-up, 3 patients underwent an HTx (all for progressive heart failure) and 34 patients died.

Prognostic value of reverse remodelling and recurrent mitral regurgitation

In univariable Cox-regression analysis, the absence of LVRR [HR (hazard ratio) 3.9 (1.7–8.9); p = 0.001] and the presence of recurrent MR ≥ grade 2 [HR 6.0 (2.7–12.9); p < 0.001] at mid-term follow-up were associated with worse HTx-free survival.

The combined effect of LVRR and recurrent MR on the primary end point is shown in **Figure 2**, where patients are divided into 3 groups: patients with LVRR (n = 29, including 1 patient with recurrent MR); those without LVRR and without recurrent MR (n = 34); and patients without LVRR and with recurrent MR (n = 14). Cumulative HTx-free survival incidences 1 and 3 years after mid-term follow-up were 100% and 88 ± 6% in patients with LVRR, 82 ± 7% and 68 ± 8% in patients without LVRR and without recurrent MR, and 49 ± 14% and 33 ± 13% in patients without LVRR and with recurrent MR. After correction for age and sex, the absence of LVRR and

the presence of recurrent MR ≥ grade 2 proved to be independently associated with worse HTx-free survival (Table 4).

One mitral valve reintervention (transcatheter valve-in-ring implantation for moderate-to-severe recurrent MR due to progressive leaflet tethering) was performed in a patient without LVRR. Readmissions for congestive heart failure were observed in 35% of patients with LVRR (26 readmissions in 181 patient-years), in 53% of patients without LVRR and without recurrent MR (60 readmissions in 167 patient-years), and in 64% of patients without LVRR and with recurrent MR (33 readmissions in 21 patient-years).

Table 3. Comparison of preoperative and mid-term echocardiographic data for patients with LVRR (n = 29) and patients without LVRR (n = 48).

Preoperative echocardiographic data			
	LVRR	No LVRR	p-value
MR grade	3.4 ± 0.5	3.5 ± 0.5	0.796
3	16 (55%)	25 (52%)	
4	13 (45%)	23 (48%)	
LVEDD (mm)	68 ± 7	69 ± 9	0.571
LVESD (mm)	60 ± 7	61 ± 10	0.733
LAD (mm)	48 ± 6	48 ± 7	0.732
LVEF (%)	27 ± 7	28 ± 8	0.580
LVEDV (ml)	215 ± 53	202 ± 74	0.430
LVESV (ml)	158 ± 43	148 ± 67	0.482
LVEDVI (ml/m^2)	112 ± 26	106 ± 36	0.465
LVESVI (ml/m^2)	82 ± 22	77 ± 33	0.504
sPAP (mmHg)	42 ± 13	41 ± 10	0.882
Mid-term echocardiographic data			
	LVRR	No LVRR	p-value
MR grade	0.6 ± 0.7*	1.3 ± 1.0*	<0.001
0	14 (48%)	8 (17%)	
1	14 (48%)	26 (54%)	
2	-	9 (19%)	
3	1 (3%)	3 (6%)	
4	-	2 (4%)	
LVEDD (mm)	60 ± 9*	68 ± 10	0.002
LVESD (mm)	52 ± 11*	61 ± 11	<0.001
LAD (mm)	44 ± 7*	45 ± 8*	0.545
LVEF (%)	38 ± 8*	26 ± 9*	<0.001
LVEDV (ml)	140 ± 40*	218 ± 75*	<0.001
LVESV (ml)	89 ± 33*	167 ± 69*	<0.001
LVEDVI (ml/m^2)	73 ± 19*	114 ± 37*	<0.001
LVESVI (ml/m^2)	46 ± 16*	87 ± 35*	<0.001
sPAP (mmHg)	32 ± 8*	40 ± 13	0.010

* p <0.05 between preoperative and mid-term echocardiographic data. Abbreviations as in Table 2.

Predictors of reverse remodelling and recurrent mitral regurgitation

Baseline predictors of LVRR and recurrent MR at mid-term follow-up were assessed by logistic regression analysis. None of the baseline or surgical variables (including preoperative LV volumes, preoperative LVEF and concomitant implantation of a CSD) was associated with LVRR at mid-term follow-up. A history of ventricular tachyarrhythmia (sustained ventricular tachycardia or ventricular fibrillation) was associated with recurrent MR at mid-term follow-up [OR (odds ratio) 4.8 (1.3–18.0); p = 0.023]. Furthermore, severe preoperative MR was correlated with the presence of recurrent MR [OR 2.8 (0.8–9.1); p = 0.092]. In contrast, concomitant implantation of a CSD was associated with the absence of recurrent MR at mid-term follow-up [OR 0.3 (0.1–1.1); p = 0.061]. In multivariable logistic regression analysis, a history of ventricular tachyarrhythmia was the only preoperative predictor independently associated with recurrent MR at mid-term follow-up [OR 4.8 (1.3–18.0); p = 0.021].

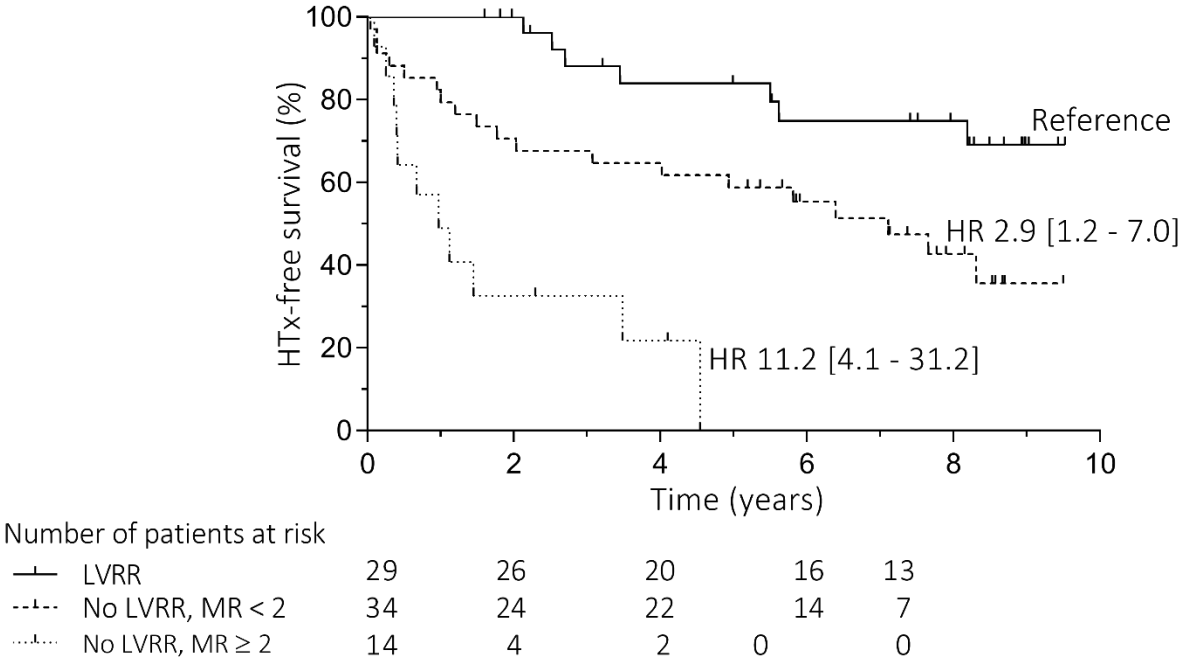

Figure 2. HTx-free survival from mid-term follow-up echocardiogram for 3 groups: 1) patients with LVRR, 2) patients without LVRR, without recurrent MR, and 3) patients without LVRR, with recurrent MR. HR = hazard ratio, HTx = heart transplantation, LVRR = left ventricular reverse remodelling, MR = mitral regurgitation.

Table 4. Predictors of long-term HTx-free survival.

	Multivariable analysis	
	HR [95% CI]	p-value
LVRR	Reference group	
No LVRR and MR <grade 2	2.9 [1.2–6.9]	0.018
No LVRR and recurrent MR ≥ grade 2	11.9 [4.3–33.0]	<0.001
Age	1.0 [0.96–1.02]	0.657
Sex	1.4 [0.7–2.8]	0.299

CI = confidence interval, HR = hazard ratio, HTx = heart transplantation, LVRR = left ventricular reverse remodelling, MR = mitral regurgitation.

Discussion

In this study, mid-term echocardiographic and long-term clinical outcomes were evaluated in patients who underwent personalised surgical treatment of refractory heart failure and moderate-to-severe or severe MR due to non-ischaemic cardiomyopathy. The main findings of this study are as follows: 1) LVRR was observed in 38% of patients and recurrent MR in 20% of patients at mid-term follow-up; 2) the absence of LVRR and presence of recurrent MR were highly associated; 3) the presence of LVRR at mid-term follow-up was associated with favourable long-term HTx-free survival, whereas HTx-free survival was significantly worse in patients without LVRR and without recurrent MR and extremely poor in patients without LVRR and with recurrent MR; and 4) none of the baseline variables in this study was predictive of LVRR; a history of ventricular tachyarrhythmia was the only independent predictor of recurrent MR at mid-term follow-up.

Personalised treatment of non-ischaemic mitral regurgitation: prevalence of left ventricular reverse remodelling and recurrent mitral regurgitation

Functional MR is independently associated with adverse clinical outcomes in patients with non-ischaemic cardiomyopathy.[1,2] Optimal guideline-directed medical therapy may reduce MR and induce LVRR in some of these patients. However, persistence of MR has been observed in a substantial number of patients and is associated with the absence of LVRR and worse clinical outcomes.[19,20] When heart failure symptoms and MR persist after nonsurgical treatment, HTx, LV assist device implantation or mitral valve repair may be considered. These surgical options should be carefully balanced by a dedicated Heart Team to obtain a personalized approach for each patient.[4-6]

Such personalised approach was applied in this study. All patients underwent mitral valve repair with concomitant procedures (implantation of an external CSD, tricuspid valve repair, ablation for atrial fibrillation and CRT/internal cardiac defibrillator implantation) when indicated. After

surgery, all patients were continued on optimal medical therapy in a dedicated outpatient programme. This integrated medico-surgical approach resulted in LVRR in 38% of patients and recurrent MR ≥ grade 2 in 20% of patients at mid-term follow-up. In previous studies, the prevalence of LVRR after mitral valve repair for non-ischaemic MR ranged from 50% to 71%.[8,10,21,22] However, patient characteristics, surgical approach and definition of LVRR (extent of LV volume reduction and both method and moment of assessment) highly differ among studies, and reported prevalences are therefore difficult to compare. The recurrent MR rate observed in this study was comparable to results in earlier studies.[10,13,14]

Association between left ventricular reverse remodelling and recurrent mitral regurgitation

In this study, the absence of LVRR and the presence of recurrent MR were highly associated. We hypothesize that in patients in whom the LV remodelling process is not halted or reversed after surgery, ongoing LV remodelling results in further displacement of the papillary muscles, progressive mitral leaflet tethering forces and eventually recurrence of MR. Once recurrent MR is present, volume overload may exacerbate the LV remodelling process. The simultaneous observation of recurrent MR and the absence of LVRR at mid-term follow-up does not elucidate the causal mechanism between the 2 ('chicken and egg'). However, the fact that 21% of patients without LVRR developed new recurrent MR after the mid-term echocardiogram when compared with 0% in patients with LVRR does suggest that the absence of LVRR precedes recurrence of MR.

The findings in this study are in line with previous reports, which also report high recurrent MR rates in patients without LVRR after mitral valve repair for functional MR.[10,13,14,23] Furthermore, Takeda et al.[22] demonstrated significantly greater degrees of postoperative mitral leaflet tethering in patients without LVRR, and reports by Lee et al.[13] and Ciarka et al.[14] described an independent association between mitral leaflet tethering and recurrent MR after mitral valve repair.

Clinical impact of left ventricular reverse remodelling and recurrent mitral regurgitation

To the best of our knowledge, this is the first study that specifically addresses the impact of LVRR and MR recurrence at midterm follow-up on subsequent clinical outcomes. LVRR was assessed at mid-term follow-up (between 1 and 2 years after surgery) because at this point in time a decrease in LV volumes reflects true reverse remodelling rather than LV volume decrease secondary to the abolishment of MR-related volume overload. The presence of MR

at mid-term follow-up almost exclusively concerns recurrent MR, and residual MR (present at discharge) was only observed in 2 patients. MR recurrence therefore reflects disease progression rather than improper surgical technique.

This study shows that both the absence of LVVR and the presence of recurrent MR at mid-term follow-up have a strong negative prognostic impact on late HTx-free survival and readmissions for congestive heart failure. When both are simultaneously present, this translates into an extremely poor prognosis.

Predictors of left ventricular reverse remodelling and recurrent mitral regurgitation

Given the prognostic impact of LVRR and recurrent MR, patients with a favourable result after mitral valve repair (and concomitant procedures) would ideally be selected before surgery. Such baseline patient characteristics could not be identified in this study.

Several studies have identified echocardiographic predictors of LVRR and/or recurrence of MR.[13,14,24,25] Typically, these parameters reflect the extent of preoperative LV remodelling, both in terms of LV size and mitral valve geometry. The fact that in this study advanced LV remodelling was not predictive of either the absence of LVRR or recurrence of MR might be due to the limited study population. The personalised use of a CSD in patients with more advanced LV remodelling (preoperative LVEDD ≥65 mm or indexed LVEDD ≥30 mm/m^2) could be an alternative explanation. As previous studies showed that the implantation of a CSD has an additional beneficial effect on both LVRR and recurrence of MR[11,12], the deleterious effect of advanced LV remodelling may have been mitigated by the implantation of the CSD in this subgroup of patients.

Clinical implications

The ideal surgical approach to patients with refractory heart failure and functional MR due to non-ischaemic cardiomyopathy remains a topic of debate. HTx and LV assist device implantation have their own limitations, which necessitates the ongoing exploration of alternative surgical and percutaneous interventions. A personalised integrated medico-surgical approach as described in this study results in favourable outcomes in many patients. However, a poor outcome was observed in a subgroup of patients. These patients can be identified by structured echocardiographic follow-up, focusing on LVRR and MR recurrence. Therefore, all patients require close echocardiographic monitoring by a dedicated heart failure team after surgery, and patients with absence of LVRR and/or presence of recurrent MR at midterm

follow-up might be periodically re-evaluated for additional procedures or interventions. Ideally, patients with potential for LVRR would be identified before surgery, given the finding that these patients benefit most from this surgical treatment strategy. Therefore, future studies should focus on preoperative assessment of the potential for reverse remodelling, for instance, by magnetic resonance imaging or stress echocardiography.

Limitations

This study is a single-centre observational study with a limited study population. However, the patient cohort was very homogeneous and only included patients with non-ischaemic functional MR.

For the purpose of this study, only patients with complete preoperative and mid-term echocardiographic data were included. However, patients with incomplete echocardiographic data had similar baseline characteristics and long-term HTx-free survival compared with the study population; therefore, exclusion of these patients presumably only had a limited effect on the outcomes of this study. Nineteen patients died and 1 underwent HTx before mid-term follow-up. These patients had more severe comorbid disease at baseline (more cerebrovascular events and higher serum creatinine levels, resulting in a higher logistic EuroSCORE) compared with the study population; preoperative echocardiographic parameters were not significantly different. The effect of surgery in terms of LVRR and recurrent MR at midterm follow-up could not be studied in these patients.

The external CSD used in this study is no longer commercially available. However, comparable new devices, also directly addressing the left ventricle, are under investigation.

Conclusion

In this study, LVRR was observed in 38% of patients and absence of recurrent MR in 80% of patients at mid-term follow-up after personalised surgical treatment of refractory heart failure and functional MR due to non-ischaemic cardiomyopathy. Patients with LVRR at mid-term follow-up showed favourable long-term HTx-free survival, whereas HTx-free survival was significantly worse in patients without LVRR and without recurrent MR, and extremely poor in patients without LVRR and with recurrent MR. These results warrant close echocardiographic monitoring for timely identification of this latter subgroup of patients, in order to re-evaluate additional treatment options and improve their poor prognosis.

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Chapter 6

10-year outcomes after left ventricular reconstruction: Rethinking the impact of mitral regurgitation

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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 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.

Introduction

Ischaemic 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 ischaemic 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 post-infarction 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 favourable 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 post-infarction 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 post-infarction 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 transoesophageal 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 (i.e., 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 analysed by 2 independent investigators.

Severity of mitral and tricuspid regurgitation was graded semi-quantitatively from colour-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 analysed 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 (hospitalisation 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 X^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).

Table 1. Baseline patient characteristics.

	Total study population (n = 159)	Survivors (n = 78)	Death (n = 81)	p-value
Preoperative clinical data				
Age	62 ± 10	59 ± 10	65 ± 8	<0.001
Male/Female	130 (82%) / 29 (18%)	62 (80%) / 16 (21%)	68 (84%) / 13 (16%)	0.531
Interval infarction to surgery(years)	7 [1 – 14]	3 [1 – 10]	10 [1 – 18]	0.008
No. of coronary vessels with stenosis >70%				
One	62 (39%)	33 (42%)	29 (36%)	
Two	43 (27%)	20 (26%)	23 (28%)	
Three	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 >60mmHg)	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*	2.3 ± 0.4	2.2 ± 0.4	2.4 ± 0.5	0.002
sPAP (mmHg)**	37 ± 15	34 ± 15	40 ± 15	0.060
TAPSE	18 ± 4	18 ± 3	17 ± 4	0.003

ICD = Implantable Cardioverter Defibrillator, LVEDV = LV end-diastolic volume, LVEDVI = LVEDV indexed to body surface area, LVEF = LV ejection fraction, LVESV = LV end-systolic volume, LVESVI = LVESV 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 VT = ventricular tachyarrhythmia.
*WMSI was available in 156 patients. **sPAP was available in 92 patients, due to absence of tricuspid regurgitation in 67 patients.

Table 2. Surgical data.

	Total study population (n = 159)	Survivors (n = 78)	Death (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 (n, %)				
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	28 [26–28]	28 [26–28]	26 [24–28]	
Tricuspid annuloplasty	38 (24%)	12 (15%)	26 (32%)	0.013
Median ring size	30 [28–32]	30 [28–32]	32 [28–32]	
Cryo-ablation	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 (min)	208 ± 63	196 ± 56	217 ± 68	0.100
Aortic cross-clamp time (min)	142 ± 43	138 ± 40	145 ± 45	0.393

BIMA = bilateral internal mammary artery, CABG = coronary artery bypass grafting, ECC = extracorporeal circulation, LIMA = left internal mammary artery, LVR = left ventricular reconstruction, RIMA = right internal mammary artery

Results

Study population

The study population consisted of 159 patients who underwent LVR surgery for refractory HFrEF due to a post-infarction 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 remodelling with mean indexed LV end-systolic volume (LVESVI) 87 ± 39 mL/m2 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 follow-up, p <0.001).

Table 3. Pre-operative and mid-term echocardiographic data (n = 116).

	Pre-operative	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 (mmHg)*	35 ± 15	36 ± 16	0.903

LVEDV=LV end-diastolic volume, LVEDVI=LVEDV indexed to body surface area, LVEF=LV ejection fraction, LVESV=LV end-systolic volume, LVESVI=LVESV indexed to body surface area, MR=mitral regurgitation, sPAP=systolic pulmonary artery pressure. *sPAP was available in 64 patients.

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 event-free survival rate was 83% ± 3% at 1-year, 68% ± 4% at 5-year, and 46% ± 4% at 10-year follow-up (Figure 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).

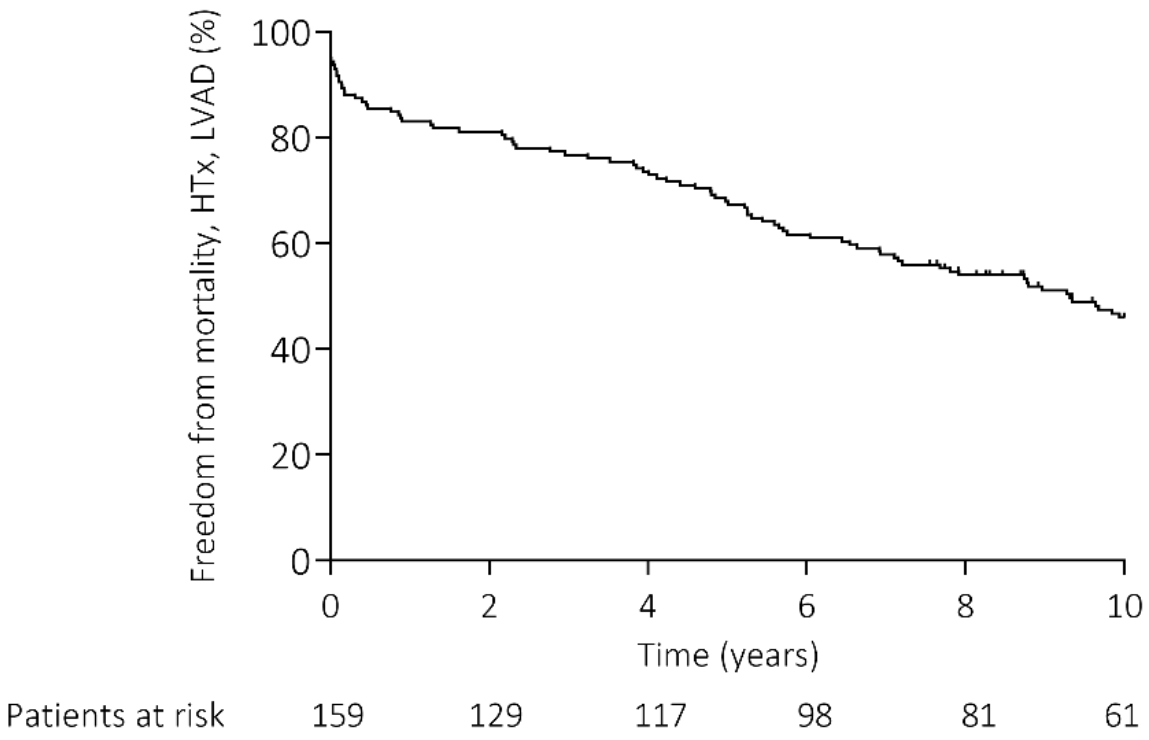

Figure 1. Overall event-free survival after surgery (n = 159). HTx = heart transplantation, LVAD = left ventricular assist device.

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.

	Univariable analysis		Multivariable analysis	
Variable	HR	p-value	HR	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 >60mmHg)	1.40 [0.70–2.68]	0.343		
NYHA class IV	1.53 [0.88–2.50]	0.135		
Interval infarction to surgery (years)	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

LVEDD = LV end-diastolic dimension, LVEDVI = LV end-diastolic volume indexed to body surface area, LVEF = LV ejection fraction, LVESD = LV end-systolic dimension, LVESVI = LV end-systolic volume indexed to body surface area, MR = mitral regurgitation, PH = pulmonary hypertension, sPAP = systolic pulmonary artery pressure, 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 with WMSI <2.5 with MR (13 readmissions per 100 patient-years), in 42% of patients with WMSI ≥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).

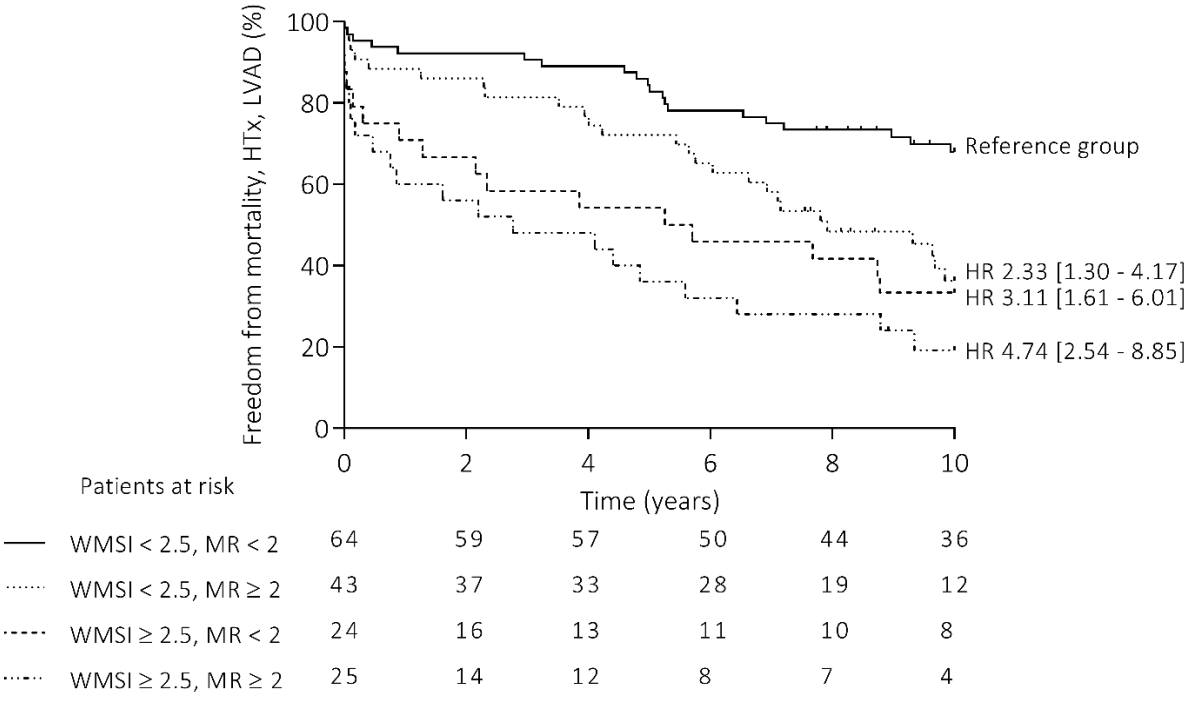

Figure 2. Event-free survival for patients with wall motion score index (WMSI) <2.5 and ≥ 2.5, and mitral regurgitation (MR) < and ≥ grade 2. HR = hazard ratio, HTx = heart transplantation, LVAD = left ventricular assist device.

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 post-infarction anteroseptal LV aneurysm. This integrated approach resulted in LV reverse remodelling 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 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 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 personalised surgical approach with LVR as the mainstay, combined with concomitant procedures based on well-defined indications. Structured outpatient follow-up and optimal medical therapy were continued after surgery in all patients. This integrated medico-surgical approach resulted in LV reverse remodelling (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. Event-free 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 optimie 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 cut-off 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 ischaemic heart failure, resulting from a combination of papillary muscle displacement, systolic leaflet tethering, annular dilatation, and reduced closing forces due to LV remodelling.[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 remodelling. 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 remodelling after myocardial infarction results in increased LV wall pressure with hypoperfusion of the remote myocardium.[23] Because LV remodelling 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 post-infarction 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 haemorrhage, 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 favourable 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-centre observational study, with a limited study population. However, 10-year follow-up 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 post-infarction 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 post-infarction anteroseptal aneurysm resulted in LV reverse remodelling and absence of functional MR at midterm follow-up. 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. 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.

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Chapter 6a

Left ventricular reconstruction with endocardectomy
Letter to the editor

Vadim Babokin

Annals of Thoracic Surgery 2019 May 3

Letter to the editor

Due to the development of new technologies in medicine, the incidence of post-infarction aneurysms has decreased significantly. Despite this, the issue of surgical treatment of left ventricular aneurysm remains to be pretty urgent. The article by Petrus[1] reports Dor procedure of left ventricular reconstruction (LVR), described in several articles.[2] But unlike the described procedure involving endoventricular circular suture, balloon, endoventricular patch, and endocardectomy for ventricular tachycardia (VT) treatment, the latter, judging by the description did not take place. Endocardial resection does not take much time, but without it elimination of all possible re-entry zones is impossible.[3] It is supported by the fact of postoperative VTs in 31% of Petrus' patients, as well as in 19% of patients from the whole cohort of the STICH trial.[4] Although Sartipy[5] talks about controlled endocardectomy, we still consider reasonable to resect scarred endocardium up to the border with healthy tissue even without electrophysiologic study. This will prevent VT spells and cardioverter-defibrillator implantation in the postoperative period. Even endocardial cryoablation of the border zone between the scar and healthy myocardium does not provide freedom from VTs. My observations at Professor Dor's operating room speak for combination of endocardium resection and cryoablation for the best outcomes.

In general, the outcomes obtained by the authors, are interesting and represent experience of the clinic. But there is still one question concerning Echocardiographic data analysis and WMSI in particular. The thing is that, the averages shown by this index have been discussed earlier. But Di Donato M. moved beyond and described three forms of LV dilatation, each of which identified further tactics of treatment and prognosis of surgical treatment outcomes. Did the authors of the article apply this classification? If LVR had not been performed in the patients with ischaemic cardiomyopathy, since they required different treatment tactics (implantation of a left ventricular assist device, heart transplantation), the survival rate could have been better.

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Chapter 6b

Left ventricular reconstruction with endocardectomy
Reply to editor

Annelieke H.J. Petrus, Robert J.M. Klautz, Jerry Braun

Annals of Thoracic Surgery 2019 July 3

Reply to the editor

We thank Dr Babokin for his comments[1] on our article.[2] Ventricular arrhythmias (VA) are an important contributor to late sudden cardiac death in patients with ischaemic heart failure. VA in these patients can be caused by scar-related re-entry (involving the scar borderzone), or to heart-failure related mechanoelectrical changes. During left ventricular reconstruction surgery (LVR), the scar tissue left behind the endoventricular patch may leave the re-entry site in place, while at the same time making it no longer accessible for endocardial catheter ablation. Concomitant arrhythmia surgery may reduce the risk of VA, as indicated by Dr. Babokin.1 We initially adopted epi-endocardial circular cryoablation at the scar borderzone. A previous study in our centre showed that the majority (71%) of patients referred for LVR without previously documented VA was inducible for aneurysm-related ventricular arrhythmia by programmed electrostimulation (PES).[3] However, there was no difference in VA occurrence and ICD therapy during long-term follow-up in patients who underwent PES-guided encircling cryoablation compared to patients without PES-guided cryoablation. This finding prompted us to reintroduce endocardectomy (removing the entire diseased endocardium down to the scar borderzone) as a standard part of LVR surgery in 2012, which is after the interval in which the patients in the current study were treated. We agree with Dr Babokin that endocardectomy should be routinely performed in LVR surgery. Di Donato classified patients with ischaemic cardiomyopathy according to the shape of the left ventricle into type 1 (true LV aneurysm, geometrically delimited by two systolic borders between thickening and nonthickening myocardium), type 2 (intermediate aneurysm, only one border between thickening and nonthickening myocardium) and type 3 LV shape (ischaemic dilated cardiomyopathy, with LV shape without borders).[4] She demonstrated a trend towards better survival after LVR for patients with type 1 and 2 compared to patients with type 3 LV shape. In our hospital, only patients with refractory heart failure due to a post-infarction anteroseptal LV aneurysm (type 1 or type 2) are considered for LVR surgery, whereas patients with ischaemic dilated cardiomyopathy (type 3) are not. Indeed, for type 3 patients the Heart Team might first consider alternatives such as LVAD implantation or cardiac transplantation. In our study[2], we identify preoperative echocardiographic parameters (high WMSI and moderate MR) that apply to type 1 and 2 patients and that may help the Heart Team in determining the best intervention for these patients.

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Chapter 7

Exercise haemodynamics after restrictive mitral annuloplasty for functional mitral regurgitation

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Abstract

Aims: Restrictive mitral annuloplasty (RMA) can provide a durable solution for functional mitral regurgitation (MR), but might result in obstruction to antegrade mitral flow. Aim of this study was to assess the magnitude of change in mitral valve area (MVA) during exercise after RMA, to relate the change in MVA to left ventricular (LV) geometry and function, and to assess its haemodynamic and clinical impact.

Methods and results: Bicycle exercise echocardiography was performed in 32 patients after RMA. Echocardiographic data at rest and during exercise were compared with preoperative echocardiographic data. Clinical endpoints were collected following the study visit. MVA increased during exercise in 25 patients (1.6 ± 0.4 cm^2 to 2.0 ± 0.6 cm^2, p <0.001), whereas MVA decreased in 7 patients (1.8 ± 0.5 cm^2 to 1.5 ± 0.4 cm^2, p = 0.020). Patients with an increased MVA showed a significant reduction in LV volumes at rest compared to preoperatively, and an increase in stroke volume and cardiac output (CO) during exercise. In patients with decreased MVA, LV reverse remodelling was absent and myocardial flow reserve limited. Patients with decreased exercise MVA had a higher increase in mean pulmonary artery pressure (PAP) with respect to CO and worse survival 36 months after the study visit (69 ± 19% vs. 92 ± 5%, p = 0.005).

Conclusions: Both increased and decreased MVA were observed during exercise echocardiography after RMA for functional MR. Change in MVA was related to the extent of LV geometrical and functional changes. A decreased MVA during exercise was associated with a higher increase in mean PAP with respect to CO, and worse survival.

Introduction

Functional mitral regurgitation (MR) is frequently observed in patients with ischaemic or non-ischaemic cardiomyopathy and is independently associated with adverse clinical outcome.[1,2] Functional MR is a dynamic phenomenon, resulting from changes in left ventricular (LV) geometry (LV dilatation with papillary muscle displacement, leading to systolic leaflet tethering) and LV function (impaired myocardial contractility, resulting in reduced closing forces).[3]

The optimal treatment for patients with functional MR is a matter of ongoing debate, as reflected by the current guidelines.[4,5] When mitral valve repair is indicated, restrictive mitral annuloplasty (RMA) with implantation of an undersized ring is generally the preferred technique. However, use of undersized rings has raised concerns, in that extensive reduction of mitral annular dimension could result in obstruction to antegrade mitral flow. This might induce functional mitral stenosis at rest that may become even more pronounced during physical exercise.[6]

Recent exercise echocardiography studies[7–9] challenge the concept that functional mitral stenosis (when present after RMA) simply results from implantation of a downsized ring. Although the mitral orifice at annular level is fixed after implantation of an annuloplasty ring, the functional mitral valve area (MVA) was found to be dynamic during exercise and to be determined by the degree of diastolic anterior leaflet tethering. Interestingly, diastolic leaflet tethering increased during exercise in the study by Kubota and co-workers,[7] resulting in a decreased exercise MVA. In contrast, Bertrand and colleagues[8] demonstrated decreased diastolic leaflet tethering leading to an increased exercise MVA.

Aim of the present study was to assess the magnitude of change in MVA in response to exercise in patients who had undergone RMA for functional MR with the smallest ring sizes available, to relate change in MVA to LV geometry and function, and to assess its haemodynamic and clinical impact.

Methods

Study population and study design

All patients with functional MR due to ischaemic or non-ischaemic cardiomyopathy, who underwent RMA between 2002 and 2011, without concomitant surgical ventricular restoration and/or aortic valve surgery, were screened. Mitral annuloplasty was performed with a complete semi-rigid ring (Carpentier-Edwards Physio ring, Edwards Lifesciences, Irvine, CA), downsized by two sizes.[10] Only patients with the smallest rings inserted (sizes 24 or 26) were

included. Exclusion criteria were: advanced age (≥85 years), atrial fibrillation, more than mild aortic stenosis/aortic regurgitation, absence of echocardiographic follow-up at our institution <1 year prior to screening and inability/refusal to undergo exercise echocardiography. Furthermore, patients with more than mild recurrent MR were excluded, since MVA was assessed by the continuity equation.[11]

Eligible patients were invited for a single study visit (6.6 ± 3.0 years after surgery) during which they underwent transthoracic resting and bicycle exercise echocardiography. Patients were followed after the study visit to assess subsequent clinical outcome. The study protocol was approved by the medical ethics committee and written informed consent was obtained from all patients.

Exercise echocardiography

At the study visit, echocardiography was performed in semi-supine mild left lateral decubitus position at rest, during peak exercise and during recovery, using a commercially available system (GE Vivid 7 and E9; General Electric-Vingmed, Horten, Norway). Bicycle exercise echocardiography was performed with an initial workload of 25W for 2 min, followed by a 10W increment per minute, with continuous 12-lead electrocardiogram recording. Beta-blocking agents were continued when applicable, to obtain results resembling patients' daily life situation. Endpoints for terminating exercise were: target heart rate reached, development of symptoms, systolic blood pressure <80 or >220 mmHg, diastolic blood pressure >120 mmHg, ischaemic ECG changes, ventricular arrhythmia, and rapid atrial tachycardia. Patients were encouraged to perform exercise until exhaustion.

Echocardiographic measurements

Preoperative echocardiographic images were retrospectively analysed for comparison with follow-up resting and exercise echocardiographic data. Left-sided cardiac dimensions were determined from parasternal long-axis acquisitions.[12] LV and left atrial (LA) volumes were measured from apical two- and four-chamber images and left ventricular ejection fraction (LVEF) was calculated by the modified biplane Simpson's method.[12] Stroke volume (SV) was measured by pulsed-wave Doppler in the LV outflow tract and multiplied with heart rate to calculate cardiac output (CO). Mean and peak transmitral pressure gradients were calculated using the modified Bernoulli equation. MVA was estimated by the continuity equation[11] and transmitral flow rate by dividing SV by diastolic filling time. Systolic pulmonary artery pressure (PAP) was calculated using the modified Bernoulli equation on the transtricuspid continuous-

wave signal, adding the estimated right atrial pressure.[13] Mean PAP was calculated using the formula: mean PAP = 0.61 x systolic PAP + 2 mmHg.[14]

Clinical outcome

The primary clinical endpoint was defined as all-cause mortality. Secondary endpoint was a composite of all-cause mortality and hospital readmissions for congestive heart failure (requiring treatment with parenteral diuretics or inotropes). All endpoints were prospectively assessed from the study visit until 1 June 2017.

Statistical analysis

Categorical variables were described as frequencies and percentages, and continuous data as mean ± standard deviation. When appropriate, the X^2 test, Fisher's exact test or paired and unpaired Student's t-test was used. Determinants of change in MVA were assessed by linear regression analysis. The Kaplan–Meier method was used to estimate cumulative time-to-event rates and groups were compared with the log-rank test. To assess variables associated with clinical endpoints after the study visit, Cox proportional hazards regression analysis was performed. SPSS statistical software version 20.0 (IBM Corp., Armonk, NY) was used for calculations and a probability value of <0.05 was considered significant.

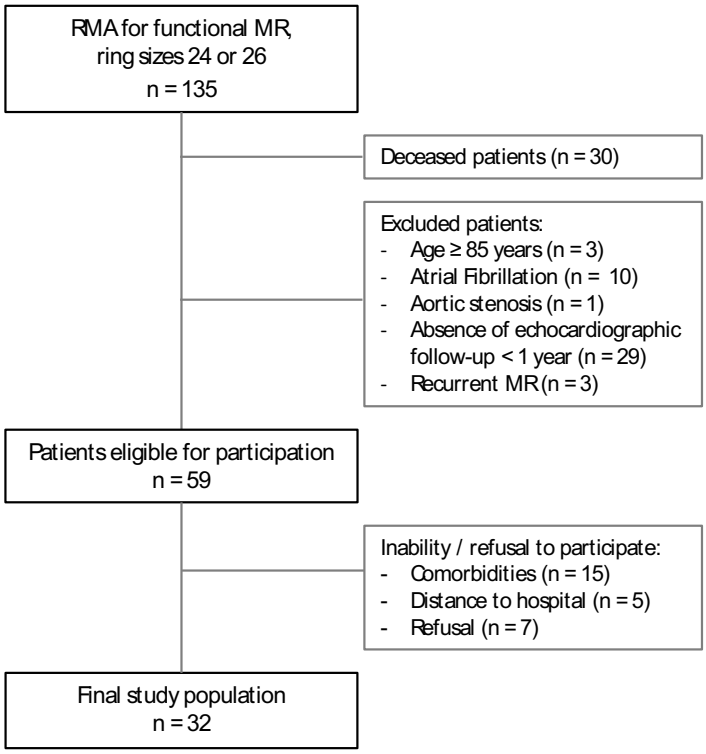

Figure 1. Study flowchart. MR = mitral regurgitation, RMA = restrictive mitral annuloplasty.

Results

Study population

The study flowchart is displayed in Figure 1; the final study population consisted of 32 patients who underwent a resting and exercise echocardiography between June 2012 and December 2013. Aetiology of functional MR was ischaemic cardiomyopathy in 24 patients and non-ischaemic cardiomyopathy in 8 patients. Ring sizes 24 and 26 were implanted in 12 and 20 patients, respectively. Baseline characteristics of the study population are presented in Table 1.

Table 1. Baseline and surgical characteristics of the study population.

	RMA patients (n = 32)	MVA increase Group (n = 25)	MVA decrease Group (n = 7)	p-value*
Preoperative data				
Age at surgery (years)	65.4 ± 9.9	65.6 ± 9.7	64.7 ± 11.3	0.826
Male gender	18 (56%)	14 (56%)	4 (57%)	0.957
Aetiology of functional MR				
Ischaemic	24 (75%)	18 (75%)	6 (86%)	0.646
Non-ischaemic	8 (25%)	7 (28%)	1 (14%)	
Intraoperative data				
Aortic crossclamp time (min)	114 ± 51	113 ± 53	120 ± 46	0.763
Ring size implanted				
24	12 (38%)	10 (40%)	2 (29%)	0.683
26	20 (63%)	15 (60%)	5 (71%)	
Postoperative coaptation length (mm)	8 ± 1	8 ± 1	7 ± 1	0.125
Concomitant CABG	20 (63%)	17 (68%)	3 (43%)	0.379
Concomitant TVP	13 (41%)	10 (40%)	3 (43%)	0.892
Data at time of exercise echocardiography				
Body surface area	1.9 ± 02	1.9 ± 0.2	1.9 ± 0.2	0.726
NYHA class	1.7 ± 0.8	1.6 ± 0.7	2.0 ± 0.8	0.221
I	14 (48%)	12 (55%)	2 (29%)	
II	10 (35%)	7 (32%)	3 (43%)	
III	5 (17%)	3 (14%)	2 (29%)	
IV	-	-	-	
Diabetes Mellitus	9 (31%)	7 (32%)	2 (29%)	1.000
Serum creatinine	104 ± 29	99 ± 26	123 ± 37	0.076
Medication				
Betablocker	25 (86%)	19 (86%)	6 (86%)	1.000
Diuretics	21 (72%)	15 (68%)	6 (86%)	0.635
ACE	15 (52%)	12 (55%)	3 (43%)	0.682
ARB	12 (41%)	8 (36%)	4 (57%)	0.403
MRA	14 (48%)	11 (50%)	3 (43%)	1.000

ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blockers, CABG = coronary artery bypass grafting, MR = mitral regurgitation, NYHA = New York Heart Association, RMA = restrictive mitral annuloplasty, TVP = tricuspid valvuloplasty.
*p-value for comparison of the MVA increase and decrease group.

Preoperative and follow-up resting echocardiographic data

Compared to preoperative echocardiographic data, LA volumes and LV diameters and volumes had decreased significantly at the follow-up resting echocardiogram, with a non-significant improvement in LVEF (Table 2).

Follow-up resting and exercise echocardiographic data

Mean peak exercise for the whole study population was 66 ± 23W. Exercise was terminated because the target heart rate was reached in three patients, chest discomfort in one patient, and exhaustion in the remainder of patients. During exercise, MVA increased, with concomitant increases in SV, CO, transmitral flow rate, transmitral gradients and systolic and mean PAP (Table 3).

Table 2. Comparison of preoperative and follow-up echocardiographic data (n = 32).

	Preoperative	Resting	p-value
LA end-diastolic diameter (mm)	43 ± 6	42 ± 6	0.438
LA end-diastolic volume (ml)	78 ± 28	59 ± 20	<0.001
LA end-systolic volume (ml)	51 ± 26	37 ± 18	0.001
LV end-diastolic diameter (mm)	62 ± 8	58 ± 9	0.002
LV end-systolic diameter (mm)	54 ± 10	49 ± 10	0.001
LV end-diastolic volume (ml)	189 ± 70	150 ± 70	0.003
LV end-systolic volume (ml)	125 ± 59	96 ± 57	0.008
LV ejection fraction (%)	36 ± 11	40 ± 10	0.061
Systolic PAP (mmHg)*	36 ± 11	32 ± 13	0.295
Mean PAP (mmHg)*	24 ± 7	22 ± 7	0.295

LA = left atrium, LV = left ventricle, PAP = pulmonary artery pressure.
*Echocardiographic assessment of systolic and mean PAP was available in 26 patients, because of absence of tricuspid regurgitation in 6 patients.

Table 3. Comparison of follow-up resting and exercise echocardiographic data (n = 32).

	Resting	Exercise	p-value
Heart rate (beats/min)	70 ± 11	103 ± 22	<0.001
Stroke volume (ml/beat)	58 ± 16	69 ± 20	0.002
Cardiac output (l/min)	4.0 ± 1.4	6.9 ± 3.0	<0.001
Mean transmitral flow rate (ml/s)	140 ± 58	260 ± 133	<0.001
Mean transmitral gradient (mmHg)	3.9 ± 2.3	9.3 ± 5.3	<0.001
Peak transmitral gradient (mmHg)	9.1 ± 3.8	17.9 ± 7.5	<0.001
MVA (cm^2)	1.6 ± 0.4	1.9 ± 0.6	0.003
Indexed MVA (cm^2/m^2)	0.9 ± 0.2	1.0 ± 0.4	0.004
Systolic PAP (mmHg)*	32 ± 13	43 ± 17	<0.001
Mean PAP (mmHg)*	21 ± 8	28 ± 11	<0.001

LV, left ventricle; MVA, mitral valve area; PAP, pulmonary artery pressure. *Echocardiographic assessment of systolic and mean PAP was available in 26 patients, because of absence of tricuspid regurgitation in 6 patients.

MVA in response to exercise

In the total study population, mean MVA increased from 1.6 ± 0.4 cm2 at rest to 1.9 ± 0.6 cm2 at peak exercise (p = 0.003). Change in MVA was significantly and positively associated with exercise induced changes in SV (r = 0.578, p = 0.001), CO (r = 0.630, p <0.001; Figure 2) and transmitral flow rate (r = 0.576, p = 0.001).

Although mean MVA increased during exercise in the whole study group, the response to exercise was not the same for individual patients. MVA was either unaltered or increased during exercise in 25 patients (MVA increase group; 1.6 ± 0.4 cm^2 to 2.0 ± 0.6 cm^2, p <0.001), whereas MVA decreased during exercise in 7 patients (MVA decrease group; 1.8 ± 0.5 cm^2 to 1.5 ± 0.4 cm^2, p = 0.020). Both groups had similar baseline characteristics (Table 1) and time intervals between surgery and the study visit.

Haemodynamics stratified for the MVA increase group vs. MVA decrease group

Preoperative, follow-up resting and follow-up exercise echocardiographic findings for the MVA increase and decrease group are summarized in Table 4. In the MVA increase group, follow-up resting LV end-systolic volume was significantly lower than preoperatively (125 ± 59 ml vs. 90 ± 50 ml, p = 0.006, respectively) — indicating LV reverse remodelling after surgery — and LVEF had significantly improved (36 ± 11% vs. 40 ± 10%, p = 0.042). In contrast, in the MVA decrease group LV reverse remodelling had not occurred (LV end-systolic volume 113 ± 50 ml preoperatively vs. 131 ± 68 ml at rest, p = 0.237) and LVEF remained unchanged (37 ± 8% vs. 33 ± 9%, p = 0.250).

Peak exercise was reached at 70 ± 24W in patients with an increased MVA during exercise, compared to 53 ± 14W in patients with a decreased MVA (p = 0.081). SV and CO significantly increased during exercise in patients in the MVA increase group, whereas no significant increase was observed in the MVA decrease group, reflecting limited myocardial flow reserve in the latter group. Transmitral flow rate significantly increased during exercise in both groups, but peak exercise transmitral flow rate was significantly higher in the MVA increase group. Although systolic and mean PAP significantly increased during exercise in both groups, the increase in mean PAP with respect to CO was 2.9 ± 4.6 mmHg/L/min in the MVA increase group, compared to 11.9 ± 7.6 mmHg/L/min in the MVA decrease group (p = 0.002).

Table 4. Comparison of preoperative, follow-up resting and follow-up exercise echocardiographic data for MVA increase (n = 25) and MVA decrease group (n = 7)

	MVA increase group			MVA decrease group		
	Preoperative	Resting	Exercise	Preoperative	Resting	Exercise
LA end-diastolic diameter (mm)	42 ± 5	40 ± 5		44 ± 7	47 ± 7‡	
LA end-diastolic volume (ml)	76 ± 30	55 ± 18*		85 ± 22	73 ± 23‡	
LA end-systolic volume (ml)	48 ± 26	33 ± 15*		60 ± 22	50 ± 22‡	
LV end-diastolic diameter (mm)	62 ± 7	57 ± 8*		63 ± 10	64 ± 11	
LV end-systolic diameter (mm)	54 ± 10	47 ± 9*		55 ± 13	57 ± 13‡	
LV end-diastolic volume (ml)	189 ± 72	144 ± 62*		174 ± 54	189 ± 80	
LV end-systolic volume (ml)	125 ± 59	90 ± 50*		113 ± 50	131 ± 68	
LV ejection fraction (%)	36 ± 11	40 ± 10*		37 ± 8	33 ± 9	
Heart rate (beats/min)		71 ± 11	106 ± 23†		67 ± 10	95 ± 17†
Stroke volume (ml/beat)		59 ± 15	74 ± 18†		59 ± 20	49 ± 11‡
Cardiac output (l/min)		4.1 ± 1.4	7.5 ± 3.0†		3.8 ± 1.4	4.3 ± 1.2‡
Mean transmitral flow rate (ml/s)		143 ± 61	283 ± 136†		130 ± 47	164 ± 56†‡
Mean transmitral gradient (mmHg)		4.1 ± 2.5	10.1 ± 5.6†		3.3 ± 1.2	6.1 ± 1.9†
Peak transmitral gradient (mmHg)		8.8 ± 3.9	19.0 ± 8.0†		10.0 ± 3.5	13.8 ± 2.9†
MVA (cm^2)		1.6 ± 0.4	2.0 ± 0.6†		1.8 ± 0.5	1.5 ± 0.4†
Indexed MVA (cm^2)		0.8 ± 0.2	1.1 ± 0.4†		0.9 ± 0.3	0.8 ± 0.2†
Systolic PAP (mmHg)||	36 ± 11	28 ± 12*	38 ± 16†	35 ± 12	43 ± 7‡	57 ± 11†‡
Mean PAP (mmHg)	24 ± 7	19 ± 7*	25 ± 10†	24 ± 7	28 ± 4‡	36 ± 7†‡

LA = left atrium, LV = left ventricle, MVA = mitral valve area, PAP = pulmonary artery pressure.

*p <0.05 preoperative vs resting, †p <0.05 resting vs exercise, ‡p <0.05 MVA increase vs MVA decrease.

|| Echocardiographic assessment of systolic and mean PAP was available in 26 patients because of absence of tricuspid regurgitation in 6 patients.

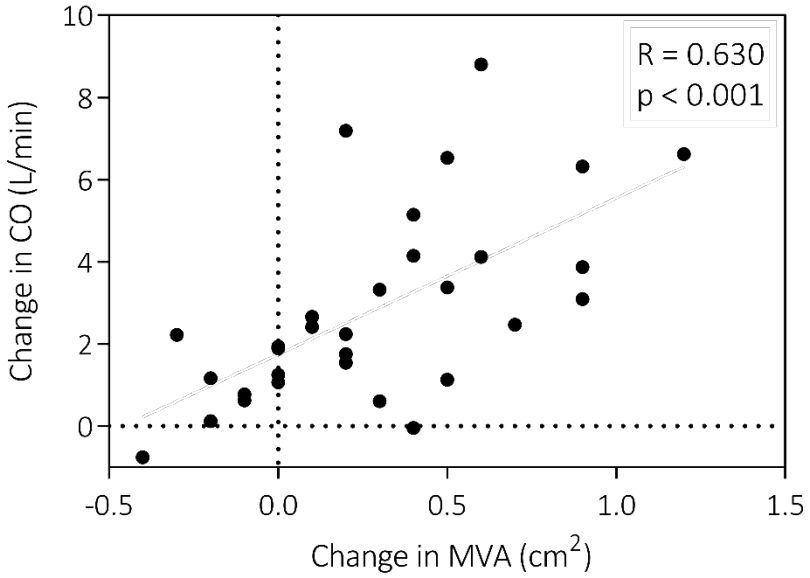

Figure 2. Association between change in mitral valve area (MVA) and change in cardiac output (CO) from rest to exercise.

Table 5. Univariable Cox proportional hazards regression analysis for survival after the study visit.

	HR	95% CI	p-value
Baseline characteristics			
NYHA functional class	1.168	0.359 – 3.796	0.797
Serum creatinine	0.996	0.969 – 1.023	0.756
Ring size	1.941	0.673 – 5.595	0.219
Echocardiographic parameters at rest			
MVA < 1.5 cm^2	0.229	0.027 – 1.903	0.172
Indexed MVA < 0.9 cm^2/m^2	0.781	0.174 – 3.514	0.747
Mean transmitral gradient > 5 mmHg	0.039	0.000 – 592.7	0.508
Stroke volume	1.025	0.979 – 1.072	0.297
Cardiac output	1.172	0.681 – 2.018	0.567
Transmitral flow rate	1.003	0.990 – 1.016	0.667
Echocardiographic parameters at peak exercise			
MVA < 1.5 cm^2	0.409	0.049 – 3.397	0.408
Indexed MVA < 0.9cm^2/m^2	0.365	0.070 – 1.893	0.230
Mean transmitral gradient > 5 mmHg	0.668	0.129 – 3.456	0.631
Stroke volume	1.003	0.963 – 1.045	0.891
Cardiac output	0.873	0.629 – 1.211	0.415
Transmitral flow rate	0.997	0.989 – 1.005	0.453
Change from preoperatively to follow-up resting echocardiogram			
Change in LVEDV (%)	1.003	0.978 – 1.029	0.817
Change in LVESV (%)	1.005	0.986 – 1.024	0.605
Change from follow-up resting to peak exercise echocardiogram			
Decreased MVA	6.534	1.450 – 29.451	0.015
Change in stroke volume	0.986	0.938 – 1.036	0.573
Change in cardiac output	0.723	0.437 – 1.199	0.209
Change in transmitral flow rate	0.993	0.981 – 1.006	0.277

CI = confidence interval, HR = hazard ratio, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, MVA = mitral valve area, NYHA = New York Heart Association.

Clinical outcome

Clinical outcome was prospectively assessed after the study visit. During follow-up (median 47 [43 – 49] months), 7 patients died. Univariable Cox proportional hazards regression model showed that ring size and static follow-up echocardiographic parameters (at rest and at peak exercise) were not associated with survival (Table 5). Furthermore, LV reverse remodelling (i.e. change in LV volumes from preoperatively to the follow-up resting echocardiogram) and myocardial contractile reserve (i.e. change in SV or CO from rest to peak exercise) did not correlate to survival. A decreased MVA during exercise was the only parameter associated with worse survival after the study visit (HR 6.5 [1.5 – 29.5], p = 0.015). Kaplan–Meier curves for freedom from all-cause mortality comparing patients with decreased MVA to those with increased MVA during exercise are presented in Figure 3 (36-month survival 69 ± 19% vs. 92 ± 5%, respectively, log-rank test p = 0.005).

During follow-up, seven patients were readmitted for congestive heart failure (of whom four patients died). A decreased MVA during exercise was the only parameter significantly associated with worse event-free survival after the study visit (HR 4.8 [1.4 – 16.9], p = 0.015). A greater extent of increase in CO (indicating better myocardial contractile reserve) from rest to exercise correlated with better event-free survival—however, not statistically significant (HR 0.7 [0.4 – 1.0], p = 0.058). None of the other variables summarized in Table 5 were associated with event-free survival.

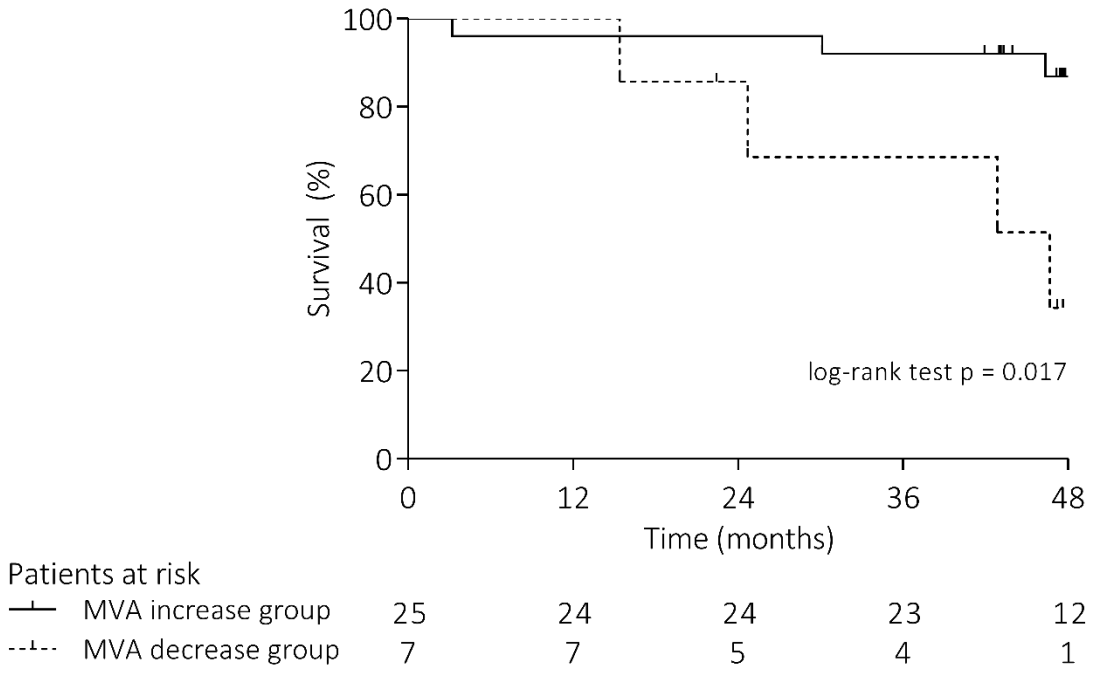

Figure 3. Kaplan-Meier time-to-event curves for freedom from all-cause mortality for patients with an increased mitral valve area (MVA) and decreased MVA during exercise.

Discussion

In the present study, mitral valve haemodynamic performance in patients after RMA for functional MR was assessed by resting and bicycle exercise echocardiography. We assessed the association between echocardiographic findings and clinical outcome up to 4 years after the study visit. Main findings of this study are: 1) Mitral valve haemodynamics in response to exercise differ between individual patients: MVA increased in 25 patients, whereas MVA decreased in 7 patients; 2) The group of patients with a decreased MVA in response to exercise was characterized by absence of LV reverse remodelling and limited myocardial contractile reserve; 3) Increase in mean PAP with respect to CO was significantly higher in patients with a decreased MVA; 4) Survival and event-free survival were significantly worse for patients with a decreased MVA compared to patients with an increased MVA during exercise.

MVA in response to exercise: comparison with other studies

RMA can provide a durable solution for functional MR, resulting in sustained LV reverse remodelling and beneficial effects on functional capacity.[10,15–17] The theoretical downside of inserting an undersized annuloplasty ring is that it may induce mitral stenosis at rest or, even more pronounced, during exercise, with potential deleterious effects. Recent studies showed that MVA is dynamic during exercise, despite implantation of a semi-rigid ring with a fixed orifice area, and that MVA is determined at the level of the leaflet tips rather than at annular level. Furthermore, MVA proved to be determined by the degree of diastolic anterior leaflet tethering, with increased tethering leading to decreased MVA and vice versa.[7–9]

In our institution, RMA is performed by implantation of a complete semi-rigid annuloplasty ring, downsized by two ring sizes. To fully appreciate the effect of stringent downsizing on mitral valve haemodynamics, only patients after RMA with the smallest rings were included in the present study. Despite implantation of these small rings, an overall significant increase in mean MVA was observed in response to exercise (from 1.6 ± 0.4 cm^2 to 1.9 ± 0.6 cm^2), which was similar to that observed by Magne et al.[6] (1.5 ± 0.4 cm^2 to 1.7 ± 0.3 cm^2) after RMA with downsizing by two ring sizes (median ring size 26) and by Bertrand et al.[8] (1.5 ± 0.4 cm^2 to 2.0 ± 0.5 cm^2) after downsizing by one or two ring sizes (median ring size 28). In contrast, Kubota et al.[7] reported a decreased exercise MVA (from 2.0 ± 0.5 cm^2 to 1.4 ± 0.2 cm^2) in patients after mitral annuloplasty without downsizing (median ring size 28). These findings clearly indicate that the degree of downsizing of the annuloplasty ring in itself does not determine the change in MVA in response to exercise.

Change in MVA in response to exercise: Relationship with LV geometry & function

Mean MVA increased during exercise in the current study population. However, a different response was observed for individual patients: MVA increased in 25 patients and decreased in 7 patients. Our data suggest that this differential response might be related to LV geometry and function.

LV geometry is reflected by the degree of LV reverse remodelling after surgery. In patients showing LV reverse remodelling, mitral leaflet tethering decreases, whereas tethering forces persist or increase when reverse remodelling is absent.[18–20] Indeed, in the present study, LV reverse remodelling was observed after surgery in the group of patients with an increased MVA during exercise, while reverse remodelling was absent in the MVA decrease group.

LV function is reflected by the extent of myocardial contractile reserve after surgery. In the current study, significant increases in SV and CO were observed during exercise in the MVA increase group, whereas contractile reserve was limited in the MVA decrease group. These findings are in line with previous work. Magne[6] and Bertrand[8] showed an increase in CO during exercise in a study population with an increased MVA, while Kubota[7] observed a decrease in LVEF during exercise in a study population with a decreased MVA. The observed association between MVA and myocardial contractile reserve in our study does not elucidate the causality between the two. Although an increase in transmitral flow (due to myocardial contractile reserve) might overcome tethering forces and increase MVA, previous studies showed that diastolic leaflet opening is independent of mitral inflow volume.[21] Therefore, a more likely explanation is that obstruction to antegrade flow (a decreased MVA) prevents an adequate rise in SV and CO.

Haemodynamic impact of different MVA responses to exercise

In healthy individuals, the increase in mean PAP with respect to CO is not expected to exceed 3.0 mmHg/L/min, due to a decreased pulmonary vascular resistance in response to exercise.[22,23] In the present study, a significantly higher increase in mean PAP was observed in patients with a decreased MVA during exercise (11.9 mmHg/L/min), compared to patients with an increased MVA (2.9 mmHg/L/min). These findings suggest that a decreased MVA during exercise has significant haemodynamic impact. Nonetheless, ‘out of proportion’ increases in mean PAP have also been reported in patients with LV systolic and diastolic dysfunction.[23] Given the absence of LV reverse remodelling in the MVA decrease group, LV dysfunction is likely to play a role in these patients as well.

Clinical impact of different MVA responses to exercise

The clinical impact of exercise mitral valve haemodynamics after mitral valve repair was investigated by Bertrand and co-workers, who demonstrated significantly worse event-free survival in patients with an indexed MVA <0.9 cm2/m^2 at peak exercise.[8] However, their follow-up started directly after surgery, and thus included events that preceded the exercise echocardiogram (thereby introducing the phenomenon known as 'immortal time bias').[24]

The current study is, to the best of our knowledge, the first to relate mitral valve exercise haemodynamics to subsequent clinical outcome. After a median follow-up duration of 47 months following the exercise echocardiography, not MVA itself (either at rest or during exercise), but a decreased MVA in response to exercise proved to be the strongest predictor of adverse (event-free) survival. As discussed before, change in MVA during exercise proved to be associated with LV geometry and function. A decreased MVA could therefore represent a more powerful marker of adverse LV changes. However, a decreased MVA was also associated with a steep increase of mean PAP with respect to CO, which might suggest significant haemodynamic consequences. Obstruction of antegrade mitral flow may result in elevated LA pressure with consequently pulmonary oedema, pulmonary hypertension and eventually right ventricular failure, which could explain the poor outcome in these patients.[25]

Clinical implications

In the present study, a decreased MVA during exercise proved to be associated with significantly worse (event-free) survival. A decreased MVA was related to LV geometry and function after surgery rather than the implantation of an undersized annuloplasty ring in itself. These findings indicate that in a subgroup of patients, even in the absence of recurrent MR, RMA alone does not offer a definitive solution. Therefore, future research should focus on identifying preoperative determinants that predict the likelihood of improvement in LV geometry (LV reverse remodelling) and function (LV contractile reserve) after mitral valve surgery for functional MR, to allow a patient-tailored approach.

Study limitations

This is a single-centre observational study with a limited study population. Since follow-up echocardiograms were performed 6.6 ± 3.0 years following RMA surgery, selection bias may have occurred. However, patients were selected for this study based on ability to perform an exercise echocardiogram as well as criteria that allowed reliable assessment of MVA by the continuity equation. Neither LV geometry nor LV function were used as selection criteria.

Therefore, the study population can be considered a representative sample of patients who underwent RMA surgery at our institution, and survived for several years. Furthermore, preoperative viability assessment is not routinely performed in our institution and was therefore not available. Also, tethering parameters (anterior and posterior mitral leaflet opening angles) were unfortunately not available in most patients, due to the quality of the echocardiographic images. Finally, patients with more than mild recurrent MR were excluded to allow reliable MVA calculations. Recurrent MR following surgery for functional MR is often seen in conjunction with persistent/progressive leaflet tethering and ongoing LV remodelling.[19] Theoretically, a decreased MVA during exercise might therefore be more prevalent in patients with recurrent MR, who were not included in this study.

Conclusion

In the present study, both increased and decreased MVA were observed during exercise echocardiography after RMA for functional MR. The extent of LV geometrical and functional changes after surgery were related to the change in MVA in response to exercise. A decreased MVA during exercise proved to be strongly associated with a higher increase in mean PAP with respect to CO and predict worse (event-free) survival following the exercise echocardiography.

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Chapter 8

Vasoplegia after restrictive mitral annuloplasty for functional mitral regurgitation in patients with heart failure

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Abstract

Objectives: Patients undergoing heart failure surgery are at risk for developing postoperative vasoplegia. The aim of this study was to determine the incidence, survival, and predictors of vasoplegia in heart failure patients undergoing mitral valve repair for functional mitral regurgitation and to evaluate the effect of ischaemic versus non-ischaemic aetiology.

Design: Retrospective.

Setting: University medical centre, single institutional.

Participants: Heart failure patients with functional mitral regurgitation who underwent restrictive mitral annuloplasty (2006-2015).

Measurements and main results: One hundred twenty-two patients were included (48% ischaemic aetiology). The incidence of vasoplegia was 19% and was not influenced by mitral regurgitation aetiology. Ninety-day survival rate was decreased in vasoplegic compared with non-vasoplegic patients (65% v 93%, p <0.001). After adjusting for age, gender, and heart failure aetiology, prior hypertension (odds ratio [OR] 0.28; 95% confidence interval [CI] 0.08 – 0.91; p = 0.034), higher creatinine clearance (OR 0.97; 95% CI 0.95 – 0.99; p = 0.009), and beta-blocker use (OR 0.25; 95% CI 0.09 – 0.73; p = 0.011) decreased the risk of vasoplegia. Anaemia (OR 3.00; 95% CI1.10 – 8.20; p = 0.032) and longer cross clamp (OR 1.03; 95% CI 1.01 – 1.04; p = 0.001), cardiopulmonary bypass (OR 1.01; 95% CI 1.00 – 1.02; p = 0.003), and procedure times (OR 1.01; 95% CI 1.00 – 1.02, p = 0.002) increased the risk of vasoplegia.

Conclusions: Vasoplegia occurs in 19% of heart failure patients undergoing mitral valve repair for functional mitral regurgitation. It is associated with a poor early outcome. Prior hypertension, a higher creatinine clearance, and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anaemia and longer procedure times were associated with an increased risk of vasoplegia, independent of heart failure aetiology.

Introduction

Functional mitral regurgitation (MR) is frequently observed in patients with ischaemic and non-ischaemic heart failure and results from a combination of increased systolic leaflet tethering and decreased closing forces secondary to left ventricular remodelling (Carpentier classification IIIb).[1,2] Presence of functional MR is independently associated with poor prognosis.[3,4] Surgical mitral valve repair — generally by implantation of a restrictive mitral annuloplasty (RMA) ring — may be considered in patients with moderate to severe MR and persisting symptoms of heart failure, despite optimal medical and device therapy.[5-9] Mitral valve repair may result in durable correction of MR, left ventricular (LV) reverse remodelling, and beneficial clinical outcomes.[10-13] However, each cardiac operation carries associated perioperative risks, which should be taken into account when considering a surgical intervention.

Vasoplegia is an important determinant for adverse postoperative outcome and is observed in 5% to 54% of patients undergoing cardiac surgery using cardiopulmonary bypass (CPB).[14-17] Postoperative vasoplegia is defined as a state with low systemic vascular resistance despite a normal or high cardiac output, and the need for vasopressor therapy, owing to an imbalance of vasodilator and vasopressor mechanisms.[14] Previous studies demonstrated that patients with heart failure with reduced ejection fraction and patients undergoing valvular procedures are at increased risk for developing vasoplegia after cardiac surgery, independent of surgical procedure times.[18-20] Therefore, the authors hypothesized that patients undergoing mitral valve repair for functional MR may be at substantial risk of postoperative vasoplegia, with potential deleterious outcomes.[21]

The aim of this study was to determine the incidence of postoperative vasoplegia in patients with functional MR because of ischaemic or non-ischaemic heart failure, to assess the prognostic impact of vasoplegia on early clinical outcome, and to identify its baseline predictors.

Methods

Study design and study population

For this retrospective cohort study, consecutive heart failure patients with reduced left ventricular ejection fraction (LVEF ≤ 35%) and functional MR, who underwent RMA (as a single procedure or with concomitant tricuspid valve annuloplasty, cardiac support device [CSD] implantation, or coronary artery bypass grafting) at the authors' institution between 2006 and

2015, were included. Patients were excluded if the diagnosis of vasoplegia could not be confirmed or ruled out because of the absence of continuous cardiac index recording during postoperative admission in the intensive care unit. This study was conducted in accordance with the declaration of Helsinki. The institutional ethical committee approved the study and waived the need for individual written informed consent.

Study outcomes and data collection

Haemodynamic, laboratory, clinical and survival data were collected prospectively in the patient information systems (EPD-Vision, Leiden, the Netherlands; Metavision, Itémedical B.V., Tiel, The Netherlands; CS-PDMS, Chipsoft, Amsterdam, The Netherlands) and analysed retrospectively. In line with the World Health Organization definition, anaemia was defined as a haemoglobin concentration <8.1 mmol/L for men and <7.4 mmol/L for women.[22] Creatinine clearance was estimated with the Cockroft-Gault formula.[23] For both variables, the last preoperative assessment was used. All patients underwent transthoracic echocardiographic evaluation before surgery. The images were digitally stored and analysed using commercially available software (GE Vingmed Ultrasound AS, Horten, Norway; EchoPAC version 112.0.1). The LVEF was determined from the apical 2- and 4-chamber views using Simpson's biplane method.[24] MR severity was graded qualitatively and semiquantitatively.[6] Pulmonary hypertension was defined as an estimated peak tricuspid regurgitation velocity >2.9 m/s, measured with continuous wave Doppler.

Vasoplegia was defined as previously described: the continuous need for vasopressors (norepinephrine ≥0.2 mg/kg/min and any dose of terlipressin) combined with a cardiac index ≥2.2 L/min/m^2 for at least 12 consecutive hours, starting within the first 3 days postoperatively.[16]

Surgical Procedures

The indication for surgery was assessed by the multidisciplinary Heart Team, consisting of cardiologists, cardiothoracic surgeons, imaging specialists, heart failure specialists, and anesthesiologists.[25] All operations were performed through midline sternotomy using CPB, aortic cross-clamping, and intermittent antegrade warm blood cardioplegia. RMA was performed for moderate to severe functional MR in all patients. Ring size was determined by measuring the anterior leaflet height and then downsizing by 2 ring sizes using a semirigid annuloplasty ring (Physio ring, Edwards Life Sciences, Irvine, CA). RMA was considered successful in case no or mild MR and a leaflet coaptation height of ≥8 mm were observed on transoesophageal echocardiography. Tricuspid valve repair was performed with an

annuloplasty ring (Edwards Life Sciences MC3 ring or Edwards Physio Tricuspid) in patients with tricuspid regurgitation ≥ grade 3 or a tricuspid annular diameter ≥40 mm (or >21 mm/m^2 body surface area). Concomitant implantation of a CorCap CSD (Acorn Cardiovascular, St. Paul, MN) was performed in patients with non-ischaemic heart failure and a preoperative left ventricular end-diastolic diameter ≥65 mm or indexed left ventricular end-diastolic diameter ≥30 mm/m^2. The CSD is a passive external fabric mesh containment device that is implanted to reduce LV wall stress by providing circumferential diastolic support in order to prevent further LV remodelling. Concomitant myocardial revascularization was performed when indicated. Patients did not receive ACE inhibitors, ARBs, or diuretics on the day of surgery.

Anaesthetics and haemodynamic monitoring

Before induction all patients received an arterial catheter for invasive monitoring of blood pressure. A central venous catheter was inserted in the internal jugular vein and a flow-directed balloon-tipped pulmonary artery catheter (Edwards LifeSciences, Irvine, CA) was introduced after induction for continuous monitoring of cardiac output and pulmonary artery pressure. These data were used to calculate the cardiac index and systemic vascular resistance. Norepinephrine, 0.04 to 0.2 μg/kg/min, was started when the mean arterial pressure was <65 mmHg and the cardiac index was normal (after adequate administration of intravascular fluids if necessary). The aim was for a mean arterial pressure >65 mmHg and adequate end-organ perfusion. When a norepinephrine dosage >1 μg/kg/min was required, terlipressin was started. Both norepinephrine and terlipressin were reduced when the mean arterial pressure was >65 mmHg and end-organ perfusion was restored.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) when normally distributed or otherwise as median and interquartile range (IQR). The normality of data distribution was determined graphically using the Q-Q plot and tested with the Shapiro-Wilk Test of Normality. Categorical variables are presented as numbers and percentages. Missing values for cross clamp time (n = 2, 2%) were replaced using multiple imputations with predictive mean matching, which was repeated 100 times. Baseline age, gender, EuroSCORE, New York Health Association (NYHA) class, creatinine clearance, cross-clamp time, and procedure time were used as predictors in the model. The pooled data were used for analysis. Heart failure patients with ischaemic and non-ischaemic MR and vasoplegic and non-vasoplegic patients were compared. Comparison of continuous data was performed using 2-tailed unpaired Student's t-test for normally distributed variables or otherwise the Mann-Whitney U test. The

Kaplan-Meier method was used to assess 30-day and 90-day survival in vasoplegic and non-vasoplegic patients; the analysis was repeated for heart failure patients with ischaemic and non-ischaemic MR. The survival distributions were compared using the log-rank test.

To explore the association of variables with the occurrence of vasoplegia, univariable logistic regression analysis was performed. Odds ratios (OR) with 95% confidence intervals (CI) were reported. For each variable with a p-value <0.100 during univariable analysis, a multivariable logistic regression analysis was performed to assess their independent association with vasoplegia after adjusting for age, sex, and ischaemic heart failure.

Results

Study Population

A total of 127 patients with LVEF ≤ 35% and moderate to severe functional MR underwent RMA (as a single procedure or with concomitant tricuspid valve annuloplasty, CSD implantation, or coronary artery bypass grafting) at the authors' institution between 2006 and 2015. Because 5 patients in whom the presence of vasoplegia could not be assessed owing to absence of cardiac index measurements were excluded, the final population consisted of 122 patients. The baseline characteristics are described in Table 1. Mean age was 65 ± 9 years and the majority of patients were male (66%). Mean LVEF was 27 ± 6%. Concomitant procedures were tricuspid valve annuloplasty (66%), CSD implantation (43%) and coronary artery bypass grafting (51%).

In total, 64 patients (52%) had functional MR owing to non-ischaemic heart failure and 58 patients (48%) because of ischaemic heart failure. As expected, baseline characteristics were different between these patient groups (Table 1). Patients with non-ischaemic MR were on average 7 years younger (p <0.001), had a 5% lower mean LVEF (p <0.001), and had more often NYHA class III and IV symptoms (73% vs. 50%, p = 0.009). In addition, patients with non-ischaemic MR had less often a history of previous cardiac surgery and more often used mineralocorticoid receptor antagonists and diuretics. Furthermore, patients with non-ischaemic MR more often received concomitant tricuspid valve annuloplasty and CSD implantation. Coronary artery bypass grafting was performed in 91% of patients with ischaemic MR. Fourteen percent of patients with non-ischaemic MR received concomitant coronary artery bypass grafting for single vessel coronary artery disease. Because coronary artery disease could not account for the degree of LV dysfunction on echocardiography in these patients, aetiology of MR was classified as non-ischaemic. A longer mean procedure time was observed in ischaemic compared with non-ischaemic MR patients (median 336 minutes [IQR 293 – 407] vs. 267 minutes [IQR 235 – 314], p <0.001). The same was seen for cross-clamp time (median

127 minutes [IQR 110 – 164] vs. 80 [IQR 63 – 100], p <0.001) and CPB time (median 186 minutes [IQR 154 – 227] v 135 [IQR 118 – 167], p <0.001).

Table 1. Characteristics of the study population (n = 122).

	Overall n = 122	Non-ischaemic MR n = 64	Ischaemic MR n = 58	p-value¥
Age (years)	65 ± 9	62 ± 9	69 ± 9	<0.001
Male sex	66%	61%	72%	0.249
Body mass index (kg/m^2)	26 ± 4	26 ± 3	27 ± 4	0.093
Diabetes	28%	27%	29%	0.840
Prior CVA or TIA	10%	11%	9%	0.766
Prior hypertension	38%	30%	47%	0.063
LVEF (%)	27 ± 6	25 ± 5	30 ± 5	<0.001
NYHA class III or IV	62%	73%	50%	0.009
Pulmonary hypertension	57%	64%	50%	0.144
Previous cardiac surgery	7%	2%	12%	0.027
EuroSCORE II (%)	9(5-13)	9 (6-13)	8 (5-15)	0.693
Preoperative laboratory assessment				
Anemia	23%	19%	28%	0.285
Creatinine clearance (ml/min)	62(49-80)	62 (54-83)	60 (44-78)	0.222
Medication				
Beta-blocker	80%	78%	81%	0.823
ACE inhibitor/ARB	83%	86%	79%	0.349
MRA	56%	67%	43%	0.010
Diuretics	91%	98%	83%	0.003
Inotropes	4%	6%	2%	0.368
Concomitant procedures				
TVP	66%	81%	48%	<0.001
CSD	43%	81%	0%	<0.001
CABG	51%	14%	91%	<0.001
Cross clamp time (min)*	104(74-133)	80 (63-100)	127 (110-164)	<0.001
CPB time (min)	155(131-205)	135 (118-167)	186 (154-227)	<0.001
Procedure time (min)	296(255-360)	267 (235-314)	336 (293-407)	<0.001
ICU time (days)	3 (1-5)	3 (2-6)	3 (1-5)	0.654

* Data based on 120 patients. ¥ comparison of patients with ischaemic vs non-ischaemic MR. Continuous data are presented as mean±SD or median(IQR). Categorical data are presented as numbers (%). ACE = Angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CABG = coronary artery bypass grafting, CPB = cardiopulmonary bypass, CSD = cardiac support device, CVA = cerebrovascular accident, ICU = intensive care unit, IQR = interquartile range, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association, TIA = transient ischaemic attack, TVP = tricuspid valvuloplasty.

Incidence and clinical impact of vasoplegia

The incidence of vasoplegia in heart failure patients with functional MR was 19% (**Figure 1**). The incidence of vasoplegia was not significantly different between ischaemic and non-ischaemic MR patients (16% vs. 22%, p = 0.488). As shown in **Figure 2**, the duration of intensive care unit (ICU) admission was longer in patients with vasoplegia (median 8 days [IQR 5 – 26]) compared with patients without vasoplegia (2 days [IQR 1 – 4], p <0.001). In addition, renal failure occurred more often in patients with vasoplegia (48% vs. 8%, p <0.001). Accordingly, patients with vasoplegia received more continuous veno-venous hemofiltration (44% vs. 4%, p <0.001). Furthermore, both 30-day (78% vs. 98%, p <0.001) and 90-day survival rates (65% vs. 93%, p <0.001) were lower in patients with vasoplegia compared with patients without vasoplegia (**Figure 3, A**). The same applies when the population is stratified for ischaemic (56% vs. 90%, p = 0.002) and non-ischaemic MR patients (71% vs. 96%, p = 0.004; **Figure 3, B**). There was no significant difference in survival when vasoplegic patients with ischaemic MR were compared with vasoplegic patients with non-ischaemic MR (p = 0.458). The same applies to non-vasoplegic patients (p = 0.234).

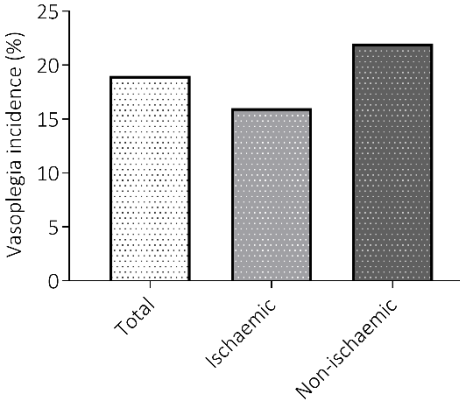

Figure 1. Incidence of vasoplegia in the total study population and in the subgroups (ischaemic and non-ischaemic heart failure patients).

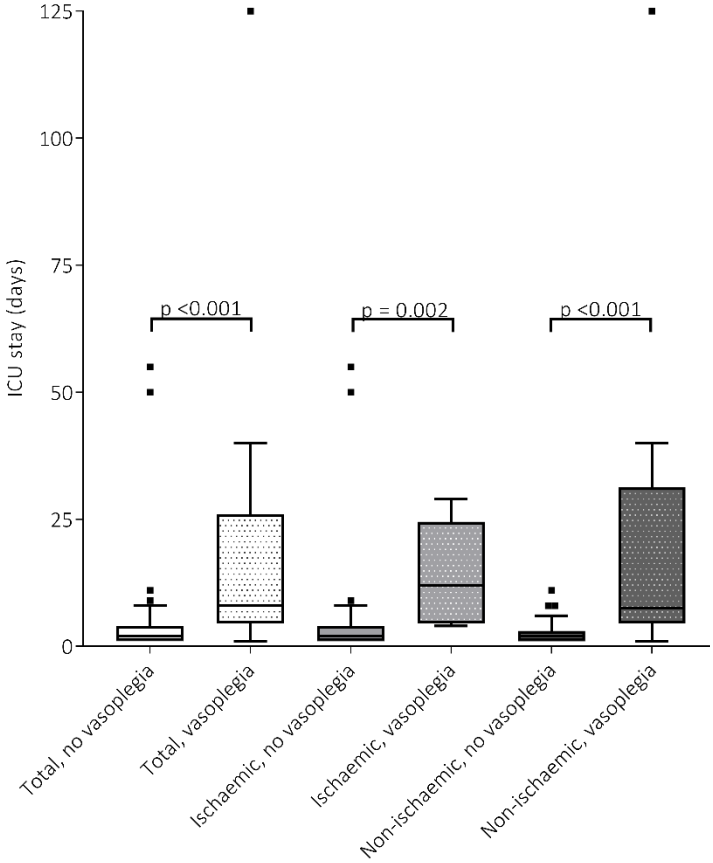

Figure 2. Duration of ICU stay in vasoplegic vs non-vasoplegic patients. Box plots of the IQR and median, with minimum and maximum indicated with whiskers. Outliers are plotted as individual

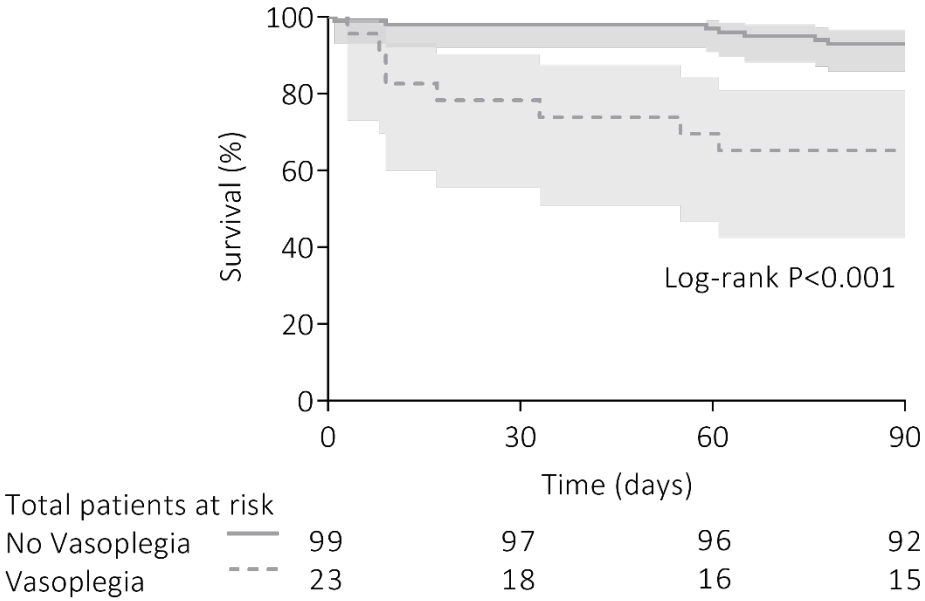

Figure 3 A. Kaplan-Meier survival curve of the total study population. Patients with (dotted line) and without (solid line) vasoplegia were compared. The shaded areas represent the 95% confidence intervals.

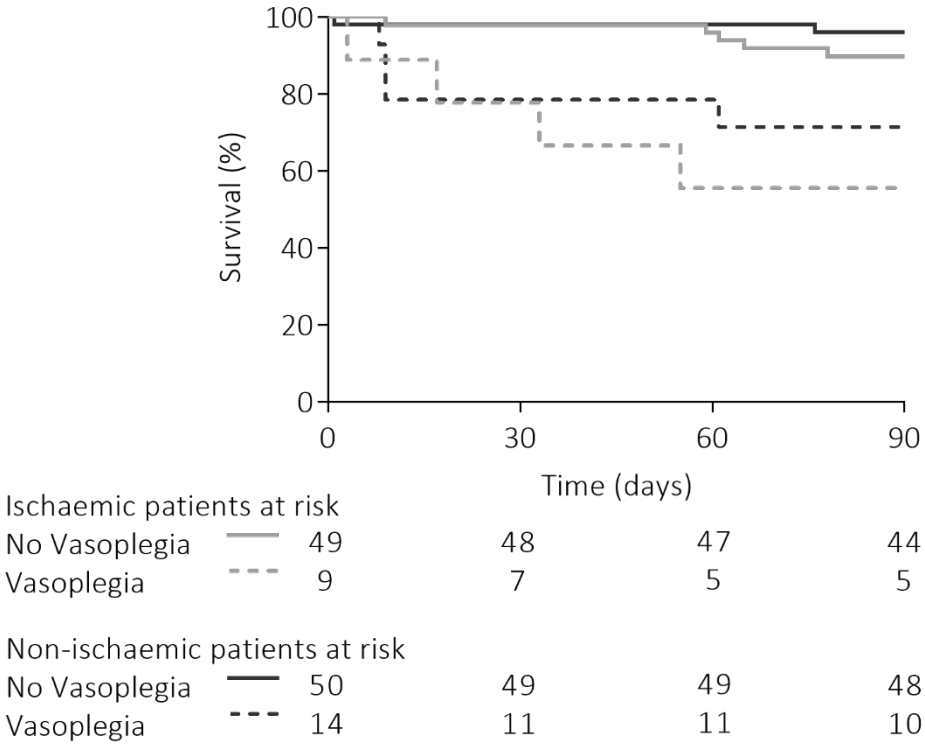

Figure 3B. Kaplan-Meier survival curve of ischaemic heart failure (black) and non-ischaemic heart failure patients (grey). Patients with (dotted line) and without (solid line) vasoplegia were compared. Survival rates were lower in vasoplegic patients for both ischaemic (p = 0.002) and non-ischaemic aetiology (p = 0.004).

Predictors of vasoplegia

Univariable analysis showed that prior hypertension and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anaemia, longer cross-clamp time, CPB time, and total procedure time were associated with an increased risk of vasoplegia (Table 2).

Subsequent multivariable analysis showed that all characteristics mentioned earlier were associated with vasoplegia independent of age, gender, and ischaemic heart failure (Table 3). In addition, a higher creatinine clearance proved to be associated with a decreased risk of vasoplegia when corrected for age, gender, and ischaemic heart failure.

Table 2. Comparison of characteristics of vasoplegic and non vasoplegic patients, and univariable analysis for predictors of vasoplegia.

	Vasoplegia n = 23	No vasoplegia n = 99	Univariable OR (95% CI)	p-value
Age (years)	65 ± 8	65 ± 10	0.99 (0.95-1.04)	0.714
Male sex	74%	65%	1.55 (0.56-4.29)	0.399
Body mass index (kg/m^2)	25 ± 3	26 ± 4	0.90 (0.78-1.04)	0.146
Diabetes	26%	28%	0.90 (0.32-2.50)	0.832
Prior CVA or TIA	9%	10%	0.85 (0.17-4.16)	0.839
Prior hypertension	17%	42%	0.29 (0.09-0.90)	0.033
LVEF (%)	27 ± 6	27 ± 6	1.00 (0.92-1.09)	0.958
Ischaemic heart failure	39%	50%	0.66 (0.26-1.66)	0.372
NYHA class III or IV	70%	61%	1.49 (0.56-3.94)	0.426
Pulmonary hypertension	70%	55%	1.91 (0.72-5.04)	0.194
Previous cardiac surgery	4%	7%	0.60 (0.07-5.11)	0.638
EuroSCORE II (%)	12(7-14)	8(5-13)	1.02 (0.96-1.08)	0.479
Preoperative laboratory assessment				
Anaemia	39%	19%	2.71 (1.02-7.18)	0.045
Creatinine clearance (ml/min)	57(40-77)	62(52-81)	0.98 (0.96-1.00)	0.058
Medication				
Beta-blocker	61%	84%	0.30 (0.11-0.81)	0.018
ACE inhibitor/ARB	83%	83%	0.99 (0.30-3.26)	0.980
MRA	48%	58%	0.68 (0.27-1.68)	0.398
Diuretics	100%	89%		0.999
Inotropes	4%	4%	1.08 (0.12-10.14)	0.947
Procedure type				
TVP	65%	66%	0.98 (0.38-2.54)	0.968
CSD	52%	40%	1.61 (0.65-4.00)	0.306
CABG	61%	49%	1.65 (0.66-4.17)	0.287
Cross clamp time (min)	112(96-154)	98(72-123)	1.01 (1.00-1.02)	0.009
CPB time (min)	197(140-262)	150(128-195)	1.01 (1.00-1.02)	0.008
Procedure time (min)	334(296-465)	285(250-340)	1.01 (1.00-1.01)	0.003

ACE = Angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CABG = coronary artery bypass grafting, CPB = cardiopulmonary bypass, CSD = cardiac support device, CVA = cerebrovascular accident, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NYHA = New York Heart Association, TIA = transient ischaemic attack, TVP = tricuspid valvuloplasty.

Table 3. Multivariable analysis assessing preoperative predictors for vasoplegia. Each variable is corrected for age, gender and ischaemic heart failure.

	Multivariable analysis OR (95% CI)	p-value
Prior hypertension	0.28 (0.08-0.91)	0.034
Anaemia	3.00 (1.10-8.20)	0.032
Creatinine clearance (ml/min)	0.97 (0.95-0.99)	0.009
Beta-blocker	0.25 (0.09-0.73)	0.011
Cross clamp time (min)	1.03 (1.01-1.04)	0.001
Cardiopulmonary bypass time (min)	1.01 (1.00-1.02)	0.003
Procedure time (min)	1.01 (1.00-1.02)	0.002

Discussion

The main findings of this study can be summarized as follows: 1) the incidence of vasoplegia in heart failure patients undergoing mitral valve repair for functional MR was 19%; 2) vasoplegia was associated with a prolonged ICU admission and an increased 30- and 90-day mortality rate; 3) prior hypertension, a higher creatinine clearance, and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anaemia and longer procedure times were associated with an increased risk of vasoplegia; and 4) the results were independent of ischaemic or non-ischaemic functional MR aetiology.

Incidence of vasoplegia

In the present study, vasoplegia was observed in 19% of patients who underwent a mitral valve repair for functional MR. The incidence of vasoplegia in this study is higher compared with the incidence observed after isolated coronary artery bypass grafting (6.9%) in patients with and without heart failure.[26] However, the incidence of vasoplegia in this study is lower compared with the incidence observed after surgical left ventricular restoration (23%), CSD implantation (25%), LVAD implantation (33% – 61%), or orthotopic heart transplantation (11% – 54%) in patients with heart failure.[15-17,27-29] The wide range of reported vasoplegia incidences may be explained by differences in definitions of vasoplegia,[28] although differences in patient and surgical characteristics play a role as well. In line with previous studies, the incidence of vasoplegia was not significantly different between patients with ischaemic and non-ischaemic MR.[15-17,28]

Clinical impact of vasoplegia

In the literature, early postoperative (30-day and in-hospital) mortality after RMA for functional MR ranges from 2.6% to 8% in ischaemic[11,12,30] and 5% to 5.8% in non-ischaemic patients.[31-33]

The overall 30-day mortality rate after RMA in this study (6%; 5% in ischaemic and 6% in non-ischaemic MR patients) is comparable to these reports. However, 30-day mortality proved to be much higher in patients who developed postoperative vasoplegia (22%) compared with non-vasoplegic patients (2%, $p < 0.001$) independent of aetiology of functional MR.

Pathophysiology and predictors of vasoplegia

Several mechanisms have been proposed in the pathophysiology of vasoplegia. Landry and Oliver suggested 3 mechanisms: 1) activation of adenosine triphosphate dependent potassium channels on the vascular smooth muscle cell; 2) activation of inducible nitric oxide synthase; and 3) deficiency of arginine vasopressin (AVP).[34] The latter was confirmed by Colson et al., showing that vasoplegic patients have higher preoperative copeptin (a precursor of AVP) plasma concentrations, but lower AVP concentrations postoperatively.[35] Furthermore, Kortekaas et al. showed that pre-existing endothelial cell activation (reflected by higher baseline von Willebrand Factor propeptide and sP-selectin levels, both markers for heart failure) is associated with vasoplegia in patients undergoing mitral valve surgery.[36,37] Further, the systemic inflammatory response caused by CPB and surgical trauma, plays a major role in vasoplegia.[38] Although the exact pathophysiology of vasoplegia has not yet been elucidated, its aetiology is multifactorial and results from activation of vasodilator mechanisms and inactivation of vasoconstrictor mechanisms.

In the present study, preoperative predictors of vasoplegia were assessed in heart failure patients undergoing mitral valve repair for functional MR. Heart failure patients proved to be at an increased risk of vasoplegia after cardiac surgery in several studies.[18-20] This might be explained by the fragile balance of the vascular system in patients with heart failure because all systems perform at maximal capacity to assure adequate perfusion pressure. This fragile balance can easily be disturbed by CPB and surgical trauma.

Several preoperative patient characteristics – no betablocker use, no hypertension, a lower creatinine clearance, and anaemia – proved to be associated with an increased risk of postoperative vasoplegia, Furthermore, prolonged CPB time was related to an increased risk of vasoplegia as well.

The authors hypothesize that these patient characteristics influence activation of vasodilation mechanisms and inactivation of vasoconstriction mechanisms (e.g., drug use, anaemia) and are a marker of the fragile balance of the vascular systems. Heart failure patients who tolerate a beta-blocker and are able to maintain an adequate haemoglobin level and renal function may simply represent a subgroup of patients better able to compensate for haemodynamic disturbances caused by surgical trauma and CPB. In contrast, studies in heart transplantation

patients did not find a difference in beta-blocker use between vasoplegic and non-vasoplegic patients.[15,28,29] Interestingly, the overall use of beta-blockers in these studies was much lower (22% – 61%)[15,28,29] compared with studies that found beta-blocker use to be protective (80% – 84%),[16] indicating an important difference in study population.

In line with previous studies in heart failure patients,[28,29] prolonged CPB time proved to be associated with an increased risk of vasoplegia (median 197 minutes in vasoplegic patients versus 150 in non-vasoplegic patients, p = 0.008). This might be explained by the systemic inflammatory response induced by CPB and surgical trauma, which disturbs the balance of the cardiovascular system. A longer CPB time and larger surgical trauma may induce a more severe systemic inflammatory response and consequently increase the risk of vasoplegia. However, a study with much longer CPB times (van Vessem et al., mean 193 ± 69 minutes16) did not observe an association between CPB time and vasoplegia after heart failure surgery. Therefore, the authors hypothesize that prolonged CPB time increases the risk of vasoplegia in heart failure patients until a certain duration threshold; when this threshold is reached, the risk of vasoplegia does not further increase. However, because a longer CPB time represents more extensive surgery, duration of CPB could simply be a marker of disease progression, although in this study left ventricular ejection fraction, NYHA class, and EuroSCORE II were not associated with an increased risk of vasoplegia.

Limitations

When interpreting the results of the current study, several study limitations should be taken into account. First, this was a retrospective observational study bearing associated biases. Second, this was a single centre study. Further research is necessary to verify if these results can be extrapolated to other centres.

Clinical Implications

Vasoplegia is a hazardous complication in heart failure patients undergoing mitral valve repair for functional MR and is related to a prolonged ICU admission and increased early mortality. Therefore, the likelihood of developing postoperative vasoplegia should be taken into account by the Heart Team when deciding on whether or not to perform surgery. Furthermore, preoperative optimization of haemodynamics and renal function could potentially reduce the risk of vasoplegia. Finally, vasopressin and methylene blue may be considered as treatment option in patients with vasoplegia resistant to fluid and vasopressor therapy.[39-42] However, further research is warranted to unravel the pathophysiologic mechanisms of vasoplegia after cardiac surgery in order to improve therapeutic and preventive treatment options.

Conclusion

Vasoplegia occurred in 19% of heart failure patients undergoing mitral valve repair for functional MR. It was associated with an impaired early outcome. Prior hypertension, a higher creatinine clearance, and beta-blocker use were associated with a decreased risk of vasoplegia, whereas anaemia and longer procedure times were associated with an increased risk of vasoplegia independent of MR aetiology.

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Chapter 9

Summary, discussion, clinical implications and future perspectives

Summary

Functional mitral regurgitation (MR) – also referred to as secondary MR – is a disease condition which results from a combination of annular dilatation, papillary muscle displacement with increased systolic leaflet tethering, and reduced closing forces, due to regional or global left ventricular (LV) remodelling. Functional MR is a common phenomenon and can be classified as either ischaemic or non-ischaemic, based on aetiology of LV remodelling. Regardless of aetiology, functional MR carries a poor prognosis.

The primary step in the treatment of patients with functional MR consists of optimal medical and device therapy. In patients with persistence of MR despite optimal medical and device therapy, surgical treatment options can be considered. Over the past decades, many surgical treatment options have been developed, of which mitral valve repair by implantation of a restrictive mitral annuloplasty (RMA) ring forms the mainstay.

In this thesis an integrated medico-surgical approach for patients with functional MR was examined, consisting of optimal medical and device therapy combined with RMA, and additional surgical interventions when indicated. The indication for each surgical intervention was determined after careful balancing of treatment options by the multidisciplinary Heart Team – consisting of heart failure specialists, interventional cardiologists, arrhythmia cardiologists and cardiac surgeons. Focus of this thesis was to determine (long-term) clinical and echocardiographic outcomes after this approach and to identify which patients are (un)likely to benefit from it.

Chapter 2 provides an overview of the surgical and interventional treatment options that have been developed for patients with functional MR over the past decades. Mitral valve repair by restrictive mitral annuloplasty forms the cornerstone in the surgical treatment of functional MR. Additional (sub)valvular procedures – such as an edge-to-edge repair, RING + STRING or papillary muscle approximation – have been introduced to reduce the risk of recurrence of MR after mitral valve repair and can be useful for patients who meet criteria for an increased failure rate after RMA alone. For these patients, mitral valve replacement may also be considered instead. Furthermore, transcatheter edge-to-edge repair (MitraClip implantation) has gained ground for the treatment of functional MR in patients who are ineligible for mitral valve surgery and meet specific criteria. Finally, left ventricular assist device implantation (LVAD) may be considered in patients with functional MR in whom LV dysfunction is too advanced, and who most likely will not benefit from any mitral valve procedure. For each of these treatment options, the rationale, indication, surgical technique, results and limitations are discussed by experts in the field.

Chapter 3 comments on the two-year results of the Cardio-Thoracic Surgery Network (CTSN) trial. This randomized controlled trial compared mitral valve repair versus mitral valve replacement for severe ischaemic MR, and demonstrated no between-group differences with regard to LV reverse remodelling (primary end-point) or survival, but recurrent MR was more frequently observed after mitral valve repair. These findings may lead to the conclusion that mitral valve replacement is better than mitral valve repair. However, recurrence of MR was observed in 30% of patientswho underwent repair only 30 days after surgery, which should be regarded as residual MR due to inadequate surgical technique rather than true recurrent MR. Furthermore, patients with a successful mitral valve repair (i.e. without recurrent MR) had a 30% reduction in LV end-systolic volume, whereas reverse remodelling was absent after mitral valve replacement. These points should be taken into account when translating the results of this trial into conclusions for clinical practice.

The results of the CTSN trial described in Chapter 3 (i.e. no difference in LV reverse remodelling or survival between mitral valve repair and mitral valve replacement, despite a 59% recurrent MR rate 2 years after mitral valve repair versus 4% after replacement), raised the question: does recurrent MR, in terms of clinical outcome, matter at all?

Chapter 4 evaluates long-term clinical and echocardiographic outcomes in 261 patients who underwent RMA and revascularization for moderate to severe ischaemic MR according to a structured surgical protocol, focusing on the mortality-adjusted incidence, clinical impact, and determinants of recurrent MR. The cumulative incidence of recurrent MR ≥ grade 2, assessed by competing risk analysis, was low, with 9.6 ± 1.8 at 1-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up. Cumulative survival was favourable with 86% [81 – 90] at 1-year, 67% [61 – 73] at 5-year and 46% [39 – 53] at 10-year follow-up. Age, preoperative New York Heart Association Class III or IV, a history of renal failure, and recurrence of MR expressed as a time-dependent variable [HR 3.28 (1.87 – 5.75), p <0.001], were independently associated with an increased mortality risk. These findings indicate that RMA with revascularization for ischaemic MR results in a low incidence of recurrent MR with favourable clinical outcome up to 10 years after surgery. However, development of recurrent MR at any moment after surgery is independently associated with an increased risk for mortality. Female gender, a history of ST-elevation myocardial infarction, a preoperative QRS duration ≥120 ms, a higher preoperative MR grade, and a higher preoperative indexed LV end-systolic volume were in-dependently associated with an increased likelihood of recurrent MR.

In non-ischaemic MR – as opposed to ischaemic MR – the underlying ventricular disease itself cannot be addressed. Consequently, treatment options for patients with MR due to non-

ischaemic cardiomyopathy who remain symptomatic despite optimal medical and device therapy, are limited and consist of mitral valve repair, LVAD implantation or heart transplantation (HTx).

In chapter 5 long-term outcomes are described of 77 patients with non-ischaemic MR and symptomatic heart failure, who underwent an integrated approach of mitral valve repair with concomitant procedures – tricuspid valve repair, implantation of a cardiac support device (CSD) and arrhythmia surgery – when indicated by the Heart Team. Left ventricular reverse remodelling was observed in 38% of patients and recurrent MR in 20% of patients at mid-term follow-up. The absence of reverse remodelling and presence of recurrent MR – which were highly related – were significantly associated with worse HTx-free survival. HTx-free survival 1 and 3 years after mid-term follow-up was favourable in patients with LV reverse remodelling (100% and 88 ± 6%), significantly worse but still acceptable in patients without LV reverse remodelling and without recurrent MR (83 ± 7% and 68 ± 8%), and extremely poor in patients without LV reverse remodelling and with recurrent MR (49 ± 14% and 33 ± 13%). None of the baseline variables in this study was predictive of LV reverse remodelling and a history of ventricular tachyarrhythmia was the only independent predictor of recurrent MR. These findings emphasize the need for close echocardiographic monitoring after surgery, to timely identify the subgroup of patients who do not show LV reverse remodelling and develop recurrence of MR, in order to re-evaluate additional treatment options and improve their prognosis.

Long-term effects of advanced surgery for patients with refractory heart failure due to a post-infarction anteroseptal aneurysm were evaluated in chapter 6. In this chapter, outcomes of 159 patients who underwent left ventricular reconstruction (LVR) with concomitant procedures – mitral valve repair, tricuspid valve repair, coronary revascularization and arrhythmia surgery – when indicated, were described. Mid-term echocardiography demonstrated decreased indexed LV end-systolic volumes (89 ± 42 ml/m^2 preoperatively to 51 ± 18 mL/m^2 at mid-term, p <0.001) and absence of MR ≥ grade 2 in all patients. 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, a measure of LV systolic function), presence of MR ≥ grade 2, age and a longer time interval after myocardial infarction, proved to be independently associated with adverse event-free survival. Event-free survival was favourable in patients with WMSI <2.5 and significantly worse in patients with WMSI ≥2.5. In both groups, the presence of preoperative MR ≥ grade 2 negatively affects event-free survival, despite successful correction of MR. These results

demonstrate that preoperative risk stratification by WMSI and MR can support the Heart Team in choosing the optimal surgical strategy for these patients.

Restrictive mitral annuloplasty has raised concerns, in that extensive reduction of the mitral annular dimension could result in obstruction to antegrade mitral flow and might induce a functional mitral stenosis at rest, that may become even more pronounced during exercise.

Chapter 7 assesses mitral valve exercise haemodynamics in 32 patients after RMA for functional MR. In this study population, mitral valve area (MVA) was found to be dynamic during exercise, and to differ between individual patients: MVA increased in 25 patients and decreased in 7 patients. Change in MVA in response to exercise proved to be related to the extent of LV geometrical and functional changes after surgery. The group of patients with an increased MVA in response to exercise showed LV reverse remodelling and a significant myocardial contractile reserve, whereas the group of patients with a decreased MVA during exercise was characterized by absence of LV reverse remodelling and limited myocardial contractile reserve. Furthermore, a decreased MVA proved to be strongly associated with a disproportionally higher increase in mean PAP with respect to cardiac output – suggesting that a decreased MVA during exercise has significant haemodynamic impact – and worse (event-free) survival, compared to patients with an increased MVA during exercise.

Each cardiac operation carries peri-operative risks, which should be taken into account when considering an intervention. Vasoplegia – defined as a state of low systemic vascular resistance despite normal or high cardiac output and the need for vasopressor therapy, due to an imbalance of vasodilator and vasopressor mechanisms – is an important determinant for adverse postoperative outcome in patients undergoing cardiac surgery.

In chapter 8, the incidence, clinical impact and preoperative predictors of vasoplegia after RMA are determined. Vasoplegia was observed in 19% of patients after RMA and its incidence was independent of the aetiology of functional MR. Patients who developed vasoplegia had significantly longer intensive care unit admissions and a significantly increased 30- and 90-day mortality. Several preoperative patient characteristics, which seem mainly related to the severity of heart failure – no beta-blocker use, no hypertension, a lower creatinine clearance and anaemia – proved to be associated with an increased risk of postoperative vasoplegia, as was a prolonged cardiopulmonary bypass time. These findings indicate that the likelihood of developing vasoplegia after surgery should be taken into account by the Heart Team when deciding on whether or not to perform surgery. Furthermore, preoperative optimisation of haemodynamic and renal function could potentially reduce the risk of vasoplegia.

Discussion

Over the past decades, major advances have been made in the treatment of functional MR, and several surgical and interventional treatment options have been developed. Despite these developments, the optimal treatment strategy for patients with functional MR remains a topic of debate, since randomized controlled trials are limited in number and have contradictory outcomes. These conflicting results are most likely explained by the fact that functional MR comprises a highly heterogeneous disease for which a "one-size-fits-all" approach does not suffice. Thus, a patient-tailored approach seems crucial for improving the outcomes of patients with functional MR.

Mitral valve repair by RMA forms the cornerstone of the surgical treatment of functional MR. The studies in the present thesis examined (long-term) clinical and echocardiographic outcomes after restrictive mitral annuloplasty – with concomitant procedures when indicated. The goal of this thesis was to identify patients likely or unlikely to benefit from this approach, in order to personalise the treatment strategy and optimise outcomes for each patient with functional MR.

To accomplish this goal, we aimed at:
1) unravelling the mechanisms attributing to outcomes after RMA surgery;
2) identifying preoperative predictors for outcomes after RMA surgery.

Mechanisms attributing to outcomes after restrictive mitral annuloplasty

Early outcomes after RMA surgery have proven to be favourable. The addition of mitral valve repair to CABG in patients with ischaemic MR did not increase the rate of perioperative complications compared to CABG alone in randomized controlled trials.[1, 2] Adverse early outcomes after RMA surgery may be affected by development of postoperative vasoplegia.

Adverse long-term outcomes may be associated with failure to restore mitral valve competence and/or failure to initiate and sustain LV reverse remodelling – the two major aims of the treatment of patients with functional MR. In addition, implantation of an undersized ring reduces mitral annular dimension and might lead to induction of a (functional) mitral valve stenosis after RMA, which may affect long-term clinical outcomes as well.

In this thesis, the role of each of these mechanisms in determining clinical outcomes after RMA surgery was assessed.

Vasoplegia

Postoperative vasoplegia is associated with adverse early outcomes after cardiac surgery, especially in patients with heart failure and in patients undergoing valvular procedures.[3-5] Adverse early outcomes after RMA surgery may therefore be partially related to vasoplegia as well.

In this thesis, the incidence of vasoplegia after RMA surgery was 19%. Patients who developed vasoplegia after surgery had a significantly longer duration of intensive care unit stay and a higher 30-day mortality rate (22% in vasoplegic patients versus 2% in non-vasoplegica patients, $p < 0.001$).

These findings demonstrate that vasoplegia is an important determinant of adverse early outcomes after RMA surgery. The risk for postoperative vasoplegia should therefore be one of the factors for the Heart Team to consider when deciding on whether or not to refer the patient for surgery. For these patients, potential adjustable risk factors (as described) should be modified, although in general preventive and therapeutic treatment options for vasoplegia (apart from symptomatic treatment) are limited. These results stress the need for developing such direct treatment options in order to improve early outcome after RMA surgery.

Recurrence of mitral regurgitation and left ventricular (reverse) remodelling

Restoration of mitral valve competence resolves the volume overload that ensues with MR and may break the cycle of progressive LV remodelling and worsening MR. Recurrence of MR after RMA leads right back to this vicious cycle and is therefore thought to negatively affect clinical outcome.

Studies in this thesis demonstrated that RMA following a structured surgical approach results in a low incidence of recurrent MR in both patients with ischaemic MR (Chapter 4 and Chapter 6) and non-ischaemic MR (Chapter 5). The incidence of recurrent MR observed in this thesis was far lower than that observed in many other studies.[6-9] However, recurrence of MR 18 months after RMA in non-ischaemic MR patients proved to be independently associated with absence of LV reverse remodelling (Chapter 5), while recurrence of MR in ischaemic MR patients occurring at any moment during the course of follow-up was related to poor long-term clinical outcome, including an increased risk of reoperation, heart failure readmissions, and death (Chapter 4).

These studies emphasize the need for durable correction of MR and demonstrate that RMA can result in such durable correction in a majority of patients when performed by a structured surgical approach, consisting of implantation of a complete semi-rigid annuloplasty ring,

stringent downsizing by two ring sizes, and aiming at absence of MR and a mitral leaflet coaptation length of at least 8 mm on intra-operative echocardiography. Residual MR was observed in only 3-4% of patients at discharge in this thesis (Chapter 4 and Chapter 5), whereas others reported considerable incidences of MR early after surgery (e.g. 30% within 30-days after surgery in the CTSN trial, where the mean number of repairs per centre was 5.2).[8, 9] MR in the early phase after surgery cannot be explained by disease progression (LV dilatation with increased mitral leaflet tethering) and should be considered residual MR due to suboptimal repair rather than true recurrent MR. Therefore, RMA surgery should only be performed in specialized centres with expertise in valvular heart disease and heart failure.

Left ventricular remodelling is the primary cause of functional MR. Initiating sustained LV reverse remodelling is therefore a key element in the treatment of functional MR.

In the present thesis, the clinical impact of LV reverse remodelling after RMA surgery was assessed (Chapter 5). Patients with LV reverse remodelling (defined as ≥15% decrease in indexed left ventricular end-systolic volume) proved to have beneficial clinical outcome, including a low risk of heart failure readmissions and beneficial long-term HTx-free survival. However, patients in whom LV reverse remodelling was absent, had an increased risk of recurrent MR and heart failure readmissions, and poor HTx-free survival.

These findings confirm that the LV plays a crucial role, not only in the development, but also as a target in the treatment of functional MR, and underline that LV reverse remodelling is of major importance for obtaining beneficial clinical outcomes after surgery.

The studies in this thesis clearly demonstrate that absence of LV reverse remodelling and recurrence of MR are both important mechanisms leading to adverse clinical outcome after RMA surgery. In line with literature[10], recurrence of MR and absence of LV reverse remodelling proved to be highly associated (Chapter 5). The simultaneous observation of recurrent MR and absence of LV reverse remodelling does not elucidate the causality between the two, since they are interrelated in a complex way. Residual or recurrent MR may lead to absence of LV reverse remodelling, whereas the absence of LV reverse remodelling may lead to recurrence of MR – with both scenarios leading to adverse clinical outcome. It is important to appreciate that the patients who developed MR after surgery in this thesis had true recurrent MR (developed in the course of follow-up), rather than residual MR due to improper correction of MR during surgery. As such, it is most likely that progression of LV disease is the primary determinant of recurrent MR, which develops when ongoing LV remodelling causes further papillary muscle displacement with progressive mitral leaflet tethering. Once recurrent MR is present, the

ensuing volume overload poses additional strain on an already fragile LV, further exacerbating the remodelling process and consequently deteriorating clinical outcome.

The hypothesis that the extent of LV dysfunction (in other words, the inability for LV reverse remodelling to occur) rather than recurrence of MR is the primary determinant of adverse clinical outcome after RMA surgery is supported by the results of the CTSN trial. In this trial there was no difference in LV reverse remodelling or survival between patients who underwent mitral valve repair versus mitral valve replacement, despite a significantly higher incidence of recurrent MR after mitral valve repair.[8, 9] These results indicate that completely resolving functional MR – which is obtained by replacing the mitral valve – does not always lead to LV reverse remodelling. This may be explained by considering that a subgroup of patients may already be at a stage of LV disease where simply resolving the volume overload that ensues with MR is insufficient to halt or reverse LV remodelling – and better clinical outcome is no longer attainable at the time of surgery. The fact that in this trail the patients after mitral valve replacement were not showing more LV reverse remodelling than patients after mitral valve repair, who had in 60% recurrence of MR, also poses the question whether the replacement itself may have a negative impact on LV reverse remodelling.

Functional mitral stenosis

Restrictive mitral annuloplasty enforces mitral leaflet coaptation by reducing the mitral annular dimension. However, such reduction might obstruct antegrade mitral flow, resulting in a mitral stenosis with potential clinical consequences.[11] Such (functional) stenosis would be even more pronounced during exercise.

In this thesis (Chapter 7), MVA during exercise after RMA proved to be dynamic: MVA increased in the majority of patients but decreased in a subgroup of patients. A decreased MVA in response to exercise was associated with LV geometry (absence of LV reverse remodelling) and function (limited myocardial contractile reserve) after surgery. Furthermore, a decreased MVA during exercise was strongly related to a disproportionate increase in mean PAP with respect to the rise in cardiac output and to significantly worse event-free survival.

The fact that MVA is dynamic during exercise – despite implantation of a semi-rigid annuloplasty ring with a fixed orifice area – suggests that MVA is determined at level of the leaflet tips and contradicts that a functional mitral stenosis simply results from implantation of a downsized annuloplasty ring. Indeed, earlier studies demonstrated that MVA during exercise after RMA surgery is associated with diastolic anterior leaflet tethering, with increased tethering leading to decreased MVA and vice versa.[12, 13] Furthermore, the association of a decreased MVA with adverse LV geometry and function implies that progressive mitral leaflet

tethering due to ongoing LV remodelling may not only lead to incomplete mitral closure during systole (i.e. recurrence of MR), but also to incomplete mitral leaflet opening during diastole (i.e. functional mitral stenosis). Once again, these findings emphasize the importance of LV reverse remodelling for beneficial outcomes after RMA surgery. The role of a functional mitral stenosis after RMA surgery, independently of LV geometry and function, should be further investigated in larger studies to draw any definitive conclusions regarding its clinical implications.

Preoperative predictors for outcomes after restrictive mitral annuloplasty

Ideally, patients who are (un)likely to benefit from RMA surgery are selected preoperatively. Given the clinical impact of vasoplegia, recurrence of MR and absence of LV reverse remodelling, we aimed to identify preoperative predictors for each of these factors and for mortality throughout this thesis (Chapters 4, 5, 6 and 8).

Several preoperative predictors (no prior hypertension, a lower creatinine clearance, no beta-blocker use and anaemia), and longer cardiopulmonary bypass time, were associated with an increased risk for vasoplegia and adverse early outcomes (Chapter 8). These predictors seem to be primarily markers of patients with a fragile balance of the vascular systems, making them less able to compensate for haemodynamic disturbances associated with the systemic inflammatory response following cardiopulmonary bypass and major surgery. This thesis presents a first step in preoperative identification of patients at risk for vasoplegia after RMA surgery. However, further research is needed to unravel the pathophysiologic mechanisms causing vasoplegia and to identify more specific preoperative predictors for patients at risk for vasoplegia, and possible preventive strategies and/or treatment options.

Female gender, a history of STEMI, a preoperative QRS duration ≥120 ms, a higher preoperative MR grade and higher indexed LV end-systolic volume were predictors for recurrent ischaemic MR after RMA surgery (Chapter 4). A history of ventricular tachyarrhythmias was the only predictor of recurrent MR after RMA surgery in patients with non-ischaemic MR. For this subset of patients no preoperative predictors – including preoperative parameters reflecting the extent of LV remodelling – could be identified to predict LV reverse remodelling (Chapter 5). This may be due to the limited study population. However, the personalised use of a CSD in patients with more advanced LV remodelling (i.e. preoperative LV end-diastolic diameter ≥65 mm or indexed LV end-diastolic diameter ≥30 mm/m^2) could also explain this, since implantation of a CSD has additional beneficial effect on LV reverse remodelling and may consequently mitigate the deleterious effect of advanced LV remodelling in this subgroup of patients. Predictors for poor survival after RMA for ischaemic MR were age, preoperative New

York Heart Association class III or IV, renal failure and recurrence of MR at any time during follow-up (Chapter 4). A preoperative WMSI ≥2.5, preoperative MR ≥ grade 2 and a longer time interval after myocardial infarction were predictors for adverse event-free survival after LVR – and concomitant RMA when indicated – for patients with heart failure due to an anteroseptal LV aneurysm (Chapter 6).

In line with literature, most predictors for recurrent MR and adverse clinical outcome in this thesis are related to the degree of MR, extent of LV remodelling (LV size, geometry and function) or severity and duration of heart failure symptoms. These parameters provide useful information and may help the Heart Team in their decision making process. However, prediction of the potential to reverse LV remodelling – which seems crucial for recovery after RMA surgery – remains difficult. In the absence of such predictors, close echocardiographic monitoring after surgery is warranted – focusing on absence of LV reverse remodelling and recurrence of MR – to allow early identification of patients at risk for adverse clinical outcomes. These patients should periodically be re-evaluated by the Heart Team to assess the possibilities and appropriateness of additional procedures (such as LVAD or HTx).

Clinical implications and future perspectives

In this thesis we have demonstrated that a personalised medico-surgical approach – consisting of optimal medical and device therapy, RMA surgery, and concomitant surgical procedures when indicated – results in beneficial (long-term) clinical and echocardiographic outcomes in the vast majority of patients with functional MR. The subgroup of patients for which this approach does not offer a definitive solution proved to be characterized by the occurrence of perioperative vasoplegia (which increases the risk of adverse early outcome after surgery), and by the development of recurrence of MR and/or absence of LV reverse remodelling (both leading to adverse long-term outcome after surgery). Several preoperative predictors for patients at increased risk for vasoplegia, recurrent MR and adverse clinical outcome after RMA surgery have been identified in this thesis. These findings should be translated into clinical practice and be incorporated into the decision-making process in the Heart Team in order to further improve outcomes of patients with functional MR.

The overall favourable long-term clinical and echocardiographic outcomes observed in this thesis underline that care for patients with persistent functional MR despite optimal medical and device therapy should be concentrated in specialized centres with expertise in valvular heart disease and heart failure. In these centres a dedicated multidisciplinary Heart Team should carefully balance the treatment options for each patient, taking into account the risk for

vasoplegia, recurrence of MR and absence of LV reverse remodelling. The preoperative risk factors identified both in this thesis and in earlier reports may help the Heart Team in this decision-making process. RMA – performed according to a structured surgical approach – should form the cornerstone in the surgical treatment of patients with functional MR. In patients with a high risk of recurrent MR, additional subvalvular procedures or replacement of the mitral valve may be considered to minimize the risk of MR recurrence – keeping in mind that this does not always lead to LV reverse remodelling. In patients accepted for mitral valve surgery, the indication for concomitant surgical procedures – coronary artery revascularization, tricuspid valve repair, left ventricular reconstruction and arrhythmia surgery – should be considered on a case-by-case basis as well. In patients who are unable to undergo mitral valve surgery due to comorbidities and in whom symptoms of heart failure are predominantly related to valvular dysfunction rather than LV dysfunction (i.e. severe MR but not so dilated LV), a percutaneous edge-to-edge mitral valve repair can be considered. Finally, the subgroup of patients with functional MR in whom LV disease is too advanced to such an extent that LV reverse remodelling is unlikely – although, as said, hard to identify – will not benefit from any mitral valve intervention but should be considered for HTx or LVAD implantation.

The results of this thesis contribute to further personalisation and optimisation of the treatment for patients with functional MR. Still, there are some major challenges to be addressed.

First, it remains difficult to identify preoperatively whether an individual patient with functional MR will or will not benefit from a mitral valve procedure, and consequently to select the appropriate procedure for each individual. This difficulty is due to the fact that functional MR comprises a highly heterogeneous disease in which the mitral valve and LV are interrelated in a complex way. Evolving imaging techniques may play a role in identifying new predictors for outcome after mitral valve procedures. 3D echocardiography may provide more advanced information regarding mitral valve geometry, LV geometry and function, and the interrelation between mitral valve and LV. Furthermore, cardiac magnetic resonance imaging focusing on fibrosis and scar, and stress echocardiography focusing on viability, may provide additional information regarding the (extent of the) underlying LV disease and the expected potential for LV reverse remodelling after surgery. In addition to these imaging techniques, technological advances may offer a solution as well. Machine learning algorithms are able to combine a vast amount of information and take the multi-dimensional correlations between different variables into account as well. Consequently, a machine learning algorithm may be able to predict outcomes after RMA surgery more accurately compared to prediction models developed by statistical analysis methods. Indeed, a recent study demonstrated that a risk score developed

using machine learning could accurately – and more accurately than existing risk scores – predict the risk of mortality in heart failure patients.[14]

Second, most current treatment options for functional MR are directed at the mitral valve and sometimes local LV geometry, whereas the underlying problem – the intrinsic myocardial disease – is largely left untouched, except for coronary revascularization in patients with ischaemic MR. Since the LV seems to play a crucial role in determining outcomes after mitral valve procedures, the underlying LV disease should become the focus of future treatment strategies. External cardiac restraining devices may be useful to break the vicious cycle of LV remodelling and worsening MR by reducing both MR and LV wall stress. However, such a device is currently not on the market, and the results of two devices which are currently being investigated – the BACE (Basal Annuloplasty of the Cardia Externally) and VenTouch device – are to be determined.[15] Ultimately, the intrinsic myocardial disease itself should be addressed, for both patients with ischaemic and non-ischaemic MR. Regenerative medicine may provide such a treatment option by restoring normal myocardial cell function, but at the moment it seems still a long way before such therapies can be used in everyday clinical practice.

Future studies should therefore focus on improving preoperative prediction of patients who are (un)likely to benefit from a mitral valve procedure and on the treatment of the underlying myocardial disease, in order to genuinely personalise the treatment strategy and optimise outcomes for all patients with functional mitral regurgitation.

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Nederlandse samenvatting

Samenvatting

Functionele mitralisinsufficiëntie (MI) – ook wel secundaire MI genoemd – wordt veroorzaakt door lokale of globale veranderingen in de geometrie en functie van de linker ventrikel (LV), ook wel 'LV remodelling' genoemd, terwijl de anatomie van de mitralisklep (in tegenstelling tot organische MI) volledig normaal is. Afhankelijk van de oorzaak van de LV remodelling, wordt functionele MI ook wel ischaemische of non-ischaemische MI genoemd. Ischaemische MI ontstaat als gevolg van een hartinfarct of ischaemie, terwijl non-ischaemische MI ontstaat als gevolg van een andere (intrinsieke) aandoening van het myocard. Functionele MI komt vaak voor en is – onafhankelijk van de onderliggende etiologie – geassocieerd met een slechte prognose.

De eerste stap in de behandeling van patiënten met functionele MI bestaat uit optimale medicamenteuze behandeling en CRT. Chirurgische behandelopties kunnen overwogen worden voor patiënten waarbij de MI persisteert ondanks medicamenteuze behandeling en CRT. De afgelopen decennia zijn er diverse chirurgische behandelopties ontwikkeld, waarvan restrictieve mitralisklep annuloplastiek (RMA) de basis vormt. Het doel van RMA is om functionele MI op te heffen en het proces van LV remodelling een halt toe te roepen of zelfs om te keren (ook wel 'LV reverse remodelling' genoemd), en zodoende de klinische uitkomsten van patiënten te verbeteren.

In dit proefschrift wordt de behandeling van patiënten met functionele MI door middel van een geïntegreerd medicamenteus-chirurgische benadering bestudeerd. Deze benadering bestaat uit een combinatie van optimale medicamenteuze therapie, CRT, RMA en – indien geïndiceerd – aanvullende chirurgische interventies. De indicatie voor ieder van deze chirurgische interventies wordt afgewogen door een multidisciplinair HartTeam van specialisten op het gebied van hartfalen, interventiecardiologen, ritmecardiologen en hartchirurgen. De focus van dit proefschrift ligt op de (lange-termijn) klinische en echocardiografische uitkomsten na deze benadering en op de (preoperatieve) identificatie van de patiënten die hier wel of geen baat bij zullen hebben.

Hoofdstuk 1 vormt de inleiding van dit proefschrift en biedt een overzicht van de beschikbare literatuur op het gebied van functionele MI. In dit hoofdstuk worden de anatomie en functie van de mitralisklep omschreven en wordt ingegaan op de pathofysiologische mechanismen die leiden tot het optreden van functionele MI. Vervolgens worden de prevalentie en de klinische impact van ischaemische en non-ischaemische MI behandeld aan de hand van een overzicht van de publicaties op dit gebied. De beeldvormende technieken en criteria voor het definiëren van de ernst van functionele MI worden besproken. De rationale en de uitkomsten van

verschillende medicamenteuze behandelopties en CRT worden gepresenteerd. Vervolgens worden de mogelijke chirurgische interventies voor functionele MI besproken. Coronaire bypass chirurgie (CABG) richt zich direct op de onderliggende LV-afwijkingen en vormt derhalve een belangrijk onderdeel in de behandeling van patiënten met ischaemische MI. Restrictieve mitralisklep annuloplastiek vormt de hoeksteen van de chirurgische behandeling van zowel ischaemische als non-ischaemische MI, en van dit proefschrift. RMA bestaat uit de implantatie van een (rigide of semi-rigide) restrictieve (of "undersized") ring, welke 2 maten kleiner is dan de gemeten klepmaat. Het doel van deze techniek is om de coaptatie van de mitralisklepbladen te herstellen en zodoende de MI op te heffen. Ten slotte worden aanvullende chirurgische behandelopties, zoals implantatie van een zogenaamde cardiac support device of linker ventrikel reconstructie (LVR), beschreven.

Hoofdstuk 2 biedt een overzicht van de chirurgische en interventionele behandelopties die de afgelopen decennia ontwikkeld zijn voor patiënten met functionele MI. Reparatie van de mitralisklep door middel van RMA vormt de hoeksteen van de chirurgische behandeling van functionele MI. Aanvullende (sub)valvulaire procedures en vervanging van de mitralisklep zijn geïntroduceerd om het risico op recidief MI te verminderen en kunnen overwogen worden voor patiënten met een verhoogd risico op recidief MI na RMA alleen. Percutane interventies (MitraClip-implantatie), kunnen worden overwogen voor patiënten die niet in aanmerking komen voor mitralisklepchirurgie en voldoen aan specifieke criteria. Ten slotte kan implantatie van een LV assist device (LVAD, ook wel steunhart genoemd) overwogen worden voor patiënten met functionele MI en ernstige LV-dysfunctie, die hoogstwaarschijnlijk geen baat zullen hebben bij een mitralisklepinterventie. Per behandeloptie worden de rationale, de indicatie, de chirurgische techniek, de resultaten en de beperkingen besproken door experts op dat gebied.

Hoofdstuk 3 bevat een commentaar op de tweejaarsresultaten van de Cardio-Thoracic Surgery Network (CTSN) trial. Deze randomized controlled vergeleek reparatie versus vervanging van de mitralisklep voor patiënten met ernstige ischaemische MI, en toonde geen verschil tussen beide groepen met betrekking tot LV reverse remodelling (het primaire eindpunt) of overleving, ondanks een significant hoger percentage patiënten met recidief MI na een reparatie. Deze bevindingen kunnen leiden tot de conclusie dat een vervanging van de mitralisklep beter is dan een reparatie. Binnen 30 dagen na chirugie werd echter al bij 30% van de patiënten recidief MI geobserveerd, dit dient derhalve gezien te worden als residuele MI als gevolg van inadequate chirugische techniek en niet als recidief MI. Bij patiënten na een succesvolle reparatie van de mitralisklep (dat wil zeggen, zonder recidief MI), werd 30%

reductie van het LV eind-systolisch volume geobserveerd, terwijl reverse remodelling niet werd geobserveerd na een mitralisklepvervanging. Deze punten dienen in overweging genomen te worden wanneer de resultaten van de CTSN trial worden vertaald naar conclusies voor in de klinische praktijk.

De resultaten van de CTSN trial omschreven in Hoofdstuk 3 (dat wil zeggen, geen verschil in LV reverse remodelling of overleving tussen patiënten na een reparatie en vervanging van de mitralisklep, ondanks 59% recidief MI 2 jaar na een mitralisklepreparatie versus 4% na een vervanging), leidde tot de vraag: maakt het, in termen van klinische uitkomsten, überhaupt uit of patiënten recidief MI ontwikkelen?

Hoofdstuk 4 evalueert de lange-termijn klinische en echocardiografische uitkomsten van 261 patiënten welke een RMA en revascularisatie ondergingen voor de behandeling van matig tot ernstige functionele MI, waarbij werd gefocust op de voor mortaliteit gecorrigeerde incidentie, klinische impact en determinanten van recidief MI. De cumulatieve incidentie van recidief MI ≥ graad 2, geanalyseerd door middel van een competing risk analyse, was laag met 9.6 ± 1.8% na 1 jaar, 20.3 ± 2.5% na 5 jaar, en 27.6 ± 2.9% na 10 jaar follow-up. De cumulatieve overleving was gunstig met 86% [81 – 90] na 1 jaar, 67% [61 – 73] na 5 jaar en 46% [39 – 53] na 10 jaar follow-up. Leeftijd, preoperatieve New York Heart Association (NYHA) klasse III of IV, een voorgeschiedenis van nierfalen, en recidief MI als tijdsafhankelijke variabele [HR 3.28 (1.87 – 5.75), p <0.001] waren onafhankelijk geassocieerd met een verhoogd risico op mortaliteit. Deze bevindingen tonen aan dat RMA met revascularisatie voor ischaemische MI resulteert in een lage incidentie van recidief MI en gunstige klinische uitkomsten tot 10 jaar na chirurgie. Echter, het ontwikkelen van recidief MI op enig moment na chirurgie is onafhankelijk geassocieerd met een verhoogd risico op mortaliteit. Vrouwelijk geslacht, een ST-elevatie myocardinfarct (STEMI) in de voorgeschiedenis en preoperatief een QRS duur van ≥120 ms, een hogere graad MI en een hoger geïndexeerd LV eind-systolisch volume, waren onafhankelijk geassocieerd met een verhoogd risico op recidief MI.

Bij non-ischaemische MI kan – in tegenstelling tot ischaemische MI – de onderliggende aandoening van de linker ventrikel niet worden behandeld. De behandelopties voor patiënten met MI ten gevolge van een non-ischaemische cardiomyopathie, die symptomatisch blijven ondanks optimale medicamenteuze therapie en CRT, zijn daardoor beperkt en bestaan uit reparatie van de mitralisklep, implantatie van een LVAD of harttransplantatie.

In hoofdstuk 5 worden de langetermijnuitkomsten beschreven van een studie naar 77 patiënten met non-ischaemische MI en symptomatisch hartfalen, die een geïntegreerde

behandeling van RMA met aanvullende procedures – reparatie van de tricuspidalisklep, implantatie van een cardiac support device en ritmechirurgie – ondergingen, zoals geïndiceerd door het HartTeam. LV reverse remodelling werd geobserveerd bij 38% van de patiënten en recidief MI bij 20% van de patiënten bij tussentijdse follow-up. Het uitblijven van LV reverse remodelling en het optreden van recidief MI – welke sterk gecorreleerd bleken – waren significant geassocieerd met ongunstige late uitkomsten na chirurgie. Overleving vrij van harttransplantatie 1 en 3 jaar na de tussentijdse follow-up was gunstig voor patiënten met LV reverse remodelling (100% en 88 ± 6%), significant slechter maar acceptabel voor patiënten zonder LV reverse remodelling en zonder recidief MI (83 ± 7% en 68 ± 8%), en zeer slecht voor patiënten zonder LV reverse remodelling met recidief MI (49 ± 14% en 33 ± 13%). Geen van de baseline variabelen in deze studie was voorspellend voor het optreden van LV reverse remodelling en een voorgeschiedenis van ventriculaire tachyaritmieën was de enige onafhankelijke voorspeller voor het optreden van recidief MI. Deze bevindingen benadrukken het belang van nauwgezette echocardiografische monitoring na chirurgie, om de subgroep van patiënten bij wie LV reverse remodelling uitblijft en recidief MI ontstaat, tijdig te identificeren zodat aanvullende behandelopties opnieuw geëvalueerd kunnen worden en de prognose van deze patiënten kan worden verbeterd.

De langetermijneffecten van geavanceerde chirurgie voor patiënten met refractair hartfalen ten gevolge van een post-infarct anteroseptaal aneurysma werden geëvalueerd in Hoofdstuk 6. In dit hoofdstuk werden de uitkomsten beschreven van een studie naar 159 patiënten die een LVR ondergingen met aanvullende procedures – reparatie van de mitralisklep, reparatie van de tricuspidaalklep, revascularisatie van de coronairen en ritmechirurgie – indien geïndiceerd. Tussentijdse echocardiografische follow-up toonde een afname in geïndexeerd eind-systolisch volume (89 ± 42 ml/m^2 preoperatief naar 51 ± 18 mL/m^2 bij tussentijdse follow-up, p <0.001) en afwezigheid van MI ≥ graad 2 in alle patiënten. Event-vrije overleving was 83 ± 3% na 1 jaar, 68 ± 4% na 5 jaar en 46 ± 4% na 10 jaar follow-up. Preoperatieve 'wall motion score index' (WMSI, een maat voor de systolische LV functie), aanwezigheid van MI ≥ graad 2, leeftijd en een langer tijdsinterval na het optreden van een myocardinfarct, bleken onafhankelijk geassocieerd met ongunstige event-vrije overleving. Event-vrije overleving was gunstig voor patiënten met een WMSI <2.5 en significant slechter voor patiënten met een WMSI ≥2.5. In beide groepen verslechterde de event-vrije overleving bij aanwezigheid van preoperatieve MI ≥ graad 2, ondanks succesvolle chirurgische correctie van de MI. Deze resultaten tonen aan dat preoperatieve risicostratificatie op basis van WMSI en MI het HartTeam kan ondersteunen in zijn besluit over de optimale chirurgische behandelstrategie voor deze patiënten.

Het implanteren van een restrictieve mitralisklep annuloplastiek ring heeft geleid tot zorgen, omdat reductie van de annulus dimensie zou kunnen resulteren in obstructie van de antegrade bloedstroom over de mitralisklep en zodoende kan leiden tot een functionele mitralisklepstenose. Een dergelijke stenose zou kunnen optreden in rust, maar zal nog uitgesprokener worden tijdens inspanning.

Hoofdstuk 7 beschrijft een evaluatie van de haemodynamica van de mitralisklep tijdens inspanning, in een studiepopulatie van 32 patiënten die een RMA ondergingen voor functionele MI. Het mitralisklepoppervlak, de mitral valve area (MVA), bleek dynamisch tijdens inspanning en verschilde tussen individuele patiënten: de MVA nam toe bij 25 patiënten en nam af bij 7 patiënten. De verandering van de MVA tijdens inspanning bleek gerelateerd aan de veranderingen van de geometrie en de functie van de linker ventrikel na chirurgie. In de groep patiënten met een toename van het mitralisklepoppervlak tijdens inspanning was sprake van LV reverse remodelling na chirurgie en een significante contractiele reserve van het myocard tijdens inspanning, terwijl de groep patiënten met een afname van de MVA tijdens inspanning gekarakteriseerd werd door het uitblijven van LV reverse remodelling na chirurgie en beperkte contractiele reserve van het myocard. Een afname van de MVA tijdens inspanning was tevens sterk geassocieerd met een hogere toename in gemiddelde pulmonale arteriële druk ten opzichte van de toename in cardiac output tijdens inspanning – hetgeen suggereert dat een afname van de MVA tijdens inspanning significante haemodynamische consequenties heeft. Tevens was een afname van de MVA tijdens inspanning geassocieerd met een ongunstige (event-vrije) overleving, vergeleken met patiënten met een toename van de MVA tijdens inspanning.

Iedere hartoperatie heeft peri-operatieve risico's, welke in beschouwing moeten worden genomen wanneer een chirurgische interventie overwogen wordt. Vasoplegie – gedefinieerd als een staat van lage systemische vaatweerstand ondanks normale of hoge cardiac output, en de noodzaak voor vasopressieve therapie, veroorzaakt door een onbalans van vasodilatatieve en vasopressieve mechanismen – is een belangrijke determinant voor ongunstige postoperatieve uitkomsten bij patiënten die een hartopeartie ondergaan.

In hoofdstuk 8 worden de incidentie, de klinische impact en preoperatieve voorspellers van vasoplegia na RMA onderzocht. Vasoplegie werd geobserveerd in 19% van de patiënten na RMA en deze incidentie was onafhankelijk van de etiologie van MI. Patiënten die vasoplegie ontwikkelden, hadden een significant langere opnameduur op de intensive care na chirurgie en een significant hogere 30- en 90-dagen-mortaliteit. Diverse preoperatieve patiëntkarakteristieken, welke met name geassocieerd lijken met de ernst van hartfalen (geen

bètablokkergebruik, geen hypertensie, een lagere creatinineklaring en anemie), en een langere cardiopulmonale bypass tijd, bleken gerelateerd aan het optreden van vasoplegie. Deze bevindingen tonen aan dat het risico op het ontwikkelen van vasoplegie na chirurgie door het HartTeam in overweging genomen moet worden wanneer het besluit om een patiënt wel of niet te opereren. Tevens zou preoperatieve optimalisatie van de haemodynamica en nierfunctie het risico op vasoplegie mogelijk kunnen reduceren.

Discussie

De afgelopen decennia zijn enorme stappen gezet in de behandeling van patiënten met functionele MI en zijn diverse chirurgische en interventionele behandelopties ontwikkeld. Ondanks deze ontwikkelingen blijft de optimale behandelstrategie voor patiënten met functionele MI een onderwerp van debat, aangezien het aantal randomized controlled trials op dit gebied beperkt is en hun resultaten tegenstrijdig zijn. Deze conflicterende uitkomsten kunnen worden verklaard door het feit dat functionele MI een heterogeen ziektebeeld is, waarin een “one-size-fits-all” benadering niet volstaat. Een gepersonaliseerde behandeling is cruciaal om de uitkomsten van patiënten met functionele MI te verbeteren.

Reparatie van de mitralisklep door middel van RMA vormt de hoeksteen in de chirurgische behandeling van functionele MI. De studies beschreven in dit proefschrift onderzochten de (langetermijn) klinische en echocardiografische uitkomsten na restrictieve mitralisklep annuloplastiek – met aanvullende procedures indien geïndiceerd. Het doel van dit promotieonderzoek was om patiënten te identificeren die wel of geen baat hebben bij deze benadering, om zodoende de behandelstrategie te kunnen personaliseren en de uitkomsten voor iedere patiënt met functionele MI te optimaliseren.

Om dit doel te bereiken, hebben we ons in dit proefschrift gericht op:

1) Het ontrafelen van de mechanismen die bijdragen aan de uitkomsten na RMA-chirurgie;
2) Het identificeren van preoperatieve voorspellers voor de uitkomsten na RMA-chirurgie.

Mechanismen die bijdragen aan de uitkomsten na restrictieve mitralisklep annuloplastiek

De vroege uitkomsten na RMA-chirurgie zijn gunstig gebleken. In randomized controlled trials bleek reparatie van de mitralisklep in combinatie met revascularisatie van de coronairen middels CABG bij patiënten met ischaemische MI het risico op perioperatieve complicaties niet te verhogen ten opzichte van CABG alleen.[1, 2] Ongunstige vroege uitkomsten na RMA-chirurgie worden mogelijk beïnvloed door het optreden van postoperatieve vasoplegie.

Langetermijnuitkomsten na RMA zijn mogelijk geassocieerd met het uitblijven van herstel van de competentie van de mitralisklep en/of het uitblijven van duurzame LV reverse remodelling – de twee belangrijkste doelstellingen van de behandeling van patiënten met functionele MI. Daarnaast reduceert implantatie van een restrictieve ring de annulus dimensie van de mitralisklep, wat kan leiden tot de introductie van een (functionele) mitralisklepstenose na RMA, welke de langetermijnuitkomsten ook zou kunnen beïnvloeden.

In dit promotieonderzoek werd de invloed van ieder van deze mechanismen op de klinische uitkomsten na RMA-chirurgie onderzocht.

Vasoplegie

Postoperatieve vasoplegie is geassocieerd met ongunstige vroege uitkomsten na hartchirurgie, in het bijzonder voor patiënten met hartfalen en patiënten die een hartklepoperatie ondergaan.[3-5] Ongunstige vroege uitkomsten na RMA-chirurgie zouden daarom ook deels gerelateerd kunnen zijn aanhet optreden van vasoplegie.

In dit proefschrift was de incidentie van vasoplegia na RMA-chirurgie 19%. Patiënten die vasoplegia ontwikkelden na chirurgie hadden een significant langere opnameduur op de intensive care en een hogere 30-dagen mortaliteit (22% voor patiënten met vasoplegie versus 2% voor patiënten zonder vasoplegie, $p < 0.001$).

Deze bevindingen laten zien dat vasoplegia een belangrijke determinant is van ongunstige vroege uitkomsten na RMA-chirurgie. Het HartTeam zou daarom het risico op postoperatieve vasoplegie in ogenschouw moeten nemen, wanneer het besluit om een patiënt wel of niet te verwijzen voor chirurgie. Potentieel modificeerbare risicofactoren (zoals beschreven) zouden moeten worden aangepast, alhoewel de algemene preventieve en therapeutische behandelopties voor vasoplegie (behalve symptomatische behandeling) beperkt zijn. Deze resultaten benadrukken het belang voor de ontwikkeling van dergelijke behandelopties om de vroege uitkomsten na RMA-chirurgie te verbeteren.

Recidief mitralisinsufficiëntie en linker ventrikel (reverse) remodelling

Herstel van de competentie van de mitralisklep leidt tot het opheffen van de volumeoverbelasting waarmee MI gepaard gaat en kan de vicieuze cirkel van progressieve LV remodelling en verslechterende MI doorbreken. Recidief MI na RMA leidt direct terug naar deze vicieuze cirkel en wordt daarom beschouwd als een belangrijke determinant van ongunstige klinische uitkomsten.

De studies beschreven in dit proefschrift, demonstreren dat RMA door middel van een gestructureerde chirurgische benadering resulteert in een lage incidentie van recidief MI voor zowel patiënten met ischaemische MI (Hoofdstuk 4 en Hoofdstuk 6) als non-ischaemische MI (Hoofdstuk 5). De in dit proefschrift geobserveerde incidentie van recidief MI was veel lager dan de incidentie in veel andere studies.[6-9] Echter bleek het optreden van recidief non-ischaemische MI, 18 maanden na RMA, onafhankelijk geassocieerd met het uitblijven van LV reverse remodelling (Hoofdstuk 5) terwijl het optreden van recidief ischaemische MI op enig moment na chirurgie gerelateerd bleek aan ongunstige langetermijn klinische uitkomsten, waaronder een verhoogd risico op reoperaties, ziekenhuisopnames voor hartfalen en sterfte (Hoofdstuk 4).

Deze studies benadrukken de noodzaak voor duurzame correctie van MI en demonstreren dat RMA kan resulteren in zo'n duurzame correctie bij de meerderheid van patiënten, mits uitgevoerd door middel van een gestructureerde chirurgische benadering. Deze benadering bestaat uit de implantatie van een semi-rigide annuloplastiek ring, 'undersizing' met 2 ringmaten en is gericht op het opheffen van de MI en het bereiken van een coaptatielengte van tenminste 8 mm op de intra-operatieve echocardiografie. Recidief MI werd bij ontslag slechts geobserveerd bij 3-4% van de patiënten in dit proefschrift (Hoofdstuk 4 en Hoofdstuk 5), terwijl in de literatuur aanzienlijke incidenties van MI vroeg na chirurgie werden gerapporteerd (bijvoorbeeld 30% binnen 30 dagen na chirurgie in de CTSN trial, waar het gemiddelde aantal reparaties per centrum 5.2 was).[8, 9] MI in de vroege fase na chirurgie kan niet verklaard worden door progressie van de ziekte (LV dilatatie met toegenomen 'tethering' van de mitralisklepbladen) en moet worden beschouwd als residuele MI door suboptimale reparatie van de mitralisklep en niet als echte recidief MI. RMA-chirurgie zou derhalve alleen uitgevoerd moeten worden in gespecialiseerde centra met expertise in hartklepaandoeningen en hartfalen.

Linker ventrikel remodelling is de primaire oorzaak van functionele MI. De initiatie van duurzame LV reverse remodelling is daarom een belangrijk element in de behandeling van functionele MI.

In dit promotieonderzoek werd de klinische impact van LV reverse remodelling na RMA-chirurgie onderzocht (Hoofdstuk 5). Patiënten met LV reverse remodelling (gedefinieerd als ≥15% afname in geïndexeerd LV eind-systolisch volume) bleken gunstige klinische uitkomsten te hebben, met een laag risico op ziekenhuisopnames voor hartfalen en gunstige langetermijnoverleving vrij van harttransplantatie. Patiënten zonder LV reverse remodelling hadden echter een verhoogd risico op recidief MI en ziekenhuis opnames voor hartfalen, en een slechte overleving vrij van harttransplantatie.

Deze bevindingen bevestigen dat de linker ventrikel een cruciale rol speelt, niet alleen in de ontwikkeling maar ook in de behandeling van functionele MI, en benadrukken dat LV reverse remodelling van groot belang is voor het bereiken van gunstige klinische uitkomsten na chirurgie.

De studies beschreven in dit proefschrift tonen duidelijk aan dat het uitblijven van LV reverse remodelling en recidief MI beide belangrijke mechanismen zijn die leiden tot ongunstige klinische uitkomsten na RMA-chirurgie. In lijn met de literatuur[10] bleken recidief MI en het uitblijven van LV reverse remodelling sterk geassocieerd (Hoofdstuk 5). De gelijktijdige observatie van recidief MI en het uitblijven van LV reverse remodelling zegt echter niets over het causale verband, aangezien beide op een complexe manier met elkaar verweven zijn. Residuele of recidief MI kan leiden tot het uitblijven van LV reverse remodelling, terwijl het uitblijven van LV reverse remodelling kan leiden tot recidief MI, waarbij beide scenario's leiden tot ongunstige klinische uitkomsten. Het is belangrijk om te beseffen dat de patiënten die MI ontwikkelden na chirurgie in dit proefschrift, echte recidief MI hadden (ontwikkeld gedurende de follow-up periode) en geen residuele MI als gevolg van suboptimale correctie van de MI tijdens de chirurgie. Het is daarom het meest waarschijnlijk dat recidief MI in dit geval primair werd veroorzaakt door progressie van de ziekte van de linker ventrikel, waarbij aanhoudende LV remodelling leidt tot verdere dislocatie van de papillairspieren en progressieve tethering van de mitralisklepbladen. Wanneer recidief MI is opgetreden, vormt de volumeoverbelasting voor extra belasting van de reeds kwetsbare LV, waardoor het remodelling proces verergert en de klinische uitkomsten verder verslechteren.

De hypothese dat de mate van LV-dysfunctioneren (in andere woorden, het onvermogen tot het ontwikkelen van LV reverse remodelling) en niet het optreden van recidief MI de belangrijkste determinant van ongunstige klinische uitkomsten na RMA-chirurgie is, wordt ondersteund door de uitkomsten van de CTSN trial. In deze trial werd geen verschil in het optreden van LV reverse remodelling of overlevingskans gevonden tussen patiënten die een reparatie versus dan wel een vervanging van de mitralisklep ondergingen, ondanks een significant hogere incidentie van recidief MI na een reparatie.[8, 9] Deze resultaten impliceren dat het volledig opheffen van functionele MI – verkregen door middel van vervanging van de mitralisklep – niet altijd leidt tot LV reverse remodelling. Dit kan verklaard worden doordat een subgroep van patiënten mogelijk al in een stadium van LV ziekte verkeert, waarin het simpelweg oplossen van de volumeoverbelasting waarmee MI gepaard gaat onvoldoende is om het proces van LV remodelling tot een halt te brengen of om te keren op het moment van chirurgie. Het feit dat de patiënten na een vervanging van de mitralisklep in deze trial niet meer LV reverse remodelling toonden dan patiënten na een reparatie, waarbij in 60% van de gevallen

recidief MI was opgetreden, leidt ook tot de vraag of een klepvervanging zelf mogelijk een negatieve impact heeft op LV reverse remodelling.

Functionele mitralisklepstenose

Restrictieve mitralisklep annuloplastiek herstelt de coaptatie van de mitralisklepbladen door de dimensie van de mitralisannulus te reduceren. Reductie van de annulus zou echter ook kunnen leiden tot obstructie van de antegrade bloedstroom over de mitralisklep en zou zodoende kunnen resulteren in een functionele mitralisklepstenose, met potentieel klinische consequenties.[11] Een dergelijke functionele stenose zou nog uitgesprokener zijn tijdens inspanning.

Zoals beschreven in dit proefschrift (Hoofdstuk 7), bleek de MVA na RMA dynamisch tijdens inspanning: de MVA nam toe in de meerderheid van de patiënten maar nam af in een subgroep van patiënten. Een afname van de MVA tijdens inspanning was geassocieerd met LV geometrie (het uitblijven van LV reverse remodelling) en functie (beperkte contractiele reserve van het myocard) na chirurgie. Een afname van de MVA tijdens inspanning was tevens sterk gerelateerd aan een hogere toename in de gemiddelde pulmonale arteriële druk ten opzichte van de toename in cardiac output tijdens inspanning, en aan significant slechtere event-vrije overleving.

Het feit dat de MVA dynamisch is tijdens inspanning – ondanks implantatie van een semi-rigide annuloplastiekring met een gefixeerd oppervlak – suggereert dat de MVA wordt bepaald ter hoogte van de uiteinden van de mitralisklepbladen en dit weerspreekt dat een functionele mitralisklepstenose simpelweg wordt veroorzaakt door de implantatie van een undersized ring. Eerdere studies toonden inderdaad aan dat de MVA tijdens inspanning na RMA-chirurgie is geassocieerd met de mate van tethering van het anterieure klepblad tijdens diastole, waarbij toegenomen tethering leidt tot een afname van de MVA en vice versa.[12, 13] De associatie tussen een afname van de MVA met ongunstige LV-geometrie en functie, impliceert tevens dat progressieve tethering van de mitralisklepbladen door voortschrijdende LV remodelling niet alleen kan leiden tot incomplete sluiting van de mitralisklep tijdens systole (ofwel recidief MI) maar ook tot incomplete opening van de mitralisklep tijdens diastole (ofwel een functionele mitralisklepstenose). Deze bevindingen benadrukken nogmaals het belang van LV reverse remodelling voor het optreden van gunstige uitkomsten na RMA-chirurgie. De rol van een functionele mitralisklepstenose na RMA-chirurgie, onafhankelijk van LV-geometrie en -functie, zou verder onderzocht moeten worden in grotere studies om definitieve conclusies te kunnen trekken met betrekking tot de klinische impact.

Preoperatieve voorspellers voor uitkomsten na restrictieve mitralisklep annuloplastiek

Idealiter worden patiënten die wel of geen baat hebben bij RMA-chirurgie, preoperatief geselecteerd. Gezien de klinische impact van vasoplegie, recidief MI en het uitblijven van LV reverse remodelling, was het doel van dit proefschrift om voor ieder van deze factoren en voor mortaliteit preoperatieve voorspellers te identificeren (Hoofdstukken 4, 5, 6 en 8).

Diverse preoperatieve voorspellers (geen hypertensie in de voorgeschiedenis, een lagere creatinine klaring, geen bètablokkergebruik en anemie), en een langere cardiopulmonale bypass tijd, bleken geassocieerd met een verhoogd risico op vasoplegie (Hoofdstuk 8). Deze voorspellers lijken voornamelijk indicatoren te zijn van patiënten met een fragiele balans van hun vasculaire systeem, die niet kunnen compenseren voor de haemodynamische schommelingen veroorzaakt door de systemische inflammatoire respons als gevolg van de cardiopulmonale bypass en het chirurgisch trauma. In dit proefschrift is een eerste stap gezet in het identificeren van patiënten met een verhoogd risico op vasoplegie. Meer studies zijn echter nodig om de pathofysiologische mechanismen van vasoplegie te ontrafelen en patiënten met een verhoogd risico op vasoplegie beter te kunnen identificeren.

Vrouwelijk geslacht, een STEMI in de voorgeschiedenis en preoperatief een QRS duur van ≥ 120 ms, een hogere graad MI en een hoger geïndexeerd LV eind-systolisch volume waren onafhankelijke voorspellers voor het optreden van recidief ischaemische MI na RMA-chirurgie (Hoofdstuk 4). Een voorgeschiedenis van ventriculaire tachyaritmieën was de enige voorspeller voor recidief MI na RMA-chirurgie voor patiënten met non-ischaemische MI. Voor het optreden van LV reverse remodelling konden geen preoperatieve voorspellers geïdentificeerd worden (Hoofdstuk 5). Voorspellers voor slechte overleving na RMA voor ischaemische MI waren leeftijd, preoperatieve NYHA klasse III of IV, nierfalen en recidief MI tijdens follow-up (Hoofdstuk 4). Een preoperatieve WMSI ≥2.5, preoperatieve MI ≥ graad 2 en een langer tijdsinterval na een myocardinfarct waren voorspellers voor ongunstige event-vrije overleving na LVR – en gelijktijdige RMA indien geïndiceerd – voor patiënten met hartfalen als gevolg van een anteroseptaal LV aneurysma (Hoofdstuk 6).

In overeenstemming met de literatuur waren de meeste voorspellers voor recidief MI en ongunstige klinische uitkomsten, die zijn gevonden in dit promotieonderzoek, gerelateerd aan de ernst van de MI, de mate van LV remodelling (LV-afmeting, -geometrie en -functie) of de ernst van de symptomen van het hartfalen. Deze parameters verschaffen informatie en ondersteunen het HartTeam in het besluitvormingsproces. Echter, het voorspellen van het

potentieel tot LV reverse remodelling – cruciaal voor het herstel na RMA-chirurgie – blijft een grotendeels onontdekt gebied. Dat blijkt ook uit het feit dat in dit proefschrift geen preoperatieve voorspellers voor LV reverse remodelling geïdentificeerd konden worden. Totdat we dergelijke preoperatieve voorspellers hebben geïdentificeerd, kan nauwlettende echocardiografische monitoring na chirurgie – gefocust op het uitblijven van LV reverse remodelling en recidief MI – resulteren in de vroege identificatie van patiënten met een verhoogd risico voor ongunstige klinische uitkomsten. Voor deze patiënten zouden aanvullende behandelopties (zoals een LVAD of harttransplantatie) periodiek opnieuw geëvalueerd moeten worden door het HartTeam.

Klinische implicaties en toekomstperspectieven

De studies beschreven in dit proefschrift hebben aangetoond dat een gepersonaliseerde medicamenteus-chirurgische benadering voor patiënten met functionele MI – bestaande uit optimale medicamenteuze (en resynchronsiatie) therapie, RMA en aanvullende chirurgische procedures wanneer geïndiceerd, resulteert in gunstige langetermijn klinische en echocardiografische uitkomsten voor de meerderheid van de patiënten. De subgroep van patiënten voor wie deze benadering geen definitieve oplossing vormt, bleek gekarakteriseerd door het optreden van perioperatieve vasoplegie (wat het risico op ongunstige vroege uitkomsten na chirurgie verhoogt) en de ontwikkeling van recidief MI en/of het uitblijven van LV reverse remodelling (beide leiden tot ongunstige langetermijnuitkomsten na chirurgie). Diverse preoperatieve voorspellers voor patiënten met een verhoogd risico op vasoplegie, recidief MI en ongunstige klinische uitkomsten na RMA-chirurgie zijn geïdentificeerd in dit proefschrift. Deze bevindingen moeten worden vertaald naar de klinische praktijk en opgenomen worden in het besluitvormings proces van het HartTeam, om de uitkomsten van patiënten met functionele MI te verbeteren.

De in het algemeen gunstige langetermijn klinische en echocardiografische uitkomsten die zijn geobserveerd in dit onderzoek, benadrukken dat de zorg voor patiënten met persisterende functionele MI ondanks optimale medicamenteuze behandeling en CRT geconcentreerd zou moeten worden in gespecialiseerde centra met expertise in hartklepziekten en hartfalen. In deze centra moet een toegewijd HartTeam de behandelstrategie voor iedere patiënt zorgvuldig afwegen, rekening houdend met het risico op vasoplegie, recidief MI en het uitblijven van LV reverse remodelling. De preoperatieve risicofactoren geïdentificeerd in dit promotieonderzoek en in eerdere studies kunnen het HartTeam ondersteunen bij dit besluitvormingsproces. RMA, uitgevoerd door middel van een gestructureerde chirurgische benadering, zou de hoeksteen moeten vormen van de chirurgische behandeling van patiënten met functionele MI. Voor

patiënten met een verhoogd risico op recidief MI, kunnen aanvullende subvalvulaire procedures of vervanging van de mitralisklep overwogen worden. Daarbij moet in het achterhoofd gehouden worden dat deze procedures niet altijd zullen leiden tot het optreden van LV reverse remodelling. Voor patiënten die geaccepteerd zijn voor mitralisklepchirurgie, moet de indicatie voor concomitante chirurgische procedures – coronair revascularisatie, reparatie van de tricuspidalisklep, linker ventrikel reconstructie en ritmechirurgie – per geval worden afgewogen. Voor patiënten die geen mitralisklepchirurgie kunnen ondergaan als gevolg van co-morbiditeit en waarbij de symptomen van hartfalen hoofdzakelijk gerelateerd zijn aan klepdysfunctie en niet aan LV-dysfunctie (dat wil zeggen ernstige MI maar geen ernstige LV-dilatatie), kan een percutane mitralisklepreparatie overwogen worden. De subgroep patiënten met functionele MI waarbij de LV-dysfunctie dermate vergevorderd is dat het optreden van LV reverse remodelling onwaarschijnlijk is – alhoewel deze patiënten, zoals eerder benoemd, lastig te identificeren zijn - heeft geen baat bij een mitralisklep procedure. Voor deze patiënten kan een harttransplantatie of LVAD implantatie overwogen worden.

De resultaten van dit promotieonderzoek dragen bij aan het verder personaliseren en optimaliseren van de behandeling voor patiënten met functionele MI. Er blijft echter nog een aantal grote uitdagingen over die geadresseerd moeten worden.

Ten eerste blijft het ingewikkeld om preoperatief te identificeren of een individuele patiënt met functionele MI wel of geen baat zal hebben bij een mitralisklepprocedure, en vervolgens om de geschikte procedure te selecteren voor ieder individu. Dit blijft lastig omdat functionele MI een zeer heterogeen ziektebeeld vormt, waarbij de mitralisklep en de linker ventrikel op een complexe manier met elkaar verweven zijn. Beeldvormende technieken ontwikkelen zich snel en zouden een rol kunnen spelen bij de identifciatie van nieuwe voorspellers voor uitkomsten na mitralisklepprocedures. 3D echocardiografie zou mogelijk meer geavanceerde informatie kunnen bieden omtrent de geometrie van de mitralisklep, de geometrie en de functie van de LV en de interrelatie tussen de mitralisklep en LV. Cardiale MRI gefocust op fibrose en littekenweefsel en stress-echocardiografie gefocust op viabiliteit van het myocard, zouden aanvullende informatie kunnen bieden omtrent de (mate van) onderliggende LV-ziekte en het verwachte potentieel voor LV reverse remodelling na chirurgie. In aanvulling op deze beeldvormende technieken zouden technologische ontwikkelingen ook een oplossing kunnen bieden. Zelflerende algoritmen (“machine learning algorithms”) bieden de mogelijkheid om enorme hoeveelheden informatie te combineren en multi-dimensionele correlaties van verschillende variabelen mee te nemen. Deze algorithmen zouden mogelijk de uitkomsten na RMA-chirurgie op een nauwkeuriger wijze wijze kunnen voorspellen dan de predictiemodellen ontwikkeld op basis van traditionele statistische methoden. Een recente studie toonde

inderdaad aan dat een risico score, ontwikkeld op basis van een zelflerend algorithme, het risico op mortaliteit voor patiënten met hartfalen accuraat – en accurater dan bestaande risicoscores – kan voorspellen.[14]

Ten tweede, richten de meeste behandelopties voor functionele MI zich momenteel op de mitralisklep en soms op de lokale LV-geometrie, terwijl het onderliggende probleem – de intrinsieke myocard aandoening – grotendeels ongemoeid blijft, met uitzondering van coronair revascularisatie bij patiënten met ischaemische MI. Aangezien de LV een cruciale rol lijkt te spelen in de uitkomsten na mitralisklepprocedures, zou de onderliggende LV-aandoening de focus moeten worden van toekomstige behandelstrategieën. Externe cardiale compressie devices zouden een rol kunnen spelen in het doorbreken van de vicieuze cirkel van LV remodelling en verslechterende MI, door zowel de MI als de LV-wandspanning te verminderen. Momenteel is een dergelijk device echter niet op de markt, en de effectiviteit van twee nieuwe devices – de BACE (Basal Annuloplasty of the Cardia Externally) en het VenTouch device – wordt momenteel nog onderzocht.[15] Uiteindelijk, zou de intrinsieke myocard-aandoening zelf behandeld moeten worden, voor zowel patiënten met ischaemische als non-ischaemische MI. De regeneratieve geneeskunde zou tot dergelijke behandelopties kunnen leiden door de normale functie van myocard-cellen te herstellen, maar op dit moment lijkt er nog een lange weg te gaan voordat zulke behandelingen in de dagelijkse praktijk toegepast kunnen worden.

Toekomstige studies zouden zich daarom moeten richten op het verbeteren van het preoperatief voorspellen welke patiënten wel of geen baat zullen hebben van een mitraaalklepprocedure en op de behandeling van de onderliggende myocard-aandoening, om de behandelstrategie daadwerkelijk te kunnen personaliseren en de uitkomsten voor alle patiënten met functionele MI te kunnen optimaliseren.

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Curriculum vitae

Annelieke Petrus was born on January 5th 1990 in The Hague. After graduating from the Gymnasium at Sint Maartenscollege in Voorburg in 2007, she started medical school at Leiden University. In 2008 she started working as an intensive care support assistant at the Intensive Care Unit of Leiden University Medical Centre (LUMC) in Leiden, and later on at the Intensive Care Unit of the Haga Hospital in The Hague. In 2011, she completed an Italian language course and studied for half a year at the medical faculty of the Università degli studi di Padova in Padova, Italy. During her Bachelor's she developed an interest in scientific research and started a research project on functional mitral regurgitation, under the supervision of Prof. Dr. Jerry Braun at the Department of Cardiothoracic surgery at Leiden University Medical Centre. This research instigated this thesis.

After graduating cum laude from medical school in 2014, she did an internship at KPMG where she worked on several healthcare projects. In March 2015, she enrolled in a PhD programme on functional mitral regurgitation, under the supervision of Prof. Dr. Robert Klautz, Prof. Dr. Jerry Braun and Dr. Laurens Tops. The results of this PhD programme are presented in the current thesis. During her PhD, she presented her research at various conferences and won first prize for her presentation at the Dutch Society of Cardiology conference and second prize for her presentation at the Dutch Heart Foundation course. She combined her PhD with the position of Chair of the LUMC Association for PhD candidates (LAP). In this function she represented the interests of PhD candidates of the LUMC, was a member of the Boerhaave continuing medical education committee and organized several events, including the 'LUMC PhD-day' and the 'LAP career event'. In 2018 she worked for a year as a medical resident at the Department of Obstetrics and Gynaecology of the Haga Hospital. Currently she is working as a senior researcher at the National e-Health Living Lab, where she focuses on eHealth interventions for maternity and birth care.

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