Personalised surgical treatment of functional mitral regurgitation

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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.

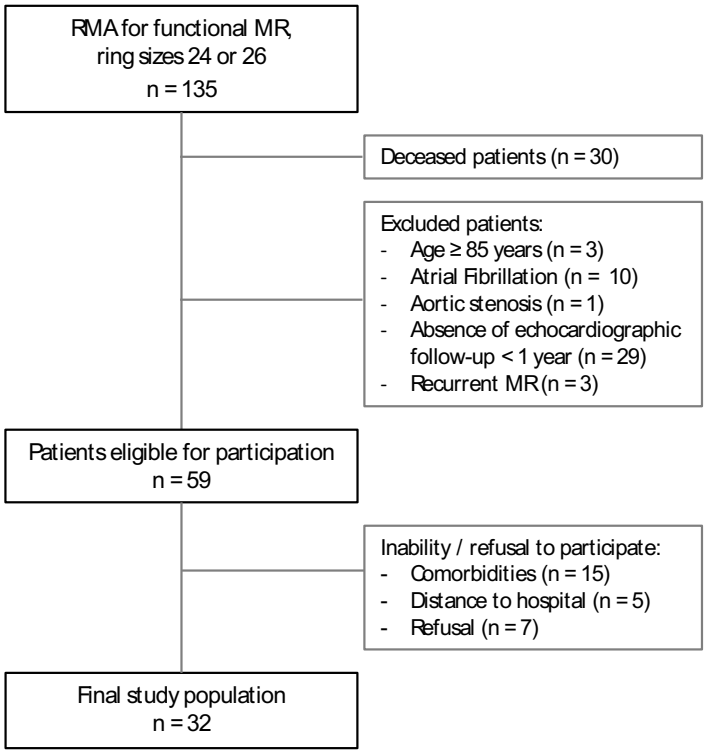

Figure 1. Study flowchart. MR = mitral regurgitation, RMA = restrictive mitral annuloplasty.

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.

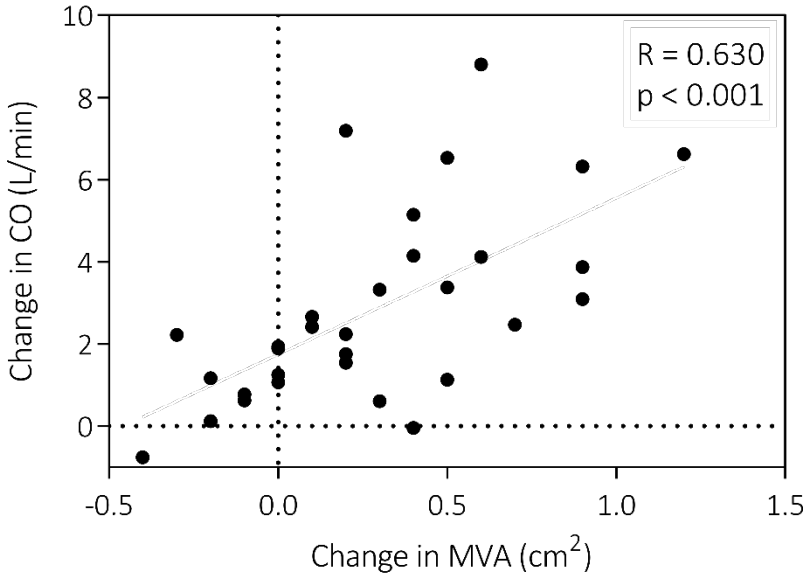

Figure 2. Association between change in mitral valve area (MVA) and change in cardiac output (CO) from rest to exercise.

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.

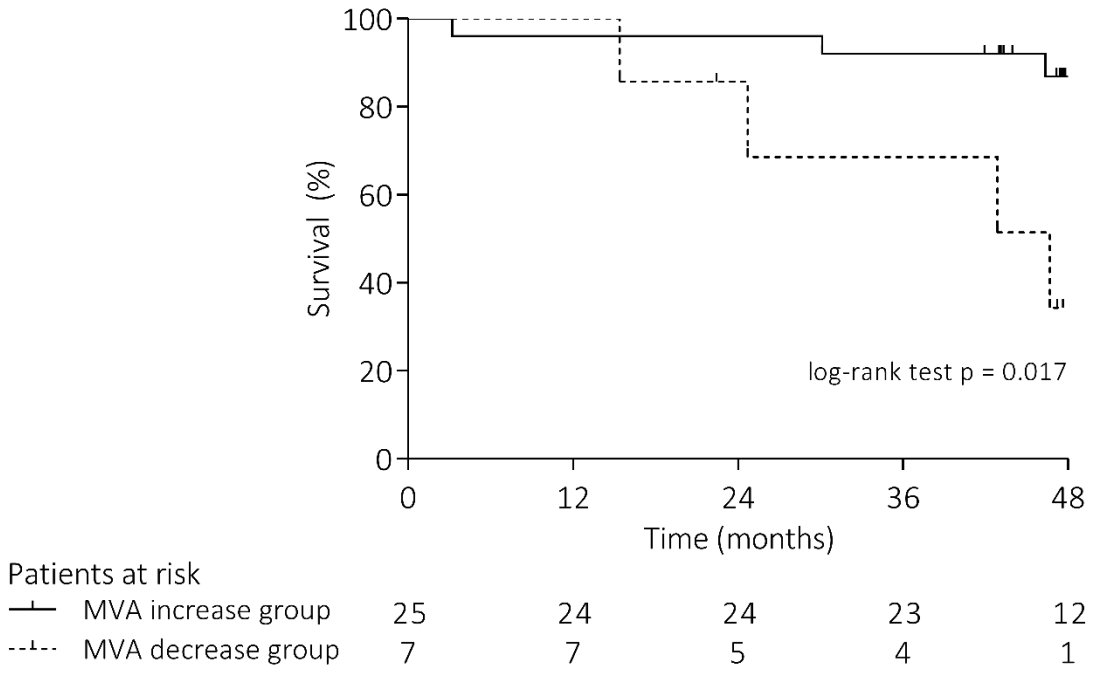

Figure 3. Kaplan-Meier time-to-event curves for freedom from all-cause mortality for patients with an increased mitral valve area (MVA) and decreased MVA during exercise.

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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