Personalised surgical treatment of functional mitral regurgitation

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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.

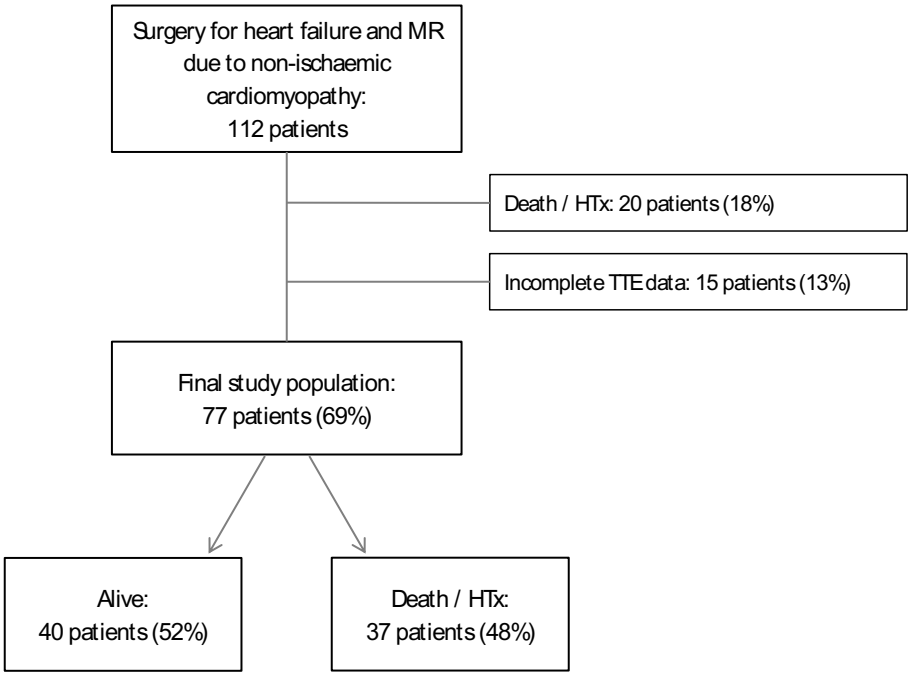

Figure 1. Flowchart of the study population.
HTx = heart transplantation, MR = mitral regurgitation, TTE = transthoracic echocardiography.

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].

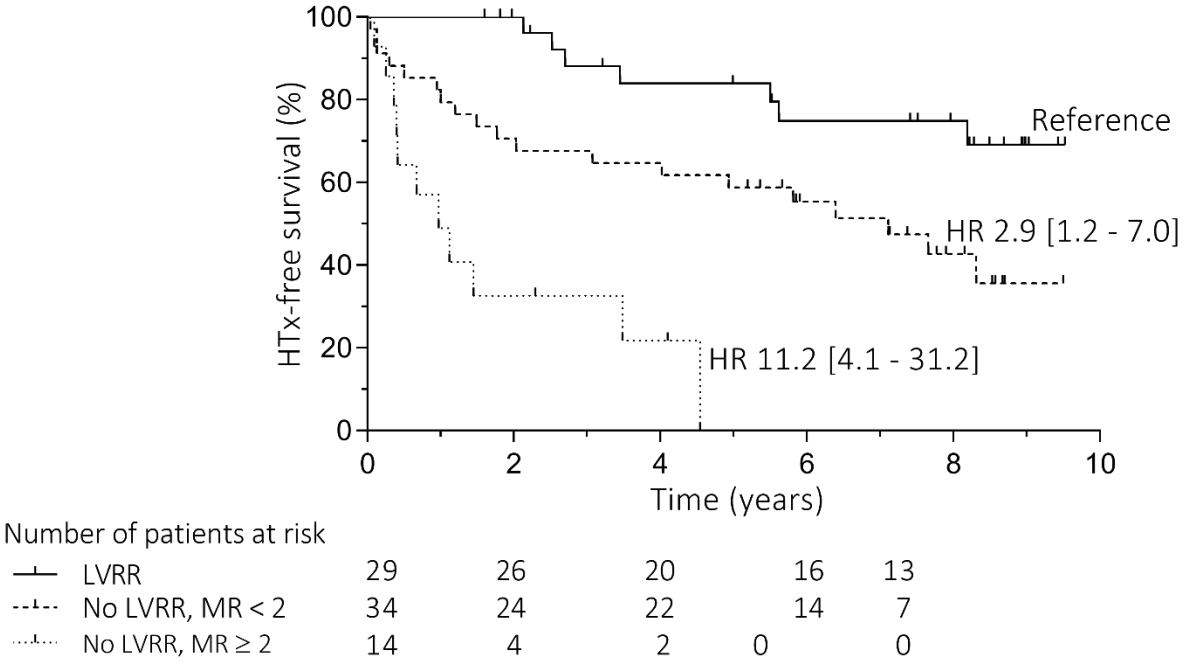

Figure 2. HTx-free survival from mid-term follow-up echocardiogram for 3 groups: 1) patients with LVRR, 2) patients without LVRR, without recurrent MR, and 3) patients without LVRR, with recurrent MR. HR = hazard ratio, HTx = heart transplantation, LVRR = left ventricular reverse remodelling, MR = mitral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