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

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CHAPTER 6

Surgical ventricular restoration in patients with ischemic dilated cardiomyopathy: Evaluation of systolic and diastolic ventricular function, wall stress, dyssynchrony, and mechanical efficiency by pressure-volume loops

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ABSTRACT

Objectives. Surgical ventricular restoration (SVR) aims at improving cardiac function by normalization of left ventricular (LV) shape and size. Recent studies indicate that SVR is highly effective with an excellent five-year outcome in patients with ischemic dilated cardiomyopathy. We used pressure-volume analysis to investigate acute changes in systolic and diastolic LV function, mechanical dyssynchrony and efficiency, and wall stress.

Methods. In three patient groups (total, n=33), pressure-volume loops were measured by conductance catheter before and after surgery. The main study group consisted of 10 patients with ischemic dilated cardiomyopathy (NYHA III/IV, LV ejection fraction <30%) who underwent SVR and CABG. In this group, 7 patients underwent additional restrictive mitral annuloplasty (RMA). To assess potential confounding effects of RMA and cardiopulmonary bypass, we included a group of 10 patients (NYHA III/IV, LV ejection fraction <30%) who underwent isolated RMA and a group of 13 patients with preserved LV function who underwent isolated CABG.

Results. After SVR, end-diastolic and end-systolic volumes were reduced: 211±54 to 169±34 mL (p=0.03), and 147±41 to 110±59 mL (p=0.04), respectively. LV ejection fraction (27±7 to 37±13%, p=0.04) and end-systolic elastance (1.12±0.71 to 1.57±0.63 mmHg/mL, p=0.03) improved. Peak wall stress (358±108 to 244±79 mmHg, p<0.01) and mechanical dyssynchrony (26±4 to 19±6%, p<0.01) were reduced, whereas mechanical efficiency improved (0.34±13 to 0.49±0.14, p=0.03). End-diastolic pressure increased (13±6 to 20±5 mmHg, p<0.01), whereas the diastolic chamber stiffness constant tended to be increased (0.021±0.009 to 0.037±0.021 mL^{-1}, NS).

Conclusions. SVR achieves normalization of LV volumes and improves systolic function and mechanical efficiency by reducing LV wall stress and mechanical dyssynchrony.

INTRODUCTION

Surgical ventricular restoration (SVR) by means of endoventricular circular patch plasty (Dor procedure) is beneficial in patients with left ventricular (LV) post-infarction aneurysm. Previous studies have shown that this procedure is safe, improves functional class, long-term survival, and LV ejection fraction.[1,2] The exclusion of akinetic or

dyskinetic segments achieves acute volume reduction, changes in LV shape, and decreases of LV dyssynchrony.[3,4] These acute changes will influence LV global and intrinsic systolic and diastolic function. The use of pressure-volume analysis to assess these effects is advantageous because pressure-volume relations accurately reflect intrinsic LV function, and are relatively independent of loading conditions.[5,6] Moreover, pressure-volume signals can be used to quantify mechanical dyssynchrony and LV wall stress.[7]

Theoretical studies predict that volume reduction surgery results in leftward and upward shifts of the end-systolic and end-diastolic pressure-volume relations in the pressure-volume diagram, indicating a positive effect on systolic function but an adverse effect on diastolic function.[8,9] However, these effects are likely to be modulated by the material properties and the size of the resected or excluded region. Artrip et al. quantified the differential effects of volume reduction on end-systolic and end-diastolic function in a mathematical model.[10] Their findings indicate that an overall negative effect on LV pump function results if weak but contracting myocardium is resected (like in the Batista procedure), beneficial effects if the excised region is dyskinetic, and equivocal effects with akinetic scar resection. However, whether these models are realistic is unknown since in-vivo data on the effects of SVR and related procedures on LV pressure-volume relations in humans are very limited. One important aspect, which is not taken into account by these particular models, is (alterations in) mechanical dyssynchrony. Recent studies demonstrated that LV mechanical synchrony substantially improves after SVR resulting in more efficient myocardial pump function.[3,4] Furthermore, a recent *Special Report* from the RESTORE group emphasized the importance of considering interaction and (re)arrangement of myocardial layers and fiber orientation, and stressed the need for additional studies to quantify the effects of SVR and to get a better insight in the underlying mechanisms.[11]

As SVR reversely remodels ventricular size and shape, this approach may alter systolic and diastolic function.[11,12] Additionally, SVR may decrease LV wall stress and myocardial oxygen consumption by reducing end-diastolic volume, resulting in improved functioning of the remote myocardium.[13] The aim of this study was to determine the acute effects of SVR on systolic and diastolic pressure-volume relationships, LV wall stress, and mechanical dyssynchrony and efficiency in patients with ischemic dilated cardiomyopathy.

METHODS

Patients

The main study group consisted of 10 patients with ischemic dilated cardiomyopathy who underwent SVR. SVR is often combined with restrictive mitral annuloplasty (RMA) and therefore we also included a group of patients with left ventricular dysfunction in which isolated RMA was performed. To assess confounding effects of cardiopulmonary bypass and cardioplegic cardiac arrest we also included a control group of patients with normal LV function who underwent elective coronary artery bypass grafting (CABG). Thus, the following groups were studied:

1) SVR-group (n=10): Chronic heart failure, New York Heart Association (NYHA) class III/IV, LV ejection fraction < 30%, LV aneurysm with or without mitral regurgitation
2) RMA-group (n=10): Chronic heart failure, NYHA class III/IV, LV ejection fraction < 30%, mitral regurgitation grade ≥ 2
3) CABG-group (n=13): normal LV function (LV ejection fraction > 40%), elective CABG

Note that some patients in the SVR-group underwent additional RMA, whereas in both the SVR- and the RMA-group, CABG was performed if indicated. Details are provided in the Results section. The study was approved by the institutional review committee and all patients gave informed consent. The patient characteristics of the three groups are summarized in Table 1.

Anaesthesia and cardioplegic arrest

All patients received total intravenous anesthesia with target-controlled infusion of propofol, remifentanyl and sufentanyl. A single dose of pancuronium bromide (0.1mg/kg) was given to facilitate intubation. Subsequently, a thermal filament catheter was placed in the pulmonary artery via the right internal jugular vein for semi-continuous 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 transesophageal echo probe was inserted. All patients underwent normothermic cardiopulmonary bypass and received intermittent antegrade warm blood cardioplegia as described by Calafiore et al.[14]

Table 1. Patient characteristics

	SVR-group	RMA-group	CABG-group
# Patients (n)	10	10	13
Male/Female (n)	8/2	5/5	11/2
Age (years)	63±7	56±18	63±8
QRS duration (ms)	122±38	105±27	91±13
LVEF (%)	26±9	25±5	58±9
Coronary disease			
2 Vessels	4	4	5
3 Vessels	6	2	8
MR-grade			
I	3	0	-
II	3	0	-
III	4	7	-
IV	0	3	-

SVR indicates Surgical ventricular restoration; RMA, Restrictive mitral annuloplasty; LVEF, left ventricular ejection fraction; MR-grade, grade of mitral regurgitation assessed by pre-operative transesophageal echocardiography

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 with a low loading dose of 0.25 mg/kg enoximone in 10 minutes and thereafter we gave continuous infusion at a rate of 0.50 µg/kg/min, which was maintained during the whole operation.

Surgical techniques

Dor plasty. SVR was performed by means of endoventricular circular patch plasty as previously described by Dor.[15,16] Briefly, the LV was opened through the infarcted area. An endocardial encircling suture (Fontan stitch) was placed at the transitional zone between scarred and normal tissue. A balloon containing 55 mL/m^2 saline was introduced into the LV and the Fontan stitch was tightened to approximate the ventricular wall to the balloon. An oval dacron patch was tailored and used to close the residual orifice. The excluded scar tissue was closed over the patch to ensure hemostasis. Care was taken to eliminate all the septal scar and to delineate a new LV apex with the goal to restore the normal elliptical shape.

Mitral valve repair. A stringent restrictive (2 sizes smaller than measured) mitral annuloplasty (RMA) was performed via an atrial transseptal approach using a

Carpentier Edwards Physio ring (Edwards Lifesciences, USA). After weaning from cardiopulmonary bypass, transesophageal echocardiographic evaluation was performed in all patients to confirm disappearance of mitral regurgitation and assess the length of leaflet coaptation (aiming at ≥ 8 mm).

Study protocol

Before and directly after cardiopulmonary bypass, conductance catheter measurements were performed as described previously.[17] Briefly, temporary epicardial pacemaker wires were placed on the right atrium to enable measurements at fixed heart rates. A tourniquet was placed around the inferior caval vein 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 transesophageal echocardiographic 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 using calibration factors alpha (α) derived from thermodilution and parallel conductance correction volume (V_c) determined by hypertonic saline injections.[5,18] 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 indexes were derived as described below.

Data analysis

Global LV function. We determined indexes of global, systolic and diastolic LV function. Cardiac output was obtained by thermodilution, heart rate, mean arterial pressure, stroke volume, LV ejection fraction, minimal and maximal rate of LV pressure change (dP/dt_{MAX}, dP/dt_{MIN}), end-diastolic volume, end-systolic volume, end-diastolic pressure, end-systolic pressure were obtained from steady state beats using custom-made software. In addition, we assessed the early, active part of relaxation by the relaxation time constant (τ), which was determined by fitting LV pressure decay (starting at the moment of minimal dP/dt) with an exponential curve, as described previously[19]: $P(t) = A + B \cdot \exp(-t/\tau)$. Time-varying wall stress, WS(t), was calculated from instantaneous LV pressure and volume signals (P(t), V(t) respectively) as

described by Arts et al.[20]: $WS(t) = P(t)\cdot[1 + 3\cdot V(t) / V_{WALL}]$. LV wall volume ($V_{WALL}$) was estimated based on the diastolic posterior wall thickness derived from M-mode echocardiography.

Mechanical work and efficiency. Stroke work (SW) was determined as the area of the pressure-volume loop, which represents the external work performed by the ventricle. Pressure-volume area (PVA), a measure of total mechanical work, was calculated as the sum of stroke work and potential energy. The latter represents mechanical energy loss converted to heat during the cardiac cycle and is quantified by the triangular area enclosed by the pressure-volume loop, the end-systolic pressure-volume relation and the end-diastolic pressure-volume relation. [21,22] Mechanical efficiency (ME) was calculated as the ratio of stroke work and pressure-volume area: ME = SW / PVA.[23]

Mechanical dyssynchrony. Nonuniform LV performance (dyssynchrony) was determined from the segmental LV conductance signals and quantified by calculating the percentage of time within the cardiac cycle that a specific segment is dyssynchronous (i.e. opposite in phase with the global LV volume signal). Overall LV mechanical dyssynchrony was determined as the mean of the segmental dyssynchronies. In addition, we calculated the internal flow fraction, which quantifies the ineffective, segment-to-segment shifting of blood volume within the LV due to nonuniform contraction and filling. This approach was described and validated vs. tissue-Doppler imaging in a previous study.[7]

Systolic and diastolic pressure-volume relations. Ventricular function was assessed by systolic and diastolic pressure-volume relations derived from pressure-volume loops acquired during gradual preload reduction by vena cava occlusion. The end-systolic pressure-volume relation (ESPVR) was obtained as a linear fit to the end-systolic pressure-volume points and characterized by its slope, end-systolic elastance (E_{ES}), and the volume intercept at an end-systolic pressure of 80 mmHg (ESV_{80}). The end-diastolic pressure-volume points were fitted with an exponential curve: $EDP = A + B\cdot\exp(K_{ED}\cdot EDV)$. As illustrated in Figure 1, this relation was quantified by the diastolic stiffness constant (K_{ED}), the pressure intercept at an end-diastolic volume of 0 mL (EDP_0), and the calculated volume intercept at an end-diastolic pressure of 14 mmHg (EDV_{14}).[24,25]

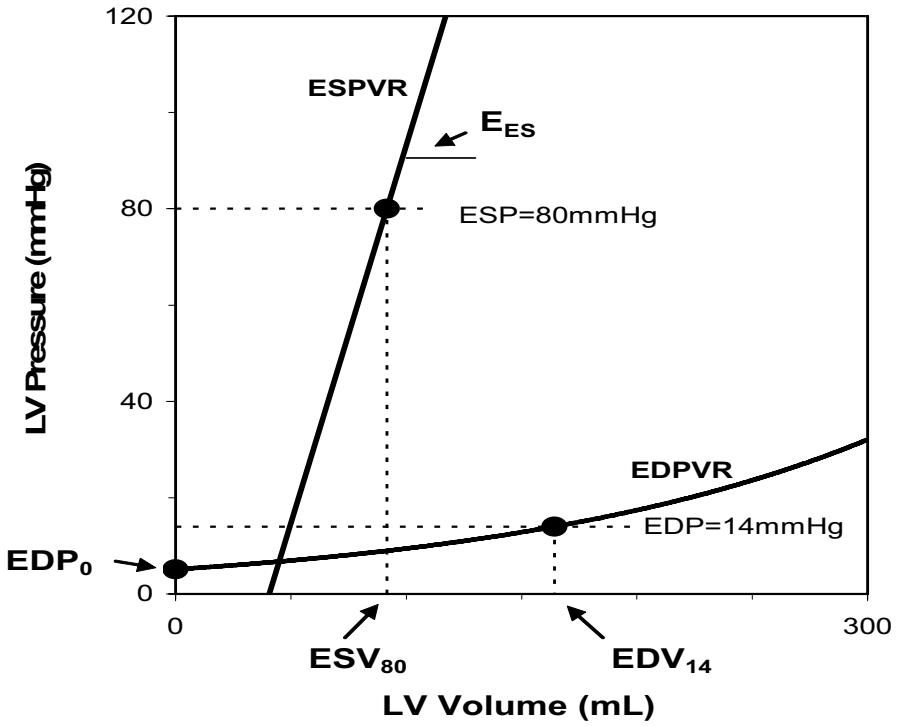

Figure 1. The end-systolic pressure-volume relation (ESPVR) and the end-diastolic pressure-volume relation (EDPVR) in the pressure-volume diagram. The linear ESPVR is characterized by its slope, end-systolic elastance (E_{ES}), and its volume intercept at an end-systolic pressure of 80 mmHg (ESV_{80}). The exponential EDPVR is characterized by the pressure-intercept at an end-diastolic volume of 0 mmHg (EDP_0), the volume intercept at an end-diastolic pressure of 14 mmHg (EDV_{14}), and the diastolic stiffness constant K_{ED}. (See text for further details)

Statistical analysis

Pre- and post-surgery clinical and hemodynamic indexes were compared with paired t-tests. Changes in systolic and diastolic pressure-volume relations were tested by multivariate analysis of covariance, using the Wilks' lambda statistic to test whether there were differences between conditions for the combination of parameters describing the relations.[26] Statistical significance was assumed at $p < 0.05$. All data are presented as the mean ± SD.

RESULTS

Surgical data are summarized in Table 2. In the SVR-group, all patients were treated with endoventricular circular patch plasty: 7 patients had a dyskinetic scar on pre-operative echocardiography, the remaining 3 patients had an akinetic scar. All patients

in the SVR-group had coronary disease and received additional CABG (2.8±1.4 distal anastomoses per patient). In the SVR-group 7 patients had mitral regurgitation of grade 2 or more and received additional restrictive mitral annuloplasty. In the RMA-group, 4 patients received additional CABG (4.0±0.8 distal anastomoses per patient), while the other 6 patients in this group underwent isolated restrictive mitral annuloplasty as 2 had irreversible ischemia and 4 had non-ischemic dilated cardiomyopathy. All patients were successfully weaned from cardiopulmonary bypass. In the SVR-group, 2 patients received intra-aortic balloon pump support and 7 patients needed inotropic support for more than 24 hours.

Table 2: Surgical data

	SVR-group (n=10)	RMA-group (n=10)	CABG-group (n=13)
Surgery			
SVR + CABG	3	-	-
SVR + CABG + RMA	7	-	-
Isolated RMA	-	6	-
RMA + CABG	-	4	-
CABG	-	-	13
CPB- time (median, minutes)	244 (range 105-287)	137 (range 105-287)	104 (range 60-167)
Aox-time (median, minutes)	172 (range 65-196)	96 (range 65-196)	75 (range 43-129)
# pts with IABP support	2	0	0
# pts with >24 hrs inotropes*	7	5	0
ICU-duration (median, days)	4 (range 3-16)	4 (range 2-7)	2 (range 1-4)
Hospital stay (median, days)	14 (range 9-30)	14 (range 7-18)	9 (range 6-35)

*SVR indicates Surgical ventricular restoration; RMA, Restrictive mitral annuloplasty; CPB, Cardiopulmonary bypass; Aox-time, aortic cross clamping time; IABP, Intra-aortic balloon pump support; ICU, Intensive care unit; * dobutamine > 2 μg/kg/min*

In the RMA-group, 5 patients needed inotropic support for more than 24 hours. None of the patients had signs of peri-operative myocardial infarction. In patients with mitral regurgitation, restrictive mitral annuloplasty suppressed regurgitation in all cases and restored leaflet coaptation (8±2 mm) with normal peak pressure gradients (3.0±2.0 mmHg). All patients were discharged from hospital in good clinical condition.

Figure 2 shows typical pressure-volume relations before and after SVR. After SVR, end-diastolic and end-systolic volumes were significantly reduced with unchanged stroke volume indicating improved LV ejection fraction. Before surgery, LV volume

decreased during the pre-systolic ('isovolumetric') contraction phase, reflecting severe mitral regurgitation. This effect disappeared in the post-SVR loops as mitral regurgitation was treated by successful RMA. After SVR, a leftward shift of the end-systolic and end-diastolic pressure-volume relation was present with an increased slope of both relations. These effects indicate improved systolic function and increased diastolic chamber stiffness after surgery.

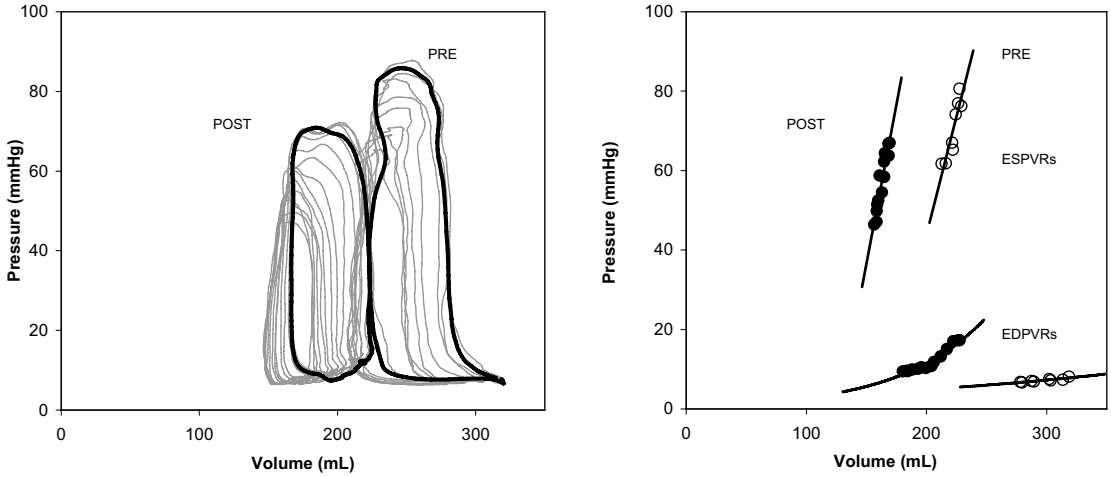

Figure 2. Typical example of pressure-volume relations in a patient with ischemic dilated cardiomyopathy before (PRE) and after (POST) surgical ventricular restoration. The steady state pressure-volume loops show a significant reduction in end-diastolic and end-systolic volumes with unchanged stroke volume indicating improved LV ejection fraction. Before surgery, LV volume decreased during the pre-systolic contraction phase, reflecting severe mitral regurgitation. This effect disappeared in the post-surgery loops as mitral regurgitation was treated by restrictive mitral annuloplasty. The load-independent end-systolic pressure volume relationship (ESPVR) showed a leftward shift with increased slope indicating improved systolic function. The end-diastolic pressure-volume relationship (EDPVR) also showed a leftward shift with increased slope indicating increased diastolic chamber stiffness post-surgery

Hemodynamic data

Mean hemodynamic data before and after SVR is summarized in Table 3 and the dyssynchrony parameters for all three groups are shown in Figure 3. LV stroke volume and cardiac output were unchanged after SVR. LV ejection fraction was significantly increased and there was an approximately 25% reduction in end-diastolic and end-systolic volumes. End-diastolic and end-systolic volumes were decreased towards "normal" values comparable to the values in the CABG-control-group. In the CABG-control-group, end-systolic volume and end-diastolic volume were unchanged after

surgery (86±49 to 82±47 mL (P=0.190) and 142±52 to 146±45 mL (P=0.720), respectively). After SVR, stroke work was not significantly altered, but potential energy was substantially reduced (-52%), resulting in a decreased total mechanical work and, consequently, a significantly increased mechanical efficiency. Peak LV wall stress was significantly reduced after SVR (from 358±108 to 244±79 mmHg, p<0.01), but remained unchanged in the RMA-group (356±91 to 346±85 mmHg, p=0.668).

Table 3: Hemodynamic data before (pre) and after (post) SVR

	SVR-group (n=10)		
	Pre	Post	P-value
HR (beats/min)	81±3	84±7	0.22
CO (L/min)	4.6±1.1	5.4±1.4	0.15
MAP	78±9	63±4	<0.01
ESP	95±18	80±15	0.03
EDV (mL)	211±54	169±34	0.03
ESV (mL)	147±41	110±59	0.04
LVEF (%)	27±7	37±13	0.04
SW (mmHg.L)	4.8±1.5	4.2±1.2	0.32
PE (mmHg.L)	10.6±6.1	5.1±3.5	<0.01
PVA (mmHg.L)	15.4±5.9	9.3±3.5	<0.01
ME	0.34±0.13	0.49±0.14	0.03
dP/dt_{MAX} (mmHg/s)	846±232	819±198	0.64
dP/dt_{MIN} (mmHg/s)	-804±191	-750±110	0.25
PWS (mmHg)	358±108	244±79	< 0.01
EDP (mmHg)	13±6	20±5	< 0.01
τ (ms)	85±13	70±12	< 0.01
DYSS (%)	26±4	19±6	< 0.01
IFF (%)	35±14	21±15	0.01

SVR indicates surgical ventricular restoration; HR, heart rate; CO, cardiac output; MAP, mean arterial pressure; ESP, end-systolic pressure; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; SW, stroke work; PE, potential energy; PVA, pressure-volume area; ME, mechanical efficiency; PWS, peak wall stress; EDP, end-diastolic pressure; τ, relaxation time constant; DYSS, mechanical dyssynchrony; IFF: internal flow fraction

Active relaxation (τ) was improved, while end-diastolic pressure was significantly increased. Mechanical dyssynchrony and the internal flow fraction were reduced in all groups, however these changes were most pronounced and only reached statistical significance in the SVR-group (Figure 3).

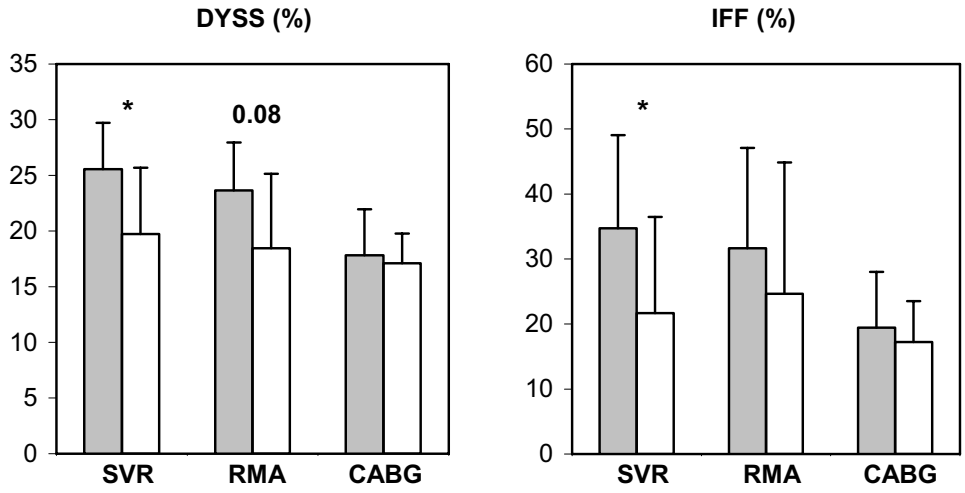

*Figure 3. Acute effects of surgery on mechanical dyssynchrony indexes in the SVR-, RMA and CABG-groups. DYSS indicates mechanical dyssynchrony; IFF, internal flow fraction. * indicates p<0.05. Marginal significances (p<0.10) are tabulated*

The effects on the load-independent pressure-volume indexes are summarized in Table 4. The end-systolic pressure-volume relation did not show significant changes in the CABG- and RMA-groups. In contrast, in the SVR-group, ESV_{80} decreased significantly and E_{ES} increased significantly, representing a leftward shift and increased slope of the end-systolic pressure-volume relation, both indicating improved systolic function. With regard to diastolic function, the end-diastolic pressure-volume relation was significantly altered only in the SVR-group (P=0.011): particularly, EDV_{14} decreased significantly indicating a leftward shift of the curve, whereas K_{ED} tended to increase, suggesting decreased diastolic compliance. The changes in the diastolic pressure-volume relations for the RMA- and CABG-groups were in the same direction but were not statistically significant, although in the CABG-group marginal significance was reached (P=0.097).

Average pressure-volume loops

To summarize the effects, Figure 4 shows schematic average pressure-volume loops for all of the three groups. The pressure-volume loops are based on the average end-systolic and end-diastolic pressures and volumes in each group. The most pronounced effects were seen after SVR. After SVR, there was a significant acute reverse remodeling, demonstrated by the substantial reduction in end-diastolic and end-systolic volumes.

Table 4: End-systolic and end-diastolic pressure-volume relations before and after surgery

			SVR-group	RMA-group	CABG-group
ESPVR	Wilks' lambda		0.439	0.942	0.591
		P-value	0.037	0.810	0.122
	r-value	Pre	0.98±0.01	0.95±0.03	0.95±0.03
		Post	0.97±0.04	0.96±0.03	0.92±0.13
	ESV_{80} (mL)	Pre	143±58	171±82	86±51
		Post	89±40	164±69	72±38
		P-value	0.015	NS	NS
	E_{ES} (mmHg/mL)	Pre	1.12±0.63	0.86±0.50	1.31±0.93
		Post	1.57±0.55	0.99±1.05	1.26±0.72
		P-value	0.032	NS	NS
EDPVR	Wilks' lambda		0.177	0.785	0.428
		P-value	0.011	0.842	0.097
	r-value	Pre	0.98±0.02	0.97±0.04	0.95±0.05
		Post	0.96±0.10	0.98±0.02	0.98±0.01
	EDP_0 (mmHg)	Pre	3.6±2.8	3.0±2.3	1.8±2.4
		Post	5.2±3.0	4.2±3.3	2.2±3.7
		P-value	0.261	NS	NS
	EDV_{14} (mL)	Pre	235±65	262±130	174±51
		Post	152±35	240±65	144±43
		P-value	0.001	NS	NS
	K_{ED} (1/mL)	Pre	0.021±0.009	0.027±0.035	0.021±0.014
		Post	0.037±0.021	0.041±0.047	0.038±0.019
		P-value	0.147	NS	NS

SVR indicates surgical ventricular restoration; RMA, restrictive mitral annuloplasty; CABG, coronary artery bypass grafting; ESPVR, end-systolic pressure-volume relation; EDPVR, end-diastolic pressure-volume relation; r-value, correlation coefficient; ESV_{80}, volume intercept of the ESPVR at end-systolic pressure 80 mmHg; E_{ES}, end-systolic elastance (slope of the ESPVR); EDP_0, pressure intercept of the EDPVR at end-diastolic volume 0 mL; EDV_{14}, volume intercept of EDPVR at end-diastolic pressure 14 mmHg; K_{ED}, diastolic stiffness constant; NS, not significant (indicated by Wilks' lambda)

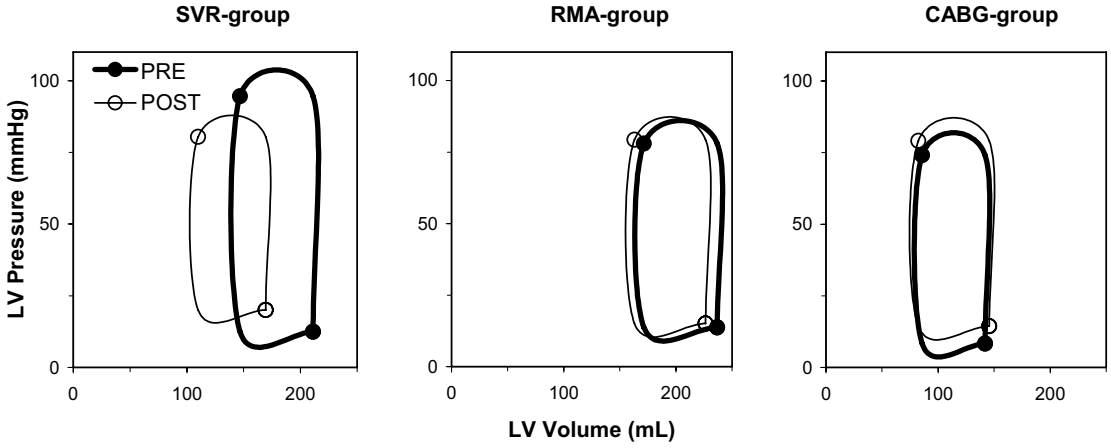

Figure 4. Average steady state pressure-volume loops before (PRE) and after (POST) SVR (surgical ventricular restoration), isolated RMA (restrictive mitral annuloplasty), and CABG (coronary artery bypass grafting). The average loops (based on mean end-systolic and end-diastolic volumes and pressure) illustrate the effects on systolic and diastolic LV volumes and pressures. Please note that the apparent stroke work (area of the pressure-volume loop) derived from these schematic loops could be misleading: First, pre-surgery the actual loops often show a volume decrease in the 'iso-volumic' contraction phase (reflecting pre-systolic mitral insufficiency), which is not shown in the schematic ('square') loops and causes the pre-surgery schematic loops to overestimate actual SW. Second, if afterload impedance is relatively low the end-systolic pressure may be substantially lower than the peak systolic pressure, which may cause the schematic post-surgery loops to underestimate the real stroke work. Thus, the change in stroke work in the SVR-group, derived from the schematic loops, appears to be larger than it, in fact, was (Table 2: non-significant 12% decrease)

DISCUSSION

Surgical ventricular restoration by means of endoventricular circular patch plasty (Dor procedure) is increasingly performed in patients with severe LV dysfunction after anterior myocardial infarction, for either akinesia or dyskinesia.[16] We quantified the immediate hemodynamic effects of SVR on load-independent systolic and diastolic LV pressure-volume relations in combination with effects on LV wall stress and mechanical dyssynchrony and efficiency in patients with ischemic dilated cardiomyopathy. Our results show that SVR significantly improved LV systolic function (LV ejection fraction, end-systolic pressure-volume relation), and reduced LV wall stress and mechanical dyssynchrony. In addition, LV mechanical efficiency was significantly improved. LV diastolic function, however, appeared to be compromised: the diastolic pressure-volume relation was significantly shifted towards smaller volumes and tended

to be steeper, evidenced by an increased diastolic stiffness constant, although the latter effect did not reach statistical significance.

The relatively small changes in systolic function in the patients who underwent isolated restrictive mitral annuloplasty and in the patients who underwent elective CABG indicate that the systolic improvements in the SVR group were mainly related to LV restoration. The increase in LV ejection fraction after SVR was attributed to the surgical reduction in end-diastolic volume, as LV stroke volume was unchanged. However, LV ejection fraction may not be an accurate parameter of systolic improvement after SVR because loading conditions may have changed substantially after surgery. Thus, load-independent pressure-volume relations are needed to quantify alterations in systolic function. The slope of the end-systolic pressure-volume relation, end-systolic elastance E_{ES}, is a load-independent parameter of systolic function and E_{ES} increased significantly after SVR. Moreover, the end-systolic pressure-volume relation was significantly shifted towards smaller volumes, also indicating improved systolic function.[26,27] This improvement may be the result of increased systolic stiffness induced by exclusion of a large compliant area, as predicted by computational models,[10] or due to improved function of the remote myocardium by reduced LV wall stress, and reduced LV mechanical dyssynchrony after exclusion of the aneurysm.[3,4]

Regarding diastolic function, relaxation time constant τ was significantly reduced, indicating faster relaxation. This time-constant quantifies the speed of LV pressure decay during isovolumic relation, i.e. between aortic valve closure and mitral valve opening, which represent the very early, and active, part of relaxation, which is considered to be importantly co-determined by systolic function.[28] This change may result from coronary revascularization - which may enhance the oxygen dependent re-uptake process of calcium by the sarcoplasmic reticulum - or from an afterload reduction as active relaxation is afterload dependent.[29] Passive diastolic function was assessed by the diastolic pressure-volume relationship. Our results show that SVR induced a substantial leftward shift of the end-diastolic pressure-volume relation as quantified by the significant decrease in EDV_{14}. In addition, the diastolic stiffness constant K_{ED} tended to increase, indicating by an enhanced steepness of the curve. Interestingly, diastolic chamber stiffness had a tendency to increase in all groups with a similar magnitude, although the effects did not reach statistical significance. This suggests that the increased diastolic stiffness may be contributed largely to the effect of the cardiopulmonary bypass and cardioplegic arrest leading to interstitial edema.[30] In our center, normothermic cardiopulmonary bypass and intermittent antegrade warm

blood cardioplegia is routinely used[31] because this approach may provide metabolic benefits[32,33] and less cell damage,[34] possibly mediated by a better protection from ischemia-reperfusion injury. Our study was not designed to investigate whether alternative cardioplegic approaches have less effect on post-operative diastolic function, but previous experimental studies do not appear to show important differences regarding myocardial edema formation and post-operative diastolic compliance between warm and cold blood approaches.[35]

The results in our study are in line with predictions of Artrip et al. which were based on a composite model of the left ventricle.[10] The results of their study emphasize the importance of the material properties of the region being removed. It was predicted that resection of weak but contracting muscle such as may occur with the partial left ventriculectomy (Batista procedure) will lead to a greater leftward shift for the end-diastolic pressure-volume relation than for the end-systolic pressure-volume relation resulting in an overall negative effects on cardiac performance. Schreuder et al. studied the acute effects of partial left ventriculectomy in humans with dilated cardiomyopathy on LV pressure-volume relations and found significant improvements of systolic function and mechanical synchrony after surgery.[36] The effects on intrinsic diastolic function like that of the end-diastolic pressure-volume relation were not described in detail, but the significant increase of end-diastolic pressure two till five days after surgery suggests diastolic impairment after surgery. Most centers have abandoned the Batista procedure because of high surgical mortality and late return of heart failure, but studies by Suma's group indicate that by utilizing intraoperative echocardiography to select the optimal excision, partial left ventriculectomy may effectively treat severe heart failure in selected patients with nonischemic dilated cardiomyopathy.[37]

However, our study focuses on patients with *ischemic* dilated cardiomyopathy, for which case Artrip's model would predict improvement of overall cardiac pump function. Recent studies assessed the acute effects of SVR on pressure-volume relations and found improved systolic function and reduced mechanical dyssynchrony.[4] However, the effects on diastolic load-independent indices, which may be important after volume reduction and insertion of an akinetic stiff patch, were not studied. To our best knowledge, the present study is the first to show the effects of SVR in patients with ischemic dilated cardiomyopathy on both systolic and diastolic pressure-volume relations in comparison to other surgical procedures. As expected, the results showed a leftward shift of both the end-systolic and the end-diastolic pressure-volume relation. Indexed by ESV_{80} and EDV_{14}, respectively, the end-systolic pressure-volume relation

shifted by -55±18 mL, whereas the end-diastolic pressure-volume relation shifted by -84±17 mL. Consequently, when compared at the same end-diastolic pressure (of 14 mmHg), the hypothetical maximal total work, quantified by the area enclosed by the end-systolic pressure-volume relation, the end-diastolic pressure-volume relation, and the end-diastolic volume at 14 mmHg was decreased (from 13.4 to 10.1 mmHg·L). This finding could be interpreted as a decrease in overall pump function.[10] However, in practice, the LV worked at a higher end-diastolic pressure after SVR, resulting in a maintained stroke work and cardiac output. Moreover, under physiological conditions the total work is only partly converted to effective external work (i.e. the area of the pressure-volume loop, stroke work), the remainder is dissipated as heat (the potential energy component of the pressure-volume area). Interestingly, our results show that, whereas stroke work remained fairly constant, the potential energy component was importantly reduced, indicating an improved mechanical efficiency of the ventricular contraction. This acute improvement presumably is caused by reduced mechanical dyssynchrony and reduced wall stress due to the restoration of LV shape. Consistent with our findings, Di Donato et al. recently demonstrated reduction of mechanical dyssynchrony after the Dor procedure.[3] Usually, LV geometry in patients with chronic dilated cardiomyopathy is associated with a more transverse orientation of apico-septal muscle fibers and this orientation results in less efficient contraction and a decrease in LV pump function.[12] SVR achieves restoration of the LV geometry towards a more elliptical shape,[11,38] and the increase in systolic function after SVR, found in our study, may be partly the result of improvement of geometric rearrangement with restoration of LV apico-septal fiber orientation.

Our approach involved the use of an intraventricular balloon filled with 55 ml/m^2 saline to standardize the surgery, to avoid creating a too small cavity, and to achieve an elliptical shape of the left ventricle. Previous studies using a shaper device recommended a similar residual volume.[39] However, at this point it is unknown which factors determine the optimal residual volume in individual patients. Also, the material properties of the patch may influence the results. A recent mathematical model study recommended repair without a patch whenever possible.[40] Potentially, the modified linear closure described by Mickleborough et al. could be advantageous.[41] However, this approach limits options for septal exclusion as compared to the Dor procedure. Therefore, as pointed out in a recent editorial by Buckberg,[42] the linear closure would only be applicable to a selected patient population. Future studies are required to investigate these issues.

Limitations

Our study is limited by the fact that the interventions were not randomized and thus baseline differences between the study groups may have introduced bias. Comparisons between groups may also be affected by differences in procedure times (Table 2), which were longer in the SVR-group. The 'recovery time' (CPB-time minus the cross-clamp time) was also longer in the SVR-group than in the RMA-group (72 vs. 41 min). Although this difference is partly explained by a more extensive echocardiographic evaluation (which is generally performed still on-pump), it may also indicate that post-operative function is affected by length of the procedure. A direct comparison between patients in the SVR group who did or did not receive additional RMA (7 vs. 3 patients) is not statistically meaningful because the numbers are too small, and any conclusion would be very speculative and could be misleading.

We anticipated that most of the heart failure patients would need inotropic support after surgery. Therefore, to avoid bias, in the SVR- and the RMA-groups inotropic support was started before surgery and, thus, pre- and post-measurement were both done during inotropic support. In the CABG group none of the patients received inotropic support. This may have resulted in slightly less pronounced differences between the CABG group on the one hand and the SVR/RMA groups on the other hand.

A methodological limitation may be present for the calculation of conductance catheter slope factor α, which corrects underestimation of volume changes, which is due to electric field inhomogeneity and mismatch of the catheter segments with the LV long axis. In our study, this factor was calculated by matching the uncalibrated conductance stroke volume with stroke volume obtained by thermodilution. Because this comparison with right-sided stroke volume determined by thermodilution would be hampered in case of mitral insufficiency, we determined uncalibrated conductance catheter stroke volume as the volume at the moment of dP/dt_{MAX} minus the volume at the moment of dP/dt_{MIN}. With this approach pre- and post-systolic mitral insufficiency is not included in the uncalibrated conductance stroke volume. However, some overestimation of actual forward stroke volume may remain, which theoretically would result in a slight underestimation of absolute volumes in patients with mitral insufficiency.

In conclusion, SVR by endoventricular circular patch plasty leads to acute normalization of LV volumes with improved systolic function. At the expense of a higher diastolic pressure resulting from altered diastolic properties, cardiac pump

function indexed by stroke work and cardiac output was not importantly altered. However, mechanical efficiency was significantly improved, presumably resulting from reduced wall stress and reduced mechanical dyssynchrony. Interestingly, the diastolic chamber stiffness constant was not more altered after SVR than after the surgical procedures in the other groups, suggesting that this effect was importantly related to procedure-induced myocardial edema and may be partially transient. Additional mitral valve repair is feasible and restores leaflet coaptation, while this procedure in itself does not importantly affect systolic and diastolic LV function in the acute phase. Future studies should be directed toward the long-term effects of SVR on systolic and diastolic pressure-volume relationships.

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