Non-pharmacological heart failure therapies : evaluation by ventricular pressure-volume loops

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CHAPTER 5

Acute-hemodynamic effects of restrictive mitral annuloplasty in patients with end-stage heart failure -Analysis by pressure-volume relations-

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ABSTRACT

Objective. Recent studies show beneficial long-term effects of restrictive mitral annuloplasty (RMA) in patients with end-stage heart failure (HF). However, concerns are raised about possible adverse effects on early post-operative systolic and diastolic function, which may limit application of this approach in HF patients. Therefore, we evaluated acute effects of RMA on left ventricular (LV) function by load-independent pressure-volume relations.

Methods. In 23 patients (HF n=10; control n=13) we determined LV systolic and diastolic function before and after surgery by pressure-volume analysis using the conductance catheter. All HF patients underwent stringent RMA (two sizes under), and 4 received additional CABG. Transesophageal echocardiography was used for evaluation of valve repair. Patients with preserved LV function who underwent isolated CABG served as controls.

Results. RMA (ring size 25±1) restored leaflet coaptation (8.0±0.2mm) with normal pressure gradients (2.9±1.8mmHg). RMA did not change cardiac output (5.0±1.8 to 5.3±0.9L/min, NS), LV ejection fraction (29±5 to 32±8%, NS) or end-systolic elastance (0.86±0.50 to 0.99±1.05mmHg/mL, NS). After RMA, end-diastolic volume tended to decrease (237±89 to 226±52mL, NS), while end-diastolic pressure remained unchanged (14±6 to 15±5mmHg, NS). Diastolic chamber stiffness tended to increase (0.027±0.035 to 0.041±0.047mL^{-1}, NS), however not significantly. Peak LV wall stress was unchanged (356±91 to 346±85 mmHg, NS). Baseline values in the control group were different, but changes in most parameters after surgery showed similar non-significant trends.

Conclusion. Mitral valve repair by RMA effectively restores mitral valve competence without inducing significant acute changes in LV systolic or diastolic function in patients with end-stage heart failure.

INTRODUCTION

Chronic mitral regurgitation is a serious complication in patients with end-stage heart failure. Patients with mitral regurgitation have a significantly decreased survival at 2 years follow-up versus patients without mitral regurgitation.[1]

The mechanism of mitral regurgitation in end-stage heart failure is multifactorial.

Briefly, it is related to changes in left ventricular (LV) geometry with a subsequent displacement of the subvalvular apparatus, annular dilatation[2] and restrictive leaflet motion (class IIIb according to Carpentier's classification[3]), which results in coaptation failure.[4,5] From a physiological point of view, mitral regurgitation in these patients will lead to LV overload and reduction of forward stroke volume. This occurs initially in response to exercise and subsequently at rest, which in turn activates systemic and local neurohormonal systems and cytokines that worsen cardiac loading conditions and promote LV remodeling and dysfunction.[6] This may create a vicious circle wherein regurgitation begets more regurgitation.

Previous studies have shown that interrupting this vicious cycle by mitral valve repair is safe, and improves clinical outcome.[7] Several groups advocate the use of a stringent restrictive ring, two sizes under, to achieve better leaflet coaptation and possibly prevent recurrence of mitral regurgitation and promote reverse remodeling.[8] Mid-term results (18 months follow-up) with this approach indicate reverse remodeling in 58% of patients.[9] However, the acute effects of restrictive mitral annuloplasty (RMA) on LV systolic and diastolic function in patients with end-stage heart failure are unknown. There are concerns that correction of mitral regurgitation may decrease LV systolic function in the acute phase due to afterload increase caused by closure of a low resistance runoff into the left atrium. In addition, it has been suggested that undersizing the mitral annulus may affect LV contractility due to increased mechanical tension on the base of heart.[10] With regard to diastolic function RMA might impair filling. In contrast, Bolling hypothesized that undersizing the mitral annulus will lead to acute beneficial geometric changes of the base of the left ventricle, which may reduce LV volume and wall stress.[11] The purpose of this study was therefore to quantify the acute effects of RMA on global and intrinsic LV systolic and diastolic function in these patients.

METHODS

A total of 23 patients were studied in the operating room before and after cardiopulmonary bypass (CPB) by pressure-volume analysis using the conductance catheter method. We included 10 patients with end-stage heart failure (HF) with co-existent severe mitral regurgitation who underwent mitral valve repair by stringent restrictive annuloplasty and 13 control patients with preserved LV function who

underwent elective CABG. The control group was used to distinguish effects of mitral annuloplasty from effects of CPB and cardioplegic cardiac arrest, per se. In both groups surgery was performed during normothermic CPB with intermittent antegrade warm blood cardioplegia. The study protocol was approved by the institutional review board and all patients provided informed written consent.

Patient selection and echocardiographic criteria

The patients in the RMA group fulfilled the following criteria:

1) NYHA class III or IV

2) LVEF < 30%

3) Mitral regurgitation grade ≥ 2 assessed by transesophageal echocardiography (TEE) preoperatively (without general anesthesia to avoid underestimation of the severity of the mitral regurgitation). The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler and characterized as: mild, 1+ (jet area/left atrial area <10%); moderate, 2+ (jet area/left atrial area 10% to 20%); moderately severe, 3+ (jet area/left atrial area 20% to 45%); and severe, 4+ (jet area/left atrial area >45%).[12] In patients with mitral regurgitation grade 2 an intra-operative dynamic loading test was performed as described by Dion et al.[5] If this test was positive, that is if it resulted in a definite worsening of the severity of mitral regurgitation, restrictive mitral annuloplasty was performed.

4) The mechanism of mitral regurgitation was based on malcoaptation due to systolic restrictive motion of the mitral leaflets.

5) Maximal medical therapy for heart failure including diuretics, afterload reduction and beta-blocking agents.

Patients with primary mitral valve dysfunction (mitral valve prolapse, rheumatic valve disease, mitral valve stenosis) were excluded from the study. Also patients with a previously implanted biological or mechanical prosthesis in aortic position were not included in this study.

The control group was recruited from patients with preserved LV function (LVEF > 40%) who underwent elective CABG for multivessel coronary artery disease and who needed no additional valvular surgery. The patient characteristics of both groups are summarized in Table 1.

Table 1. Patient characteristics

	RMA	Control
No. of patients	10	13
Male/ Female	5/5	11/2
Age (years)	56±18	63±8
NYHA	3.6±0.5	-
LVEF (%)	25±5	58±9
Mitral Regurgitation (grade)	3.3±0.5	-

Anesthesia

All patients received total intravenous anesthesia with target-controlled infusion of propofol, remifentanil and sufentanil. Hypnotic state was monitored with a Bispectral Index (BIS) monitor (Aspect medical systems, Newton, MA). A single dose of pancuronium bromide (0.1mg/kg) was given to facilitate intubation. During surgery the propofol concentration was adjusted between 1.5µg/ml and 2.0µg/ml to maintain a BIS value below 60. Remifentanil was titrated between 5 and 10ng/ml in response to the patient's hemodynamic reaction on surgical stimuli. Sufentanil was started at a targeted concentration of 0.1ng/ml after start of surgery to allow smooth transition of the patient analgesic state from the operating room to the ICU. The patients were ventilated with an oxygen/air mixture (FiO_2=40%) at a ventilatory rate of 12-15/min and ventilatory volume was adjusted to maintain normal $PaCO_2$. A thermal filament catheter was placed in the pulmonary artery via the right internal jugular vein for semi-continuous thermodilution cardiac output measurements (Edwards Lifesciences, Uden, The Netherlands). To facilitate positioning of the conductance catheter and to evaluate the effects of mitral valve repair a multiplane TEE probe was inserted. We anticipated that the heart failure patient would need inotropic support after surgery. Since this would bias our LV function measurements, we started inotropic support directly after induction of anesthesia with a low loading dose of 0.25mg/kg enoximone in ten minutes and thereafter we gave continuous infusion at a rate of 0.50µg/kg/min, which was maintained during the whole operation.

Surgical techniques

After median sternotomy and, if indicated, harvesting of bypass material, the pericardium was opened and normothermic cardiopulmonary bypass was instituted with intermittent antegrade warm blood cardioplegic arrest.[13] After completion of the

anastomosis, a stringent restrictive mitral annuloplasty was performed via a transseptal approach using a Carpentier Edwards Physio-ring (Edwards Lifesciences, USA).[14] The ring size was determined by measuring the size of the anterior mitral leaflet and a ring two sizes smaller than the measured size was implanted. After weaning from CPB, TEE evaluation was immediately performed in all patients to assess residual mitral regurgitation, transmitral diastolic pressure gradient (determined from continuous-wave Doppler) and the length of coaptation of the leaflets.

Study protocol

Before and directly after CPB, conductance catheter measurements were performed as described previously.[15] Briefly, temporary epicardial pacemaker wires were placed on the right atrium to enable pre-CPB and post-CPB measurements at fixed equal heart rates. A tourniquet was placed around the inferior vena cava to enable temporary preload reductions. An 8F sheath was placed in the ascending aorta for introduction of the conductance catheter. The conductance catheter was introduced under TEE guidance and placed along the long axis of the LV. Position was optimized by inspection of the segmental volume signals. Conductance catheter calibration was performed before and after CPB using calibration factors alpha (α) derived from thermodilution and parallel conductance correction volume (V_C) determined by the hypertonic saline method.[16] At each stage we performed at least two injections of 7 mL 10% saline into the pulmonary artery via the distal port of the thermodilution catheter. Continuous LV pressure and volume signals derived from the conductance catheter were displayed and acquired at a 250 Hz sampling rate using a Leycom CFL-512 (CD Leycom, Zoetermeer, The Netherlands). Data were acquired during steady state and during temporary caval vein occlusion, all with the ventilator turned off at end-expiration. Acquisition was performed at a fixed atrial pacing rate of 80 beats/min. From these signals hemodynamic indices were derived as described below.

Pressure-volume analysis

Global LV function: Parameters of global systolic and diastolic function (heart rate (HR), cardiac output (CO), stroke volume (SV), stroke work (SW), pressure-volume area (PVA), LV ejection fraction (LVEF), dP/dt_{MAX}, dP/dt_{MIN}, end-diastolic volume (EDV), end-systolic volume (ESV), end-diastolic pressure (EDP), end-systolic pressure (ESP), relaxation constant (Tau) were calculated from steady state beats using custom-made software. Mechanical dyssynchrony (DYSS) and internal flow fraction (IFF) was

calculated as previously described.[17] Effective arterial elastance (Ea), a measure of afterload, was calculated as ESP/SV. Time-varying wall stress, WS(t), was calculated from the LV pressure and volume signals (P(t), V(t)) as described by Arts et al.: $WS(t)= P(t)\cdot[1+3\cdot V(t)/V_{WALL}]$. LV wall volume ($V_{WALL}$) was estimated based on the diastolic posterior wall thickness derived from M-mode echocardiography.[18] The gradient across the LV outflow tract was calculated as the difference between peak LV pressure and peak aortic pressure.

Systolic and diastolic LV pressure-volume relations: Systolic function was characterized by the slope of the end-systolic pressure-volume relationship (End-systolic elastance, E_{ES}), the slope of the relation between the dP/dt_{MAX} and EDV (S-dP), and the slope of the preload recruitable stroke work relation (S-PRSW). The position of the ESPVR was quantified by calculating the ESV-intercept at a fixed end-systolic pressure (ESV_{IND}). The positions of the dP/dt_{MAX} - EDV relation and the PRSW relation were determined by calculating the intercepts at a fixed end-diastolic volume, $dP/dt_{MAX, IND}$ and SW_{IND}, respectively. As previously described, the fixed end-systolic pressure and end-diastolic volume levels were set retrospectively as the mean ESP and EDV in each group.[17] Diastolic chamber stiffness (K_{ed}) was quantified by exponential regression of the end-diastolic pressure-volume relationship.[19,20]

Statistical analysis

Pre- and post-CPB data were compared with paired t-tests. Statistical significance was assumed at $p<0.05$. All data are presented as the mean±SD.

RESULTS

All HF patients were successfully weaned from CPB after successful mitral valve repair. In six patients the origin of HF was ischemic, in four non-ischemic. In four ischemic patients additional CABG was performed; the other 2 patients had irreversible ischemia and did not receive CABG. In three patients with severe tricuspid regurgitation, a concomitant restrictive tricuspid ring annuloplasty (ring size 26) was performed. Six (60%) patients needed inotropic support more than 24 hours postoperatively. However, none of the patients required intra-aortic balloon pump support. The median stay in the intensive care unit in this group was 4 days (range 2 to

7 days) with a median total hospital stay of 14 days (range 7 to 18 days). All patients could be discharged in good clinical condition from the hospital. The surgical details of both groups are summarized in Table 2.

Table 2. Surgical data

	RMA (n=10)	Control (n=13)
CPB- time (median, minutes)	137 (range 105-287)	104 (range 60-167)
Aox-time (median, minutes)	96 (range 65-196)	75 (range 43-129)
Pre-MR	3.3±0.5	-
- AM-size (mm)	4.1±0.4	-
- AML-size (mm)	2.9±0.3	-
- AM/AML ratio	1.4±0.2	-
Ring-size	25±1	-
CABG No. pts	4	13
Anastomosis	3.8±1.0	3.7±0.9
Length of coaptation	0.8±0.2	-
Transmitral gradient (mmHg)	2.9±1.8	-
ICU-duration (median, days)	4 (range 2-7)	2 (range 1-4)
Hospital stay (median, days)	14 (range 7-18)	9 (range 6-35)

RMA: restrictive mitral annuloplasty, CPB: cardiopulmonary bypass, Aox: aortic cross clamping time, MR: mitral regurgitation, AM: mitral annulus, AML: anterior mitral leaflet

Echocardiography

Mitral regurgitation quantified before the operation was due to annular dilation and systolic restrictive motion of the mitral leaflets, and ≥ grade 3 in all patients. After weaning from CPB intra-operative TEE showed a mean length of coaptation of 8±2mm without residual mitral regurgitation (Table 2, Figure 1). The mean transmitral diastolic pressure gradient was 2.9±1.8mmHg (range 1.2 to 7.5mmHg). None of the patients showed systolic anterior movement of the anterior leaflet.

Hemodynamic indices in RMA and control patients (Table 3)

Cardiac output and LV ejection fraction remained unchanged after RMA. End-systolic and end-diastolic volume tended to decrease, but these changes did not reach statistical significance. The active relaxation (Tau) was significantly improved, from 73±18 to 63±15ms (p=0.047). End-diastolic pressure did not increase significantly, and dP/dt_{MAX}, dP/dt_{MIN} and stroke work were also unchanged. Effective arterial elastance (Ea, a measure of afterload) was unchanged after RMA. After ring insertion the pressure

gradient across the LV outflow tract was unchanged (from 2.1±3.3 to 2.8±3.3mmHg; p=0.662). Mechanical dyssynchrony showed a clear tendency to decrease after RMA, but the changes did not reach statistical significance (p=0.084).

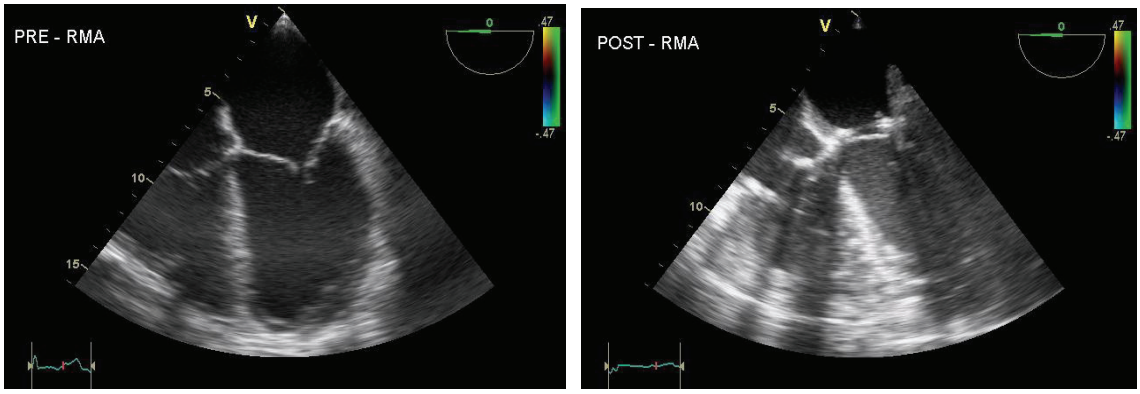

Figure 1. Transesophageal echocardiographic long-axis view before and after restrictive mitral annuloplasty in a 41 year-old patient with ischemic dilated cardiomyopathy (LVEF: 20%) and severe mitral regurgitation (grade 4). Mitral annular dilatation was demonstrated as the relative ratio between the diastolic mitral annular diameter (5.2mm) and the diastolic length of the anterior mitral leaflet (3.6mm) exceeded 1.3 (1.44). Restrictive mitral annuloplasty (Edwards Physio-ring size 26) was performed and postoperative mitral leaflet coaptation was 12mm with a normal inflow pressure gradient (3.5mmHg) and no residual mitral regurgitation. Additional restrictive tricuspidal ring annuloplasty was performed for severe tricuspidal regurgitation (grade 3)

The mechanical efficiency, calculated as SW/PVA, was unchanged after RMA. Similarly, peak LV wall stress (PWS: 356±91 to 346±85mmHg, p=0.668) and end-diastolic wall stress (WS_{ED}: 64±30 to 68±17mmHg, p=0.639) were unchanged. Although baseline values of most parameters in the control patients were substantially different from those in the RMA patients (consistent with the depressed LV function in the RMA patients), the changes after surgery were very similar. Like in the RMA patients, most parameters were unchanged except Tau, which was significantly improved in both groups, but the change in Tau was approximately the same in both groups (-10.1±5.0ms in the RMA patients, and -11.1±5.4ms in the control group, p=0.829). As a difference, LV ejection fraction was significantly improved in the control patients (46±15% to 52±18%, p=0.025), whereas the increase in the RMA patients did not reach statistical significance (29±5% to 32±8%, p=0.315).

Table 3. Hemodynamic data pre- and post surgery in RMA and control (CABG) patients

	RMA (n=10)			Control (n=13)		
	Pre	Post	p	Pre	Post	p
HR (beats/min)	85±7	88±13	0.491	82±3	86±8	0.113
CO (L/min)	5.0±1.8	5.3±0.9	0.516	4.9±1.2	5.9±1.4	0.193
SV (mL)	68±25	69±10	0.905	59±15	69±19	0.350
LVEF (%)	29±5	32±8	0.315	46±15	52±18	0.025
EDV (mL)	237±89	226±52	0.564	142±52	146±45	0.720
ESV (mL)	171±67	163±51	0.459	86±49	82±47	0.190
ESP (mmHg)	78±8	79±14	0.706	74±13	79±14	0.517
EDP (mmHg)	14±6	15±5	0.356	8±2	14±5	0.001
dP/dt_{MAX} (mmHg/s)	713±154	775±197	0.444	992±282	970±137	0.701
dP/dt_{MIN} (mmHg/s)	-754±105	-802±161	0.351	-880±208	-954±185	0.474
SW (mmHg.mL)	4,299±1,335	4,162±1,258	0.703	4,400±1,605	5,004±1,827	0.714
PVA (mmHg.mL)	9,422±3,460	9,072±2,924	0.808	5,873±2,079	6,376±2,517	0.761
SW/PVA	0.50±0.17	0.49±0.15	0.826	0.75±0.06	0.80±0.10	0.306
Tau (ms)	73±18	63±15	0.047	62±6	51±5	<0.001
E_A (mmHg/mL)	1.39±0.60	1.29±0.36	0.546	1.27±0.20	1.22±0.38	0.984
DYSS (%)	23.6±4.3	18.5±6.7	0.084	17.8±4.1	17.1±2.7	0.217
IFF (%)	31.7±15.4	24.6±20.2	0.459	19.4±8.6	17.2±6.3	0.127
E_{ES} (mmHg/mL)	0.86±0.50	0.99±1.05	0.688	1.31±0.93	1.26±0.72	0.836
ESV_{IND} (mL)	169±81	161±68	0.572	82±50	69±37	0.048
S-dP (mmHg/s/mL)	6.6±5.4	7.2±8.9	0.858	8.5±5.4	7.4±4.2	0.583
$dP/dt_{MAX,,IND}$(mmHg/s)	734±633	771±264	0.832	1,160±625	1,129±467	0.313
S-PRSW (mmHg)	64±54	60±41	0.855	65±30	55±20	0.594
SW_{IND} (mmHg.mL)	4,693±3,140	5,093±3,702	0.725	5,678±3,532	5,473±2,544	0.985
PWS (mmHg)	356±91	346±85	0.668	-	-	-
WS_{ED} (mmHg)	64±30	68±17	0.639	-	-	-
K_{ED} (mL^{-1})	0.027±0.035	0.041±0.047	0.542	0.021±0.014	0.038±0.019	0.015

HR: heart rate, CO: cardiac output, SV: stroke volume, LVEF: left ventricular ejection fraction, EDV: end-diastolic volume, ESV: end-systolic volume, ESP: end-systolic pressure, EDP: end-diastolic pressure, SW: stroke work, PVA: pressure-volume area, Tau: relaxation time constant, E_A: effective arterial elastance, DYSS: mechanical dyssynchrony, IFF: internal flow fraction, E_{ES}: end-systolic elastance, ESV_{IND}: intercept of ESPVR at mean ESP, S-dP: slope of dP/dt_{MAX}–EDV relation, $dP/dt_{MAX, IND}$, intercept of dP/dt_{MAX}–EDV relation at mean EDV, S-PRSW: slope of the PRSW relation, SW_{IND}, intercept of PRSW relation at mean EDV, PWS: peak wall stress, WS_{ED}: end-diastolic wall stress, K_{ED}: diastolic chamber stiffness constant

Pressure-volume relations (Figure 2)

Because steady state hemodynamic indices, as reported in the previous section, are load-dependent we also assessed systolic and diastolic function by pressure-volume relations. The slopes of these relations are sensitive and load-independent measures of LV function. Pressure-volume relations were determined from data acquired during temporary preload reduction obtained by vena cava occlusion. The mean reduction in EDV was 33±13mL in the control group and 39±16mL in the RMA group. In both the RMA and control groups the slopes of the systolic relations (E_{ES}, S-dP, S-PRSW) did not show significant changes after surgery. Baseline values confirmed depressed LV function in the RMA group. With regard to diastolic function, the diastolic chamber stiffness constant (K_{ED}) increased in both groups (control: 0.021±0.014 to 0.038±0.014mL^{-1}, p=0.015; RMA: 0.027±0.035 to 0.041±0.047mL^{-1}, p=0.542), but the increase did not reach statistical significance in the RMA group.

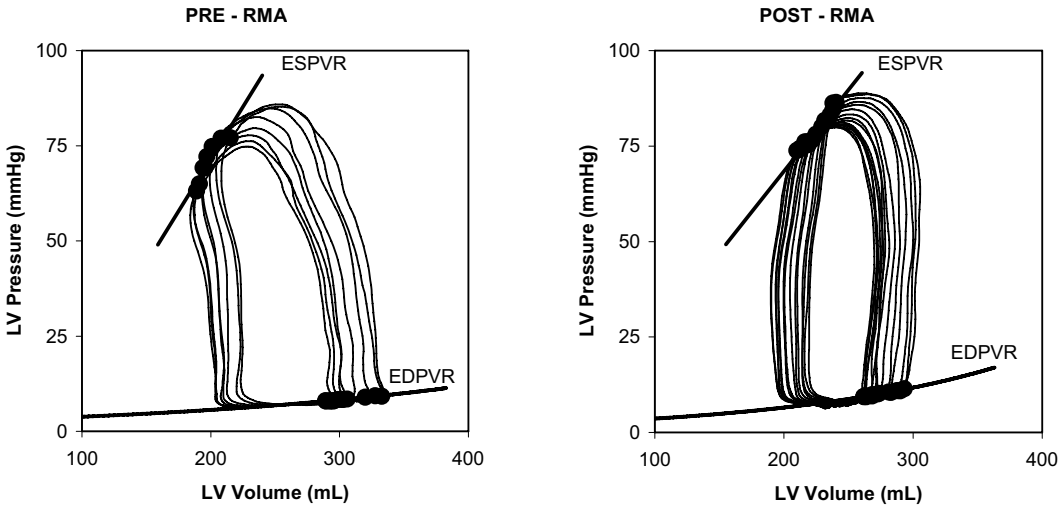

Figure 2. Pressure-volume relations before and after RMA in a patient with end-stage heart failure. In this patient the end-diastolic pressure-volume relation (EDPVR) demonstrates an increased diastolic stiffness. This was also found in the group as a whole, but the effect was not statistically significant. The slope (E_{ES}) of the end-systolic pressure-volume relation (ESPVR) in this patient decreased slightly. On the average, there was a small increase in E_{ES} in the RMA patients, but this change did not reach was not statistical significance

DISCUSSION

Mitral valve regurgitation is an important pathology in end-stage heart failure characterized by annular dilatation and restrictive leaflet motion.[21] Morbidity and

mortality is high if mitral regurgitation is treated conservatively.[22] Grigioni et al. clearly demonstrated that the severity of mitral regurgitation is directly related to mortality risk.[1]

Therefore, it seems reasonable to correct mitral regurgitation in patients with end-stage heart failure to improve prognosis. Currently, mitral annuloplasty is not routinely performed in these patients because substantial mortality and high recurrence rates are reported, and no evidence from randomized studies is available.[7,23] However, several recent studies have shown relatively low operative mortality and suggest improved long-term survival after stringent restrictive mitral annuloplasty.[9,11,24] Unfortunately, insights in the acute effects of RMA on systolic and diastolic LV performance are still limited and concerns are raised about possible adverse acute effects on systolic and diastolic LV function, which would limit application of this approach in patients with end-stage heart failure. The aim of our study was therefore to quantify these effects by use of load-independent pressure-volume indices.

We found unchanged systolic function after RMA. This is interesting, because earlier studies had predicted adverse effects, which would be the result of an afterload mismatch created by closure of a low-resistance run off into the left atrium. However, this "pop-off" effect may not exist and the high mortality in earlier studies appears mainly related to loss of LV function by disruption of the sub-valvular apparatus, because in that time, valve replacement (rather than repair) was mostly performed.[25] Effect on systolic function may also result from acute remodeling of the base of the heart due to the undersized ring. Bolling et al. argue that this would improve systolic function, however a study by David et al. implies a negative effect on systolic function because an undersized ring presumably impairs stretching and shortening of the proximal part of the basoconstrictor muscles (similar to a rigid ring).[26,27] In our study, we did not find any evidence for an altered, either reduced or improved, systolic function. In addition, systolic anterior motion of the anterior leaflet leading to LV outflow tract obstruction was not found in our series.

With regard to diastolic function we found an increase in diastolic chamber stiffness. This effect was present in both groups, but it was only statistically significant in the control patients. This increase in diastolic chamber stiffness is probably mainly an effect of cardioplegic arrest, leading to interstitial myocardial edema.[28] LV wall stress was unchanged after RMA consistent with largely unchanged end-diastolic volume and pressure.

The number of studies, in which effects of RMA on LV performance are evaluated, is limited. Several studies show improved LV ejection fraction and reduced end-diastolic volume.[8,11,24,29] Bishay et al. reported improved LV function and reversed remodeling at two years follow up in patients with severe LV dysfunction.[30] However, this group was heterogeneous and the patients underwent either mitral annuloplasty with various techniques or mitral valve replacement. Bax et al. studied patients who strictly underwent restrictive mitral annuloplasty, and showed that reverse remodeling of the LV is a gradual and time-dependent process.[9] These results are consistent with our findings, which show no acute effects on LV performance after RMA. Interestingly, our results show a clear tendency for a reduced mechanical dyssynchrony after RMA. This index has recently been shown a very sensitive marker of LV dysfunction and potentially this improvement may contribute to beneficial long-term effects.[17]

Limitations

The sample size in our study was relatively small and potentially positive effects on systolic function may be demonstrated in a larger group of patients. However, we performed pre- and post-CPB measurements in each patient, which optimizes the statistical power to detect possible effects of the surgical intervention. In addition, the RMA group was heterogeneous since in four patients additional CABG was performed. This subgroup was too small for meaningful statistical analysis, but the effects on pressure-volume relations in these patients did not appear to be different compared to the effects in the whole group. Furthermore, beneficial effects on LV systolic function in these patients would not be expected early after surgery as effects of revascularization on hibernating myocardium often occur later after surgery.[31] Measurements of global LV function were performed immediately after surgery with open chest and during inotropic support. The confounding effects of inotropic support were limited by also performing the measurements before surgery under inotropic support, but possible altered β-receptor sensitivity cannot be excluded. Assessment of regional function and of long-term effects under physiological conditions requires further studies.

In conclusion, mitral valve repair by RMA effectively restores mitral valve leaflet coaptation in patients with end-stage heart failure and severe mitral regurgitation, without significant acute changes in baseline hemodynamics and LV systolic and

diastolic function. Our findings support the use of this approach even in patients with severely depressed LV function in view of the expected beneficial long-term results.

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