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

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CHAPTER 10

Beneficial mid-term hemodynamic and clinical effects of surgical ventricular restoration in patients with ischemic dilated cardiomyopathy

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ABSTRACT

Background. Surgical ventricular restoration (SVR) is increasingly applied in patients with ischemic dilated cardiomyopathy. Previous studies show promising results with regard to survival and clinical outcome. However, a comprehensive mid-term analysis of this approach on left ventricular (LV) and right ventricular (RV) function is not yet available. We investigated biventricular function and clinical status at 6-months follow-up.

Methods. We investigated the effects of SVR on clinical parameters, LV volume and RV reverse remodeling, LV dyssynchrony, tricuspid regurgitation, and pulmonary artery pressure in 21 patients with ischemic dilated cardiomyopathy (NYHA class III/IV) who underwent SVR and CABG. Additional surgery included mitral annuloplasty (n=14) and tricuspid valve annuloplasty (n=8). Clinical parameters (NYHA, quality-of-life questionnaire, 6-min hall-walk test) and echocardiographic parameters were assessed at baseline and at 6-months.

Results. At 6-months follow-up, all clinical parameters were significantly improved. LV ejection fraction improved from 27±10 to 36±11% (P<0.01), LV end-diastolic volume decreased from 248±78 to 152±50mL (P<0.001), and LV end-systolic volume from 186±77 to 101±50mL (P<0.001). LV dyssynchrony decreased from 61±41 to 12±12ms (P<0.001). RV annular diameter decreased from 30±7 to 27±6mm, RV short-axis from 30±9 to 27±7mm, and RV long-axis from 90±7 to 79±10mm (all P<0.05). Finally, significant reductions in severity of tricuspid regurgitation (from 1.3±1.1 to 0.9±0.6, P=0.001) and pulmonary artery pressure (42±11 to 28±10mmHg, P=0.015) were observed.

Conclusions. SVR resulted in improvement of clinical parameters, significant LV volume reduction and reduced LV dyssynchrony at 6-months follow-up. In addition, RV reverse remodeling was noted with reductions in tricuspid regurgitation and pulmonary artery pressure.

INTRODUCTION

Chronic heart failure is one of the major healthcare problems in the world both in terms of patient numbers, hospitalizations, and economic costs.[1] The prognosis is extremely poor with a 5-year survival rate being less than 40%.[2] Recently, it has been

demonstrated that surgical ventricular restoration (SVR) improves symptoms and long-term survival in patients with ischemic cardiomyopathy and severe heart failure.[3] Several studies have reported on the beneficial effects of SVR, including left ventricular (LV) volume reduction with an improvement in LV ejection fraction (LVEF), associated with a reduction in ventricular arrhythmias and reduced mitral regurgitation.[4-6] In addition, recent studies have shown that SVR results in an acute reduction of LV mechanical dyssynchrony.[7,8]

In patients with valvular insufficiencies who undergo SVR, additional mitral and or tricuspid valve repair may be needed to optimize patient outcome.[9] Therefore, our current approach in patients undergoing SVR is to always correct mild to moderate mitral and tricuspid regurgitation using annuloplasty. Although preliminary data indicate acceptable survival, larger studies are required to establish survival rate. In addition, comprehensive data on clinical and hemodynamic status of these patients at mid-term follow-up are limited. Therefore, we analyzed clinical status and biventricular function in patients with ischemic dilated cardiomyopathy treated at our institution before and 6 months after surgery. In particular, we report the effects of our approach on LV volume, LV dyssynchrony, right ventricular (RV) reverse remodeling and RV functional parameters (severity of tricuspid regurgitation and pulmonary artery pressure).

METHODS

Patients and Study Protocol

We studied a group of 21 patients with ischemic dilated cardiomyopathy, who underwent SVR and who had complete echocardiographic follow-up including tissue Doppler imaging at 6 months. All patients had severe heart failure symptoms and 13 patients (62%) had accompanying angina pectoris. In particular, 13 (62%) patients were in New York Heart Association (NYHA) class III and 8 (38%) were in class IV. All 21 patients had a previous anteroseptal infarction and the interval between infarction and SVR procedure averaged 2.5 years (range 0.25-12 years). All patients had coronary artery disease (on average 2.4±0.9 stenosed coronary arteries) and were scheduled for additional CABG. Patients with severe mitral and/or tricuspid regurgitation underwent additional mitral and/or tricuspid valve repair. Patients who underwent valvular repair

were evaluated before and immediately after surgery by transesophageal echocardiography (TEE). The baseline characteristics are presented in Table 1.

Table 1. Patient characteristics

Variable	N=21
Age, yrs	63±11 (35-76)
Gender (M/F)	14/7
Delay from previous infarction, mo	30±45 (4-144)
QRS duration, ms	107±28 (80-202)
NYHA class	
- class III	13 (62%)
- class IV	8 (38%)
Rhythm	
- sinus rhythm	20 (95%)
- atrial fibrillation	1 (5%)
Coronary artery disease	
- 1-vessel	4 (19%)
- 2-vessel	8 (38%)
- 3-vessel	9 (43%)
Medication:	
- Diuretics/spironolactone	18 (86%)
- Nitrates	7 (33%)
- ACE-inhibitors/A-II antagonists	17 (81%)
- β-blockers	16 (76%)
- Anticoagulants/aspirin	15 (71%)

ACE, Angiotensin Converting Enzyme; A-II, Angiotensin II; NYHA, New York Heart Association

In all patients, before SVR and 6 months after surgery, two-dimensional transthoracic echocardiography (TTE) at rest was performed to calculate LV volumes and LVEF, and to assess RV chamber size. Next, tissue Doppler imaging was performed to evaluate LV dyssynchrony. At the same time points, clinical status was assessed using NYHA classification, the Minnesota quality-of-life questionnaire, and the 6-minute hall-walk test. The institutional review board approved the study protocol and all patients provided informed consent.

Surgical Procedures

The surgical procedures were performed with the use of normothermic cardiopulmonary bypass with intermittent antegrade warm blood cardioplegia for myocardial protection.

After median sternotomy, patients underwent conventional CABG, and internal mammary arteries were used whenever possible. Next, SVR was performed by means of endoventricular circular patch plasty as previously described by Dor.[10,11] 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 body surface area 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. Care was taken to provide an elliptical shape to the residual LV cavity. The excluded scar tissue was closed over the patch to ensure hemostasis. In patients with concomitant severe mitral regurgitation (grade ≥2), additional mitral valve repair was indicated. In these patients, restrictive mitral annuloplasty with implantation of an undersized semi-rigid ring (aiming at stringent downsizing of the mitral annulus by 2 sizes) was performed via the transseptal approach. After weaning from cardiopulmonary bypass, TEE evaluation was performed in these patients to exclude residual mitral regurgitation and assess the length of mitral leaflet coaptation (aiming at ≥0,8 cm). In patients with severe tricuspid annular dilatation (>3.5 cm) and/or regurgitation (grade ≥2), a concomitant tricuspid annuloplasty was performed.

Echocardiography

Resting echocardiography and tissue Doppler imaging was performed at baseline (pre-operatively), and at 6-months follow-up. Patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed system Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal and apical views (standard long-axis and two- and four-chamber images). Standard two-dimensional and colour Doppler data, triggered to the QRS complex were saved in cine loop format. LV volumes (end-systolic, end-diastolic) and LVEF were calculated from the conventional apical two- and four-chamber images, using the biplane Simpson's technique.[12]

Evaluation of mitral and tricuspid regurgitation

In patients with severe mitral and tricuspid regurgitation (grade ≥2) on TTE, additional TEE was performed within 5 days before surgery. The TTE and TEE were performed without general anesthesia to avoid underestimation of the severity of mitral and tricuspid regurgitation. The severity of mitral and tricuspid regurgitation was graded

semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images. Mitral and tricuspid regurgitation were classified as: mild=1+ (jet area/atrial area <10%), moderate=2+ (jet area/atrial area 10-20%), moderately severe =3+ (jet area/atrial area 20-45%), and severe=4+ (jet area/atrial area >45%).[13,14] The severity and precise mechanism of mitral regurgitation was confirmed from the TEE images.

Immediately after surgery, TEE was repeated to assess residual mitral or tricuspid regurgitation, transmitral diastolic gradient (determined from continuous-wave Doppler), and length of coaptation of the mitral leaflets. Six months after surgery, TTE was performed to assess possible recurrence of mitral and tricuspid regurgitation. Continuous-wave Doppler examination was also performed to estimate pulmonary artery systolic pressure from the trans-tricuspid maximal regurgitant flow velocity. All TTE measurements were analyzed in random order by two independent observers without knowledge of the clinical status of the patient and the timing of the echocardiogram.

Assessment of RV chamber size

RV end-diastolic chamber size was assessed using three parameters, which were described previously by Foale et al.[15] The first parameter is the diameter of the annulus of the tricuspid valve (TV ANN), defined as the point of attachment of the septal and posterior leaflets to the atrioventricular junction. The second measurement is the maximal dimension of the middle third of the RV, parallel to the tricuspid annulus (RV SAX). The last measurement is the major axis of the RV (RV LAX) and is defined as the distance between the RV apex to the mid-point of the tricuspid annulus.

Inter- and intra-observer agreement for assessment of RV chamber size were 98% and 96% for TV ANN, 90% and 92% for RV SAX, and 94% and 95% for RV LAX respectively.

Tissue Doppler Imaging

In addition to the conventional echocardiographic examination, tissue Doppler imaging was performed to assess LV dyssynchrony. For tissue Doppler imaging, color Doppler frame rates varied between 80 and 115 frames/s depending on the sector width of the range of interest; pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. Tissue Doppler imaging parameters were measured from color images of three consecutive heart beats by offline

analysis. Data were analyzed using commercial software (Echopac 6.1, General Electric - Vingmed).

To determine LV dyssynchrony, the sample volume was placed in the basal portions of the septum and the LV lateral wall; peak systolic velocities and time-to-peak systolic velocities were obtained and the delay in peak velocity between the septum and the LV lateral wall was calculated as an indicator of LV dyssynchrony (referred to as the septal-to-lateral delay).

Inter- and intra-observer agreement for assessment of the septal-to-lateral delay were 90% and 96%, respectively.[16]

Assessment of Functional Status

Functional status was assessed according to the NYHA classification, quality-of-life score (using the Minnesota quality-of-life questionnaire) and 6-minute hall-walk test. In all patients, QRS duration was measured from the surface ECG using the widest QRS complex from the leads II, V1 and V6. The ECGs were recorded at a speed of 25 mm/sec and were evaluated by two independent observers without knowledge of the patient's clinical status. All parameters were assessed within 1 week before surgery and approximately 6 months post-surgery.

Statistical Analysis

Data are presented as mean ± SD, and compared using the paired or unpaired Student's t-test when appropriate. For all tests a P-value <0.05 was considered statistically significant.

RESULTS

Twenty-one patients were evaluated: 12 patients (57%) had dyskinesia and 9 patients (43%) had akinesia. (Peri-)operative data and early operative complications (<30 days) are summarized in Table 2. Note that we only included a selected group of patients with complete echocardiographic follow-up at 6 months. Therefore, data regarding mortality are not relevant and clinical findings reflect only patients who survived 6 months follow-up.

Table 2. Surgical information, complications

Variable	N=21
Additional valve procedures	
- RMA	14 (67%)
- TVA	8 (38%)
Number of distal anastomoses	3.1±0.9
CPB, min	223±57
AoX, min	131±38
Early complications (<30 days)	
- SVT	1 (5%)
- VT	1 (5%)
- IABP	3 (14%)
- Reoperation for bleeding	1 (5%)
- Inotropy >24 hours	12 (57%)
ICU-duration, days	7±8
Hospital stay, days	17±10

AoX, aortic cross clamp time; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; ICU, intensive care unit; RMA, restrictive mitral annuloplasty; SVT, supraventricular arrhythmias; TVA, tricuspid valve annuloplasty; VT, ventricular tachycardia

Clinical Parameters

At 6-months follow-up a significant improvement in clinical status was observed. NYHA class improved significantly from 3.4±0.5 to 1.4±0.5 (P<0.001), the Minnesota quality-of-life score improved from 39±21 to 15±23 (P<0.001) and the 6-minute walking distance improved from 234±124 m to 416±106 m (P<0.001). QRS duration at baseline was 107±28 ms (range 80-202 ms) and remained unchanged (111±22 ms, range 90-172 ms, P=0.3481) at 6-months follow-up.

Echocardiography

Echocardiographic results at baseline and at 6-months follow-up are summarized in Table 3.

Left ventricular dyssynchrony: At 6-months follow-up, tissue Doppler imaging demonstrated a significant reduction in septal-to-lateral delay from 61±41 ms to 12±12 ms (P<0.001), indicating improved LV mechanical synchrony after surgery.

Left ventricular volume reduction: Significant LV volume reduction was shown at 6-months follow-up. LV end-diastolic volume decreased from 248±78 ml to 152±50 ml (P<0.001), whereas LV end-systolic volume decreased from 186±77 ml to 101±50 ml (P<0.001). This resulted in an increase of the LVEF from 27±10 to 36±11% (P=0.0072).

Right ventricular remodeling: At 6-months follow-up, significant reverse remodeling of the RV was demonstrated. All three parameters reflecting RV chamber size showed a significant decrease 6 months after surgery. The TV ANN showed a significant decrease from 30±7 mm to 27±6 mm (P=0.04), RV SAX decreased from 30±9 mm to 27±7 mm (P=0.03) and RV LAX showed a reduction from 90±7 mm to 79±10 mm (P<0.001). Moreover, after surgery, pulmonary artery pressure significantly decreased from 42±11 mmHg to 28±10 mmHg (P=0.02).

Table 3. Echocardiographic data

	Baseline TTE	6- months follow-up TTE	P-value
LVEF, %	27±10	36±11	0.0072
LVEDV, ml	248±78	152±50	<0.001
LVESV, ml	186±77	101±50	<0.001
Septal-to-lateral delay, ms	61±41	12±12	<0.001
RV chamber size:			
- TV ANN, mm	30±7	27±6	0.0430
- RV SAX, mm	30±9	27±7	0.0326
- RV LAX, mm	90±7	79±10	<0.001
Pulmonary artery pressure, mmHg	42±11	28±10	0.0157
MR, grade	2.0±1.0	1.0±0.7	0.0013
TR, grade	1.3±1.1	0.9±0.6	0.0018

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RV, right ventricle; TV ANN, tricuspid valve annulus; RV SAX, right ventricular short axis; RV LAX, right ventricular long axis; MR, mitral regurgitation; TR, tricuspid regurgitation

Mitral and tricuspid regurgitation: In 14 patients additional restrictive mitral annuloplasty (median ring size 24; range 24-28) was performed. In 9 (43%) of these patients, severe (grade 3 to 4+) mitral regurgitation was confirmed by TTE and TEE performed within 5 days before surgery. In the other 5 (24%) patients, grade 2+ mitral

regurgitation was observed during the TTE and TEE performed within 5 days before surgery. In these patients, provocative testing was performed in the operating room, resulting in grade 3 to 4+ mitral regurgitation in all patients. None of the patients had primary organic valvular disease. The mechanism underlying mitral regurgitation was systolic restrictive leaflet motion with annular dilatation, which resulted in coaptation failure (resulting in a central regurgitant jet). The patients who underwent mitral valve repair (n=14) had grade 2.8±0.7 mitral regurgitation on pre-operative TEE, which improved to grade 0.1±0.3 immediately after restrictive mitral annuloplasty. TTE after 6 months showed no significant recurrence (grade 0.9±0.7). In these patients, pre-operative TEE showed a mean length of coaptation of 0.23±0.06 cm, and 0.78±0.12 cm after restrictive mitral annuloplasty, with a mean transmitral diastolic gradient of 3.1±1.5 mmHg. No systolic anterior movement of the anterior leaflet was observed in any patient. In the patients who did not receive additional mitral valve repair (n=7), mitral regurgitation was unchanged at 6-months follow-up (mitral regurgitation grade 1.3±0.9 at baseline versus 1.1±0.8 at follow-up, P=0.604). In the group as a whole, mitral regurgitation was grade 2.0±1.0 at baseline, and 1.0±0.7 at 6-months follow-up (P=0.0013).

In 8 patients additional tricuspid annuloplasty (median ring size 28; range 28-32) was performed for severe tricuspid regurgitation (pre-operative TEE: grade 2.5±0.5). The tricuspid regurgitation was successfully treated (post-operative TEE: grade 0.1±0.1). In the group as a whole, tricuspid regurgitation was grade 1.3±1.1 at baseline and 0.9±0.6 at 6-months follow-up (P=0.0018).

DISCUSSION

The number of patients presenting with heart failure is increasing exponentially.[17] In these patients, severe LV dilation and mitral/tricuspid regurgitation are frequently observed and conservative treatment of both complications is associated with a poor prognosis.[18,19]

Therefore, surgical therapies (SVR and if indicated mitral and/or tricuspid annuloplasty) to correct these complications have evolved with acceptable survival rates. However, limited data is available about the effects on clinical status and LV and RV hemodynamics. In the current study, we analyzed clinical status and biventricular function in a group of patients with ischemic dilated cardiomyopathy undergoing SVR

and revascularization with, if needed, mitral and/or tricuspid valve repair before and 6 months after surgery. In particular, we report the effects of this approach on LV volume, LV dyssynchrony, right ventricular (RV) reverse remodeling and RV functional parameters (severity of tricuspid regurgitation and pulmonary artery pressure).

Clinical Status

In the total group of patients, an improvement in heart failure symptoms was observed, illustrated by a significant reduction of NYHA class from 3.4±0.5 to 1.4±0.5, with all patients in NYHA class I or II at follow-up. Similar observations were reported by Di Donato et al. and Suma et al.[20,21] In addition, more objective parameters of symptoms were also evaluated in the present study, including quality-of-life score and 6-minute walking distance, which improved in parallel to the improvement in NYHA class.

Echocardiographic Evidence of Remodeling

LV function: Besides the improvement in clinical status, previous studies demonstrated improvement in LVEF and LV volume reduction after SVR. Maxey et al. showed an acute increase in LVEF from 22±3 to 33±1% in 56 patients who underwent SVR combined with CABG.[22] Qin et al. reported an increase in LVEF from 27±9 to 36±11% at 6-months follow-up in patients who underwent SVR combined with mitral valve repair.[23] A similar increase in LVEF (from 27±10 to 36±11%, $P<0.001$) was noted in the current study. The improvement in LVEF was associated with the decrease in LV volume, with a mean reduction of 39% in LV end-diastolic volume and 46% in LV end-systolic volume. Qin et al. showed a comparable reduction in patients undergoing SVR and mitral valve repair; the LV end-diastolic volume decreased from 235±87 ml at baseline to 156±73 ml at discharge, whereas the LV end-systolic volume decreased from 175±80 ml at baseline to 104±63 ml at discharge.[23] At 6-months follow-up, however, LV volume reduction was not fully maintained and re-dilatation occurred with a final LV end-diastolic and LV end-systolic volume of 177±94 ml (NS vs. baseline) and 114±66 ml (NS vs. baseline) respectively. The re-dilatation was most outspoken in patients with recurrent mitral regurgitation, indicating that effective mitral valve repair is warranted in these patients to prevent re-dilatation. In our series, successful mitral valve repair without significant recurrence of mitral regurgitation was performed resulting in significant reduction in LV volumes at 6-months follow-up. Recently, Fujii et al. demonstrated that LV volume reduction may even be maintained at 3-years

follow-up; in 14 patients undergoing SVR, LV end-systolic volume was significantly reduced from 165±74 ml at baseline to 94±70 ml at 3-year follow-up.[24] Also, Yamaguchi et al. demonstrated a long-term reduction in LV volumes at 5-year follow-up after successful SVR with mitral valve repair.[25] These preliminary results suggest a long-term benefit from SVR and mitral annuloplasty, but additional studies with larger patient populations are needed to confirm these findings. Previous studies indicate an *acute* volume reduction after SVR in a range between 33% to 40%, which suggests that the 39% volume reduction found in our study at 6 moths follow-up is achieved largely immediate after surgery.[7,8,23,24]

RV function: The results in the current study illustrate that our surgical approach in patients with ischemic dilated cardiomyopathy is associated with a significant reduction in pulmonary artery pressure, with reduction in severity of tricuspid regurgitation and reverse RV remodeling. Currently, no other data are available regarding the effect of SVR and mitral and or tricuspid annuloplasty on RV function in patients with heart failure. One could hypothesize that successful mitral valve repair may lead to a reduction in pulmonary artery pressure with a recovery in RV function.[26] Similarly, tricuspid annuloplasty would be expected to improve RV function.[27] However, in our series we could not demonstrate significantly different effects on RV function between the patients who did or did not receive mitral and/or tricuspid annuloplasty. However, the number of patients in the subgroups is too small for adequate statistical analysis. The improvement in RV function is clinically important, since decreased RV function and RV dilatation have been shown to negatively affect hemodynamics, resulting in deterioration in heart failure symptoms with a worse prognosis.[28,29]

LV Dyssynchrony

LV dyssynchrony appears to be an important co-determinant of LV dysfunction in patients with heart failure.[30,31] Recently, Di Donato et al. showed an acute reduction of LV mechanical dyssynchrony after SVR assessed by using centerline analysis of LV angiographic data.[7] Similarly, Schreuder et al. showed that the reduction in LV dyssynchrony after SVR induced acute improvements in contractile status, energy efficiency, and LV relaxation.[8] In the current study, a significant reduction in LV dyssynchrony at 6 months after surgery was shown using tissue Doppler imaging. Recent data suggested that LV dyssynchrony was associated with a worse outcome, whereas LV resynchronization was associated with a better long-term prognosis.[32,33]

Additional studies on LV dyssynchrony and subsequent resynchronization in patients undergoing SVR are needed to determine the clinical value of LV resynchronization.

Limitations of the study

In this study, we evaluated the hemodynamic and clinical status in a group of patients after SVR with, if indicated, mitral and/or tricuspid annuloplasty, who survived 6 months follow-up. Therefore, this study did not provide data regarding clinical outcome in terms of mortality and morbidity. Another limitation of this study is the lack of acute data and therefore we cannot compare mid-term effects of SVR with effects immediately after surgery.

The effects of additional valve procedures on biventricular function could not be established as the number of patients in this study was too small and treatment was not randomized.

In conclusion, SVR with, if indicated, additional mitral and/or tricuspid annuloplasty resulted in significant improvement of clinical status and heart failure symptoms at 6 months follow-up, combined with an improvement in LV function, reduction in LV volume, and a reduction in LV dyssynchrony with minimal residual mitral regurgitation. In addition, a decrease in pulmonary artery pressure, RV reverse remodeling and reduced tricuspid regurgitation was observed.

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