Non-pharmacological heart failure therapies

Evaluation by ventricular pressure-volume loops

Sven A.F. Tulner

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"How could you describe the heart in words without filling a whole book"

Leonardo da Vinci, 1513

Voor mijn ouders

Aan Mies

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Cover image: Front: "Study of the valves and muscles of the heart"; Back: "Section of the heart with the left ventricle and mitral valve" c. 1513 by Leonardo da Vinci, Windsor Castle Royal Library.

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CHAPTER 1

General introduction and outline of the thesis

END-STAGE HEART FAILURE

Chronic heart failure is one of the major healthcare problems in the world both in terms of patient numbers, hospitalizations, and economic costs. In the United States, 4 to 5 million people have chronic heart failure, which leads to more than 2 million hospitalizations each year.[1,2] Recently, the Rotterdam study showed an overall incidence of chronic heart failure of 1.4% in the Netherlands with an overall prevalence of 7.0%.[3]

Despite optimal medical therapy (β-blockers, angiotensin-converting enzyme inhibitors, spironolactone), many patients develop end-stage heart failure and remain severely symptomatic.

In these patients, cardiac transplantation remains the most effective surgical therapy with 1-, 5- and 10-year survival rates of 94, 78, and 46 percent, respectively.[4,5] Although effective, heart transplantation is hindered by donor shortage and its limited applicability. The International Society of Heart and Lung Transplantation has reported a progressive worldwide decline of cardiac transplantation.[6]

Given the limitations of medical therapy and cardiac transplantation, several alternative therapies for end-stage heart failure have been adopted in the last decade. Most prominent is cardiac resynchronization therapy (CRT), after the first implant in 1995, large multi-center trials have been performed indicating improved symptoms, exercise tolerance and quality of life.[7] A recent study shows an additional survival benefit in patients treated by CRT and pharmacological therapy above patients treated with only pharmacological therapy.[8] In addition, new surgical therapies such as restrictive mitral annuloplasty and surgical ventricular restoration have evolved and are currently widely performed in patients with end-stage heart failure.[9,10] These therapies aim to correct frequently observed end-stage complications as mitral regurgitation and left ventricular (LV) aneurysm. If not treated, these complications have important adverse effects on long-term survival.[11-13]

The long-term survival rates of patients with end-stage heart failure treated with several therapies are summarized in table 1. Obviously, comparison is hampered by the fact that the etiology of heart failure is different in the various subgroups.

Other alternative therapies in patients with end-stage heart failure involve the use of LV devices. Heerdt et al. showed that chronic unloading by LV assist devices reverses contractile dysfunction and alters gene expression in patients with end-stage heart failure.[14] Recently, the cardiac support device (Acorn device) was introduced, which seems to reverse LV dilatation and improves functional capacity of heart failure

patients.[15] However, long-term studies with these devices implanted in more patients should be awaited. Finally, preliminary data suggest that cell transplantation or stem cell therapy may be applied for repairing damaged myocardium.[16-18] These therapies are currently under clinical investigation and future data should define their clinical efficacy.

Table 1. Survival in patients with NYHA III/IV heart failure after different treatments

	Follow-up (years)		
Therapy (ref)	1-year	5-year	10-year
Medical [3,19]	63%	35%	9%
HTX [4,5,20]	94%	78%	46%
CRT [8,21]	86%	75%	-
RMA [22-25]	84%	50%	-
SVR [26]	88%	69%	-

Ref: references; HTX: cardiac transplantation; CRT: cardiac resynchronization therapy; RMA: restrictive mitral annuloplasty; SVR: surgical ventricular restoration

PHARMACOLOGICAL THERAPIES

Currently, angiotensin-converting-enzym inhibitors and beta-blockers constitute the most important pharmacological therapies for heart failure and large trials have shown their capacity to improve survival and to lower morbidity.[27-32] Aldosterone antagonists and angiotensin receptor blockers may provide additional benefit.[33-35,36,37] However, the sustained benefit of medical treatment appears relatively short-lived.[38] Non-pharmacological therapies such as heart transplantation and implantable assist devices are only considered in the late stage of the disease and access to such therapies is limited.[39] Alternative non-pharmacological treatments for the failing heart such as CRT, mitral valve repair and surgical ventricular restoration are currently widely performed.

NON-PHARMACOLOGICAL THERAPIES

Cardiac resynchronization therapy

LV mechanical dyssynchrony in patients with end-stage heart failure is related to electrical, structural, and morphological features.[40,41] Mechanical dyssynchrony is

present in the normal heart, but becomes more apparent in pathological conditions such as heart failure. [42,43] In patients with heart failure, LV electrical dyssynchrony typically results from left bundle-branch block. Notably, left bundle-branch block changes LV contraction patterns, leading to early and late contraction.[44,45] This, in turn, impairs systolic function, reduces cardiac output, and increases end-systolic volume and LV wall stress.[40]

CRT is a novel treatment option in symptomatic patients with end-stage heart failure and LV mechanical dyssynchrony. Current indications for CRT in patients with drug-refractory end-stage heart failure are NYHA class III/IV symptoms, LV ejection fraction below 35 percent, QRS duration above 120 ms and left bundle branch block configuration. Large randomized placebo controlled studies have demonstrated the beneficial effects of CRT on symptoms, exercise capacity, and quality of life.[46,47] In addition, a recent prospective randomized study showed that CRT substantially reduced the risk of complications and death among patients with heart failure and cardiac dyssynchrony.[8] In this study, a total of 404 patients were assigned to receive medical therapy alone and 409 patients to receive medical therapy plus cardiac resynchronization therapy and all patients were evaluated in a mean follow-up period of 29 months. The mortality rate in the medical-therapy group was 13% at one year and 25% at two years, as compared with 10% and 18%, respectively, in the CRT group. This study therefore concluded that implantation of CRT should routinely be considered in patients with moderate to severe heart failure and cardiac dyssynchrony. Several studies have demonstrated that CRT has beneficial effects on LV hemodynamics including reverse LV remodeling.[48-50] Recently, Yu et al. demonstrated that LV reverse remodeling is a strong predictor of lower long-term mortality and heart failure events.[51] In addition, CRT is associated with reduced sympathetic nervous activity, suggesting potentially favourable neurohormonal effects.[40] These benefits are pacing dependent, because discontinuation of pacing resulted in a rapid loss of cardiac improvement. Penicka et al. have recently demonstrated that the degree of baseline LV dyssynchrony is the main predictive factor for LV functional recovery and reversed remodeling after CRT.[52] Therefore, LV dyssynchrony assessed by tissue Doppler imaging may be an important additional selection criterium for CRT.[53] Bax et al. have recently shown that patients with septal to lateral delay above 65 ms will respond to CRT and will have an excellent prognosis after CRT. Furthermore, CRT also has beneficial effects on mitral regurgitation.[54,55] Improved coordinated timing of mechanical activation of papillary muscle insertion sites appears to be a mechanistic contributor to immediate reduction of

mitral regurgitation by CRT in patients with heart failure. Despite the clear clinical benefit, accurate hemodynamic data, i.e. effects on systolic and diastolic LV function, remain largely limited to the acute effects of CRT. Long-term effects are reported mainly in terms of ejection fraction and reversed remodeling. More detailed hemodynamic studies would provide potentially important insight in the working mechanisms of long-term CRT.

Restrictive mitral annuloplasty

Patients with chronic heart failure due to LV systolic dysfunction frequently develop mitral regurgitation.[56] Several studies have shown that coaptation failure arises in these patients as a consequence of geometric alterations, which affects mitral annular size and the geometric position of the subvalvular apparatus.[57,58] Previously, surgical treatment of mitral regurgitation was avoided in patients with heart failure owing to concerns about operative risk and peri-operative complications.[59] However, patients with mitral regurgitation have a significantly decreased survival at 2 years follow-up versus patients without mitral regurgitation.[11] More recently, with improvements in surgical techniques, surgical mitral annuloplasty for mitral regurgitation in the setting of heart failure has become a more popular treatment option. Bolling et al. have demonstrated the feasibility of mitral valve repair in patients with heart failure by downsizing the annulus using a flexible ring.[23] Their initial results in 48 patients who underwent restrictive mitral annuloplasty showed an early mortality rate of approximately 5% with 1- and 2-year survival rates of 82% and 71% respectively. Several recent studies have confirmed that early mortality is low (between 5 and 7%), heart failure symptoms are ameliorated, LV size and ejection fraction improve, and intermediate outcome is favorable.[24,25] However, several studies in patients treated with mitral annuloplasty demonstrated a high recurrence rate (30%) of mitral regurgitation after six months follow-up.[60,61] In contrast to these results, Bax et al. reported no recurrences of mitral regurgitation in 51 patients with ischemic LV dysfunction at 2-years follow-up.[22] Similarly, Szalay et al. reported in 121 patients with end-stage heart failure a recurrent rate of 3% with a mean mitral regurgitation grade 0.6 at 1-year follow-up.[25] The low recurrence rates in these latter studies may be associated with a more truly restrictive annuloplasty performed in these patients.

The effects of restrictive mitral annuloplasty on systolic and diastolic LV performance are relatively unknown. Bolling and coworkers hypothesized that restrictive mitral annuloplasty leads to LV systolic improvement by acute remodeling of the base of the

heart and re-establishing the ellipsoid shape.[62,63] Recent data from Bax et al. reported that 50% of patients showed significant reduction in LV end-systolic diameter over time.[22] Of note, a substantial percentage (60%) of patients in this study especially those with a preoperative LV end-diastolic diameter and LV end-systolic diameter of 65 mm and 51 mm, respectively, showed reverse remodeling at late follow-up. These findings indicate that the process of reverse remodeling may need substantial time in some patients. These issues are clinically relevant, since a reduction of LV dimensions and an increase in LV ejection fraction are associated with a favorable prognosis.[64,65] However, until now there is no randomized clinical trial that demonstrates that surgical correction of mitral regurgitation by mitral annuloplasty improves survival or leads to reverse LV remodeling. Wu and colleagues have recently demonstrated that there is no clearly demonstrable survival benefit conferred by mitral annuloplasty for significant mitral regurgitation in patients with chronic heart failure.[66] In addition, Enomoto et al. demonstrated in an animal model that mitral regurgitation might not contribute significantly to adverse remodeling suggesting that it is likely a manifestation rather than an important impetus for post-infarction remodeling.[67]

In summary, current data demonstrates that restrictive mitral annuloplasty is safe in patients with heart failure. Still, data about long-term survival benefits, recurrent mitral regurgitation, and LV reverse remodeling is inconclusive. Future prospective randomized controlled trials should answer these questions. In addition, hemodynamic studies may provide insight in the effects of restrictive mitral annuloplasty on LV systolic and diastolic function.

Surgical ventricular restoration

In patients with ischemic heart failure, structural changes like LV aneurysm, may contribute to substantial mechanical LV dyssynchrony. At least 88% of dyskinetic LV aneurysms result from anterior-septal infarctions, while the remainder follow after inferior infarction.[68] The LV nonuniformity of contraction and relaxation reduces mechanical efficiency of LV filling and ejection and contributes to diastolic and systolic dysfunction.[42,69] Furthermore, scarring and LV dilatation associated with aneurysm formation may provide a substrate for LV arrhythmias. Surgical ventricular restoration is increasingly applied in patients with heart failure and LV aneurysm. Controversy still exists regarding the question whether similar techniques may also be useful in treating patients with dilated ventricles and scarred regions of the heart when the shape is not seriously distorted by an LV aneurysm. Dor et al. described the endoventricular circular

patch plasty for LV reconstruction and demonstrated that the results of this technique were just as good in patients with akinetic regions as in patients with dyskinetic regions.[70] Several studies further advocated the use of the endoventricular circular patch technique above the simple linear technique in patients with LV aneurysm.[71,72]

Although surgical ventricular restoration is increasingly performed, it has not yet found general acceptance. Possible reasons include a lack of evidence that demonstrates improvement in morbidity and mortality with this technique in patients with ischemic heart failure. A recent retrospective analysis has demonstrated that the outcome was significantly better in patients who received CABG plus surgical ventricular restoration compared to patients who received CABG alone.[73] In most studies, operative mortality ranges between 0 and 20% and the reported 1- and 5-year survival hovers around 85% and 70%, respectively.[74-76] Patients in these studies had a subjective clinical benefit, as indicated by a significant improvement of their NYHA classification (from III-IV to I-III) with significant improvement of LV ejection fraction and reduction in end-diastolic and end-systolic volumes. However, none of these studies has been conducted in a prospective, randomized manner with an acceptable number of patients.

Initial results with surgical ventricular restoration have recently been published in a 3-year observational study by the RESTORE group.[26] The surgeons in this international group performed the surgical ventricular restoration in 662 patients who mainly had akinetic defects of the anterior wall. The results have been promising, although any conclusions on the incremental efficacy of surgical ventricular restoration relative to CABG must be made with caution because of the absence of a control group in the RESTORE registry. LV ejection fraction was improved on an average of 10% and all patients had significant improvement of NYHA classification. Despite these promising data, Elefteriades et al. demonstrated a similar improvement in contractile function in a small and selected group of patients who underwent isolated CABG.[77] Therefore, controversy remains regarding the question whether surgical ventricular restoration or CABG alone provide additional benefit above medical therapy. These questions will not be answered unless they are investigated in a prospective randomized fashion. The STICH (Surgical Treatment for IschemiC Heart failure) trial is the first prospective randomized study in the history of coronary artery surgery to specifically assess the potential benefit of CABG in patients with ischemic heart failure. This trial is designed and powered to answer fundamental clinical questions regarding the ischemic heart failure population. The trial tests two hypotheses: (1) CABG combined with intensive medical therapy improves long-term survival compared with medical therapy alone and

(2) surgical ventricular restoration combined with CABG and medical therapy improves survival free of cardiac events compared to CABG and medical therapy without surgical ventricular restoration.

Several studies demonstrated beneficial hemodynamic effects of surgical ventricular restoration in patients with ischemic heart failure. These studies reported acute improvements in contractile state, energy efficiency, and relaxation, together with a decrease in LV mechanical dyssynchrony in patients with heart failure.[78,79] Buckberg et al. emphasized the importance of considering size, shape and LV fiber orientation in patients with heart failure.[80-82] It has been proposed that surgical ventricular restoration of the dilated LV will restore myofibers in the diseased ventricle to a normal, oblique orientation.[83] However, this issue remains still controversial and data supporting these claims are lacking.[84,85]

In conclusion, despite the promising results of these alternative therapies in patients with end-stage heart failure, the working mechanisms and effects on LV function are relatively poorly defined.

AIM AND OUTLINE OF THE THESIS

The aim of this thesis was to study the hemodynamic effects of CRT, surgical ventricular restoration and restrictive mitral annuloplasty in patients with end-stage heart failure by use of pressure-volume loops derived by the conductance catheter. An important rational for this approach is that pressure-volume derived indices reflect intrinsic systolic and diastolic LV function in a relative load-independent fashion, whereas conventional methods are importantly influenced by changes in loading conditions. This may be particular relevant during cardiac procedures such as valve surgery and surgical ventricular restoration where loading conditions may change substantially. Moreover, it is increasingly recognized that mechanical dyssynchrony, importantly influence LV function and that benefit of CRT and surgical therapies may be partly explained by reduced mechanical dyssynchrony. The ability of the conductance catheter to quantify mechanical dyssynchrony in an objective and on-line fashion may therefore add to the diagnostic power of this methodology.

The quantification of effects of these therapies on global and intrinsic LV systolic and diastolic function and mechanical dyssynchrony may provide further insight in the

working mechanisms of these therapies. This may help to explain improved survival, functional status and exercise tolerance in heart failure patients treated with these therapies. In this thesis, acute effects of surgical therapies on LV function were assessed by peri-operative measurements by the conductance catheter in the operating room, whereas chronic effects of CRT and surgical therapies were assessed in the catheterization laboratory at baseline and at 6 months follow-up.

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CHAPTER 2

Peri-operative assessment of left ventricular function by pressure-volume loops using the conductance catheter

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ABSTRACT

Interpretation of peri-operative measurements of cardiac function during cardiac surgery is complicated by changes in loading conditions induced by anesthesia, cardiopulmonary bypass (CPB) and the surgical procedure itself. Quantification of left ventricular (LV) function by pressure-volume relations as obtained by the conductance catheter would be advantageous because load-independent indices can be determined. Accordingly, we evaluated methodological aspects of the conductance catheter technique and documented LV function pre- and post-CPB in 8 patients undergoing CABG. LV pressure-volume loops by TEE-guided trans-aortic application of the conductance catheter were obtained at steady state and during preload reduction by temporary occlusion of the inferior caval vein. All patients remained hemodynamically stable and no complications occurred. Complete data were acquired within 15 minutes pre- and post-CPB. Cardiac output (5.2±1.3 to 6.0±1.4 L/min) and LV ejection fraction (46±17 to 48±19%) did not change, but end-diastolic pressure increased significantly post-CPB (8±2 to 16±7mmHg, $p<0.05$). Load-independent systolic indices remained constant (end-systolic elastance: 1.31±1.20 to 1.13±0.59mmHg/mL). Diastolic function changed significantly post-CPB, as Tau decreased from 64±6 to 52±5ms ($p<0.05$) and the chamber stiffness constant increased from 0.016±0.014 to 0.038±0.016/mL ($p<0.05$). We conclude that the conductance catheter method provides detailed data on peri-operative myocardial function. Therefore, the conductance catheter method may be used to evaluate the effects of new surgical and anesthetic procedures for which the present data may serve as reference data.

INTRODUCTION

Recently, several new approaches were introduced in cardiac surgery such as restrictive mitral annuloplasty, endoventricular circular patch plasty, and off-pump CABG. Generally, the efficacy of new techniques is assessed by long-term follow-up of patients. However, the acute effects on left ventricular (LV) function of these procedures are not well documented and may be predictive for long-term outcome. Peri-operative assessment of LV function may allow better evaluation of new surgical procedures and may help post-operative management by providing insight in the cardiac pathophysiology. During cardiac surgery cardiac output, aortic pressure, central venous

pressure and the pulmonary arterial wedge pressure usually assess hemodynamic status. In addition, transesophageal echocardiography (TEE) is used to assess regional contractile function. However, interpretation of all these parameters is complicated by their load-dependency. Therefore, given the substantial changes in loading conditions that may occur during the operation, these parameters may not reflect intrinsic myocardial function. Pressure-volume relations as obtained by the conductance catheter, have been shown to provide load-independent indices of systolic and diastolic function.[1,2] Accordingly, the aim of present study was twofold. Firstly, we described and evaluated the application of the conductance technique in the operating room including catheter placement, calibration procedures and heart rate-controlled measurement of systolic and diastolic pressure-volume relations. Secondly, we compared various indices of LV function before and after CPB in patients undergoing CABG. These data obtained in patients with relatively normal LV function may provide reference data for future studies in which more complex cardiac surgical procedures are evaluated.

METHODS

The study protocol was approved by the Local Ethics Committee and all patients gave informed consent. Eight patients with multivessel coronary artery disease elected for CABG were included. Patients with severely depressed LV function (LVEF < 35%), unstable angina or atrial fibrillation were excluded.

Anesthesia

After 2mg lorazepam as sublingual premedication two hours before surgery, all patients received total intravenous anesthesia with target-controlled infusion of propofol, remifentanil and sufentanil.[3-5] Hypnotic state was monitored with a Bispectral Index (BIS) monitor (Aspect medical systems, Newton, MA). Induction of anesthesia was started with targeted concentration of 1.5µg/ml propofol and 3ng/ml remifentanil. Before intubation the remifentanil-targeted concentration was increased to 9ng/ml and the targeted propofol concentration to 2µg/ml. 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 $PaCO_2$ between 4.5 and 5.5kPa (34-41mmHg). 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 monitor cardiac function and facilitate positioning of the conductance catheter peri-operatively a multiplane TEE-probe was inserted.

Conductance catheter technique

We used a 7F integrated pressure-conductance catheter (CD-Leycom, Zoetermeer, The Netherlands) incorporating a solid-state pressure sensor and 12 electrodes with an inter-electrode spacing of 10mm. A pigtail facilitates placement through the aortic valve and positioning within the LV apex (Figure 1).

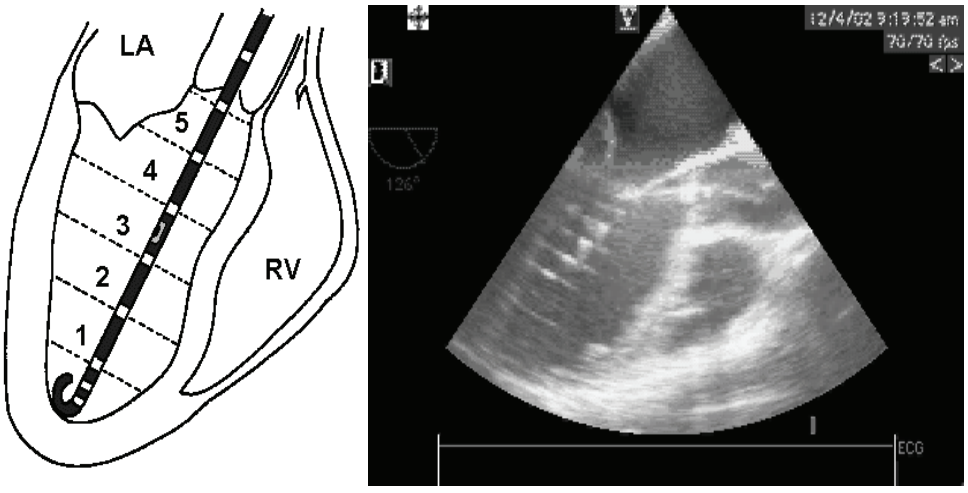

Figure 1. Left: The optimal position of the conductance catheter along the long-axis of the left ventricle. Right: the conductance catheter viewed by long-axis view by TEE peri-operatively

The catheter is connected to a Leycom Cardiac Function Lab (CFL) signal-processor. Between the two most proximal and two most distal electrodes a dual electric field (20kHz, 30μA) is generated.[6] The remaining 8 electrodes are used to measure 5 segmental volume signals. The user may select from three settings the best match with the LV long axis: by skipping electrodes one or two 1-cm segments may be converted to 2-cm segments thereby extending the effective length of the catheter. The optimal setting is selected based on inspection of the segmental volume signals. An aortic

volume signal is easily distinguished from a ventricular signal because it resembles an aortic pressure signal and is out-of-phase with the ventricular volume signals. The segmental conductance's are summed to yield total conductance G(t) and, taking into account the specific resistivity of blood and the electrode spacing, converted to a time-varying volume signal, V(t), which follows through the equation:

$$V(t) = (1/\alpha)\cdot(rho\cdot L^2)\cdot(G(t)-G^P)$$

where α is a slope factor, L is the inter-electrode spacing, rho is the specific resistivity of blood measured from a 5ml blood sample using a special 4-electrode cuvette connected to the CFL, and G^P is the parallel conductance. G(t) is the sum of the conductance of the blood in the LV and G^P. The latter results from the conductance of the ventricular wall, other cardiac chambers and to some extent all electrically conductive structures outside the LV cavity. Baan et al. devised a method to determine G^P by injecting a small bolus (7ml) of hypertonic saline solution (10%) in the distal port of the pulmonary artery catheter.[1] The highly conductive saline transiently changes blood conductivity, which is measured only in the LV. By analyzing the conductance signal registered during passage of the bolus through the LV, G^P can be determined.[1] The correction volume (V_c) corresponding to G^P equals:

$$V_c = (rho\cdot L^2)\cdot G^P$$

After correction for G^P the volume signal is directly proportional to actual ventricular volume, but generally underestimates true volume by a fixed factor. There are two main causes for this underestimation. First, there may be a mismatch between the measured segments and the LV long-axis. Secondly, the conversion of conductance to volume assumes that the electric field is homogeneous within the cavity. In reality this is not entirely the case resulting in underestimation. The development of dual field excitation has substantially improved electric field homogeneity, but some underestimation remains especially in large hearts.[6] To correct for this underestimation the factor α was introduced, which is obtained by comparing conductance-derived stroke volume (SV) with an independent measure of SV. In most studies α is calculated by dividing SV of the conductance catheter by SV obtained by thermodilution: $\alpha = SV_{conductance}/SV_{thermodilution}$. In the present study we used the 'stat' cardiac output

measurements recorded from a Vigilance® Continuous Cardiac Output Monitoring System (Edwards Lifesciences, Uden, The Netherlands).

Instrumentation and surgical technique

After harvesting bypass material, the pericardium was opened and epicardial pacemaker leads were placed on the right atrium. A caval tourniquet was applied around the inferior caval vein to perform temporary preload reductions by caval vein occlusion. After systemic heparinization, a sheath (F8, Cordis, Roden, The Netherlands) was introduced in the ascending aorta for placement of the conductance catheter. Subsequently the conductance catheter was inserted into the LV and positioned along the long axis toward the LV apex. Catheter introduction and positioning was guided and verified by TEE and inspection of the segmental conductance signals. Positioning was aimed at locating the pigtail in the apex while the most proximal electrodes should be located just above the aortic valve. Measurements were started if 5 segmental LV volume signals were obtained.

Measurement protocol and data acquisition

The protocol included measurements at a paced heart rate of 80bpm pre- and post-CPB. If intrinsic rate was above 80bpm the pacemaker was set slightly above the intrinsic rate. Pressure-volume loops were measured at steady state and during transient caval vein occlusion (typical pressure drop of 20mmHg within 5-10s) in order to obtain systolic and diastolic pressure-volume relationships. The ventilator was turned off to exclude the effects of respiration. Rho was measured just before data acquisition, both before and after CPB. Additional acquisitions (before and after CPB) were done for determination of G^P after injection of 7ml 10% hypertonic saline solution through the distal port of the pulmonary artery catheter. Independent cardiac output measurements by thermodilution were obtained during steady state. The thermodilution catheter provides update measurements approximately every minute indicating average cardiac output over the preceding period. An analog signal reflecting the 'stat' signal was recorded simultaneously with the pressure-volume signals for off-line calculation of α.

Data analysis

Baseline hemodynamic data were calculated from steady state pressure-volume loops: heart rate (HR), end-systolic volume (ESV), end-diastolic volume (EDV), end-systolic pressure (ESP), end-diastolic pressure (EDP), cardiac output (CO), stroke volume (SV),

stroke work (SW), maximal and minimal rate of LV pressure change (dP/dt_{MAX}, dP/dt_{MIN}), ejection fraction (EF) and the relaxation time constant (Tau). Tau, reflecting the early active relaxation process, was calculated as the time constant of mono-exponential pressure decay during isovolumic relaxation. The isovolumic period was defined as the period between the time-point of dP/dt_{MIN} and the time-point at which dP/dt reached 10% of the dP/dt_{MIN} value. From pressure-volume loops during caval vein occlusion indices of systolic and diastolic function were derived. For systolic function, the end-systolic pressure-volume relation (ESPVR), the dP/dt_{MAX}-EDV relation and the preload recruitable stroke work relation (PRSW: SW versus EDV) were determined as for diastolic function the chamber stiffness constant (CS) was determined. The systolic relationships were characterized by their slope and volume intercept. The slope of the ESPVR (Ees) as well as its volume intercept, at a fixed systolic pressure of 75mmHg (V75) have been shown to be indices of contractility, largely independent of loading conditions.[7,8] The ESPVR was determined by linear regression of end-systolic pressure-volume points obtained during caval vein occlusion. Similarly, the PRSW slope (S-PRSW) was determined by plotting SW against EDV and the same was done for the slope of the dP/dt_{MAX}-EDV relation (S-dP/dt). The slopes of these two relationships have also been shown to reflect contractility.[9,10] The chamber stiffness constant (CS) was determined by exponential regression of the end-diastolic pressure-volume relation (EDPVR) by means of the following equation:

$EDP = y_o + A.e^{CS \cdot EDV}$

where y_o is the pressure asymptote and A is a constant.

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

Patients

Patient characteristics are shown in table 1. All patients underwent normothermic CPB and received intermittently antegrade warm oxygenated blood cardioplegia. The surgical procedure and postoperative intensive care stay were uncomplicated. Peri-operative and post-operative ECGs did not show signs of ischemia. Furthermore

troponin T levels were measured at least up to 12 hours post-surgery and did not exceed 0.6 μg/L at any time point indicating that in none of the patients peri-operative myocardial infarction occurred.[11]

Table 1. Patient-characteristics

Variable	Mean ± SD	Range
Age (yr.)	63 ± 11	42-75
Male sex (%)	88	-
EF (%)	58 ± 9	40-68
CPB-time (min)	100 ± 31	60-162
Aox-time (min)	70 ± 22	49-80
Duration of surgery (min)	301 ± 72	200-381
Grafts (number)	4 ± 1	2-5

EF = Ejection fraction; CPB = Cardiopulmonary bypass; Aox = Aortic cross clamp

Technical considerations

In all patients complete pressure-volume data were acquired before and after CPB. Preparation of the pacemaker wires, application of the caval tourniquet and introduction of the sheath were uncomplicated. The introduction of the conductance catheter through the aortic valve and catheter placement required careful monitoring by use of TEE (figure 1) to reduce the risks of perforation and to obtain an optimal catheter position.

The optimal transesophageal long-axis view was obtained with the multiplane TEE-probe from the midesophageal transducer position with the array at 135 º of rotation. Occasionally, placement of the catheter within the apex caused ventricular extrasystolic beats, but a stable catheter position without arrhythmias could always be obtained. After the pre-CPB measurements the conductance catheter was withdrawn, rinsed with normal saline, and placed on a sterile table to be re-used post-CPB. During the CPB, the introducer sheath on the ascending aorta was used to infuse cardioplegia. Catheter placement and measurements before and after CPB were completed within approximately 15 minutes.

Calibration of the conductance measurements

Rho measurements, assessment of V_c and α were performed in each patient before and after CPB. Results are summarized in table 2. Rho decreased significantly post-CPB as

expected due to hemodilution. On the average, V_c and α were not significantly altered post-CPB but showed a substantial interindividual variability.

Table 2. Conductance catheter calibration factor, hemoglobin and hematocrit, pre- and post CPB

Variable	Pre-CPB	Post-CPB	P
V_c (ml)	129 ± 54	139 ± 50	0.696
α	0.54 ± 0.24	0.67 ± 0.21	0.267
Rho (ohm·cm)	129 ± 23	105 ± 9	0.015
Hemoglobin (mmol/L)	7.5 ± 1.1	5.3 ± 0.7	<0.001
Hematocrit (%)	0.40 ± 0.05	0.26 ± 0.03	<0.001

V_C = Parallel conductance correction volume; α = slope factor; rho = blood resistivity

Hemodynamic data

Measurements were obtained in each patient before and after CPB. Figure 2 shows typical steady state volume, pressure and dP/dt signals and pressure-volume loops.

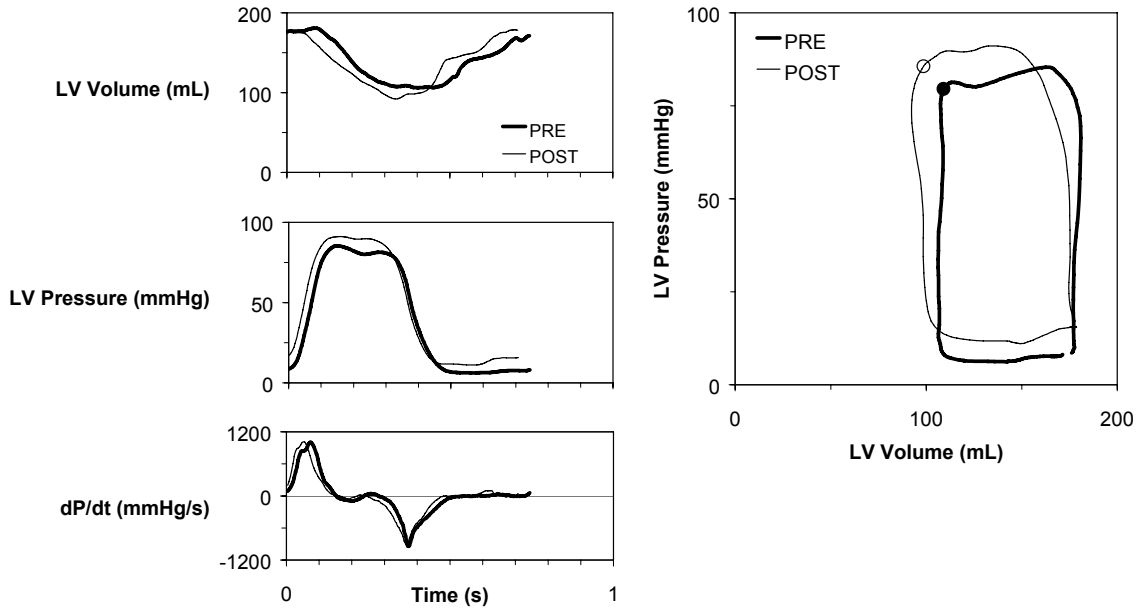

Figure 2. Typical steady state volume, pressure and dP/dt signals, and corresponding pressure-volume loops before (PRE: thick lines) and after (POST: thin lines) cardiopulmonary bypass (CPB). As shown by the open and closed circles marking the end-systolic pressure-volume points on the pressure-volume loops, ESP increased and ESV decreased after CPB indicating increased systolic function. Diastolic function, however, appears decreased since diastolic pressure is higher at any given diastolic volume. However, while the average values for the whole group showed the same trend, the changes in ESV and ESP did not reach statistical significance

Systolic and diastolic pressure-volume relations (ESPVR, EDPVR, PRSW and dP/dt_{MAX}-EDV) in the same patient derived from pressure-volume loops during caval vein occlusion are shown in Figure 3.

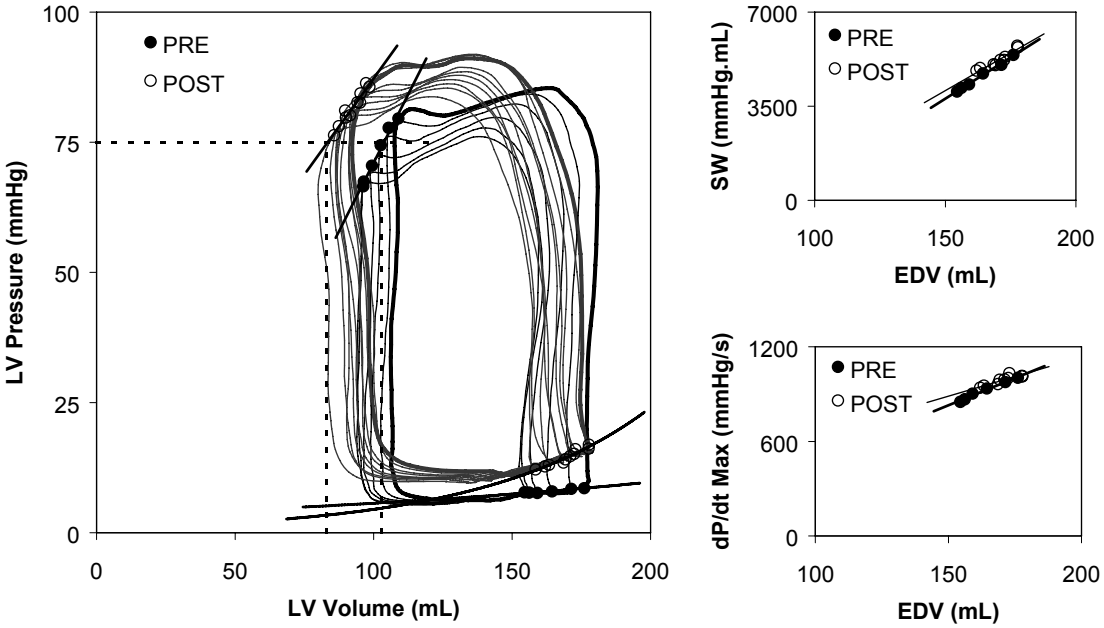

Figure 3. Example of pressure-volume relations derived by caval vein occlusion before and after CPB. The ESPVRs (left panel) show the increased contractile performance after CPB in this patient: although Ees is slightly decreased, the position of all end-systolic P-V points to the left and above the pre-CPB ESPVR suggests higher contractility. The dotted lines indicate the position of the ESPVR at 75-mmHg (V75). The same holds for the PRSW relation (upper-right panel) and the dP/dt_{MAX}-EDV relation (lower-right panel) although the differences are much less pronounced. The EDPVRs (left panel) provide clear evidence for substantial increase in chamber stiffness after CPB, as observed in all patients. As shown in table 3, the average position and slope of the ESPVR were not significantly altered after CPB in this group of patients

All patients had sinus rhythm and were paced at 80-90bpm during measurements. Hemodynamic data are summarized in table 3: Only EDP, Tau and CS changed significantly post-CPB

DISCUSSION

Assessment of peri-operative ventricular function during cardiac surgery is complicated by the fact that substantial changes in loading conditions may occur. Therefore the quantification of systolic and diastolic function requires load-independent indices, which can be determined from ventricular pressure-volume relations as obtained by the

conductance catheter. Accordingly, the purpose of this study was twofold: we evaluated methodological aspects of peri-operative application of the conductance catheter and documented changes of various indices of LV function pre- and post-CPB in patients undergoing CABG.

Table 3. Hemodynamic measurements before and after CPB

Variable		PRE-CPB	POST-CPB	t-test
		Mean ± SD	Mean ± SD	p
HR	bpm	82 ± 3	85 ± 4	0.024
CO	L/min	5.2 ± 1.3	6.0 ± 1.4	0.293
EF	%	46 ± 17	48 ± 19	0.521
SV	mL	64 ± 14	72 ± 18	0.402
SW	mmHg·L	4.5 ± 0.9	5.1 ± 1.4	0.364
ESV	mL	109 ± 93	99 ± 57	0.625
EDV	mL	169 ± 104	164 ± 51	0.845
ESP	mmHg	73 ± 9	83 ± 15	0.198
EDP	mmHg	8 ± 2	16 ± 7	0.004
dP/dt_{MAX}	mmHg/s	926 ± 224	1016 ± 183	0.226
dP/dt_{MIN}	mmHg/s	-825 ± 127	-958 ± 147	0.093
Tau	ms	64 ± 6	52 ± 5	0.001
V75	mL	104 ± 10	87 ± 13	0.216
Ees	mmHg/mL	1.31 ± 1.20	1.13 ± 0.59	0.496
S-dP/dt	mmHg/s/mL	6.9 ± 3.7	6.3 ± 3.7	0.524
S-PRSW	mmHg	62 ± 35	59 ± 24	0.822
CS	1/mL	0.016 ± 0.014	0.038 ± 0.016	0.017

CO: cardiac output; EF: ejection fraction; SV: stroke volume; SW: stroke work; ESV: end-systolic volume (mL); EDV: end-diastolic volume (mL); ESP: end-systolic pressure; EDP: end-diastolic pressure (mmHg); Tau: relaxation time constant, V75: ESPVR volume intercept (at ESP=75 mmHg); Ees: end-systolic elastance; S-dP/dt: slope of dP/dt_{MAX} – EDV relation; slope of the PRSW relation; CS: chamber stiffness constant

Methodological aspects

Previous studies have extensively shown that the conductance catheter can be applied to obtain pressure-volume relationships. Although most patient studies were performed in

the catheterization laboratory, several groups have demonstrated feasibility of the technique in the operating room under various conditions.[12-14] Consistent with these previous studies, our study demonstrates that peri-operative pressure-volume measurements by the conductance catheter can be used to quantify detailed intrinsic systolic and diastolic function within an acceptable time-window. Measurements were uncomplicated and no technical difficulties during instrumentation; catheter placement and loading interventions were encountered. New technical aspects of our study were the use of retrograde insertion of the conductance catheter using TEE guidance compared to the trans-mitral approach used in previous studies in the operating room. Both approaches may have theoretical advantages and disadvantages: The trans-aortic approach provides a better match of the catheter position with the LV long axis. Compared with the anterograde placement this gives a better registration especially of the volume changes in the basal segments. In contrast anterograde placement through the mitral valve may complicate interpretation of segmental volume signals because of changes in the mitral valve plane during ejection and filling. On the other hand with retrograde placement eccentric (antero-medial) displacement of the catheter at the base of the heart may occur but the electric field is such that the measurement electrodes will move approximately parallel to the equipotential planes field and thus the eccentric movement is unlikely to strongly influence the conductance signal. Another reason for using the trans-aortic approach is that we aim to apply this methodology in future studies to evaluate the effects of mitral valve surgery, in which case placement through the aortic valve is clearly preferable. Furthermore we analyzed the changes in the calibration factors. As a disadvantage, substantial between-patient variability was found for calibration factors (rho, α and V_c) indicating the need for careful assessment of these factors in each individual patient. In addition, after CPB calibration factors rho and, to a lesser extent α and V_c, were changed due to reduced hematocrit, fluid shifts and possibly altered catheter position with re-insertion. Although the average α and V_c were not significantly changed, substantial differences were present in individual patients indicating that re-assessment is required at the various stages of surgery. Besides influencing between and within-patient variability, the calibration factors importantly determine the absolute accuracy of the conductance-derived volumes. Calibration factors α and V_c are both obtained by means of indicator-dilution methods: thermodilution and, respectively, saline dilution. Thermodilution is widely used in the surgical setting and the accuracy is generally found to be acceptable.[15] In the present study we used 'stat' continuous cardiac output measurements using a thermal filament

catheter which has been shown to have accuracy comparable to the bolus injection method.[16,17] The saline dilution method has been used extensively to obtain parallel conductance and was found to be accurate with a slight tendency to underestimate parallel conductance obtained by alternative methods.[18] An important advantage of these indicator-dilution methods compared to imaging modalities such as TEE is that they do not require assumptions regarding the geometry of the ventricle. This may be relevant especially when comparing conditions in which geometrical changes would be anticipated such as after ventricular reconstruction or mitral valve surgery. Furthermore the inter- and intra-observer variability of indicator-dilution methods is very limited.

Physiological aspects

Our main physiological findings were that systolic function was unchanged after CPB in these patients undergoing CABG, whereas early relaxation was improved and diastolic stiffness was increased. Previous pressure-volume studies comparing pre- and post-CPB cardiac function in patients undergoing CABG have shown conflicting data. Schreuder et al. reported unchanged systolic function and increased diastolic stiffness, while Wallace et al. found a decrease in systolic function, but no changes in relaxation or diastolic stiffness.[13,14] Both studies used cold cardioplegia whereas our study was performed with warm blood cardioplegic arrest, which may explain the preserved systolic function in our study as compared to the decrease found by Wallace et al. The unchanged systolic function found by Schreuder et al. may be explained by the fact that during their pre-CPB measurement the temperature was lowered below 35^{O}C, which according to a recent study significantly reduces Ees by approximately 50%. [19] Since the post-CPB measurements in Schreuder's study were done at 37^{O}C this may have masked an actual reduction in systolic function. With regard to diastolic function all studies report an increase in diastolic stiffness although in Wallace's study this effect did not reach statistical significance.[14] Also in Schreuder's study the increase was less pronounced as compared to our study (39% increase vs. 138%).[13] However, Schreuder et al. described the end-diastolic pressure-volume relation as linear, whereas we derived the diastolic stiffness constant from an exponential relation. The increase is most likely due to myocardial edema post-CPB as myocardial lymph flow has been shown to almost cease during cardioplegic arrest.[20] De Hert et al. have shown that a more rapid normalization of diastolic stiffness may be obtained by optimizing preload conditions prior to weaning from CPB.[21] Furthermore, Allen et al. demonstrated that increasing contractility by dobutamine infusion enhanced myocardial lymphatic function, thus

speeding edema removal post-CPB.[22] Thus, for patients who are difficult to wean from CPB due to increased diastolic stiffness, inotropic support could be considered. However it should be used with caution because it may adversely affect energetics, raise heart rate, and induce ischemia.[23] In addition several pharmacological substances added to the cardioplegia composition have been shown to be associated with reduced edema formation.[24-26] Remarkably, although diastolic stiffness was increased, early relaxation was improved in our study as shown by the significantly reduced Tau. After revascularization, enhanced oxygen dependent re-uptake of calcium into the sarcoplasmic reticulum would indeed be expected to improve active relaxation.[27] Our findings are consistent with the results of Humphrey et al. who demonstrated a reduced Tau post-CPB in patients undergoing CABG.[28] In contrast, De Hert et al. found an increased Tau in a similar patient group.[21] Differences may be due to the applied anesthetic and cardioplegic protocol which influence post-CPB relaxation directly or indirectly via changes in contractility or loading, which are tightly coupled with relaxation.[23,29] Thus unchanged or even increased Tau as found in some studies may be related to post-CPB changes in systolic function and/or loading conditions. In our study EDV, ESP, dP/dt_{MAX} and Ees were not significantly altered after CPB, whereas De Hert et al. report a reduced dP/dt_{MAX} indicating reduced contractile state.[21]

Comparison with TEE

As an alternative to invasive volume measurements several groups have used TEE to obtain on-line area determination.[30-33] This method is less invasive but when used to construct pressure-area loops it still requires a LV catheter for pressure measurements, and a loading intervention. Schmidlin et al. tested whether pressure-area relations may be used as a surrogate for pressure-volume relations to detect changes in contractile state and they concluded that pressure-area analysis provides the same changes as pressure-volume analysis.[33] However the calculations derived from area estimates have several limitations. During the cardiac cycle the through-plane motion of the LV complicates volume calculations by short axis area estimates. This effect is even more prominent during acute loading interventions. On the contrary, the intraventricular placement of the conductance catheter provides on-line volume measurements of almost the whole ventricle unaffected by translations or rotations of the heart within the thorax. In general, on-line area determination by TEE requires optimal image quality and the stability and reproducibility of measurements is more successful at higher preload conditions by minimizing effects of tracing errors.[31] Area estimates derived during caval

vein occlusion could become very small thereby decreasing precision of the digital echocardiographic quantification method for calculation of pressure-area relations. In addition the precision is reduced in the presence of regional wall motion abnormalities.[30] Conventional assessment of diastolic function by TEE (i.e. without simultaneous LV pressure measurement) has two disadvantages compared with the conductance catheter method. First, assessment of both active and passive components requires two separate TEE views, being the midpapillary esophageal long-axis and transgastric short-axis view, respectively.[32] Second, the active diastolic relaxation measured by mitral Doppler flow analysis is heart-rate and load-dependent.

In conclusion, despite the above limitations, the limitations of TEE are outweighed by its proven clinical value to visualize the endoventricular wall and to quantify segmental wall motion. On the other hand, the important value of the conductance catheter is that it yields accurate, load-independent quantitative data on basic systolic and diastolic function. The possibility to measure these fundamental quantities in addition to the data provided by TEE may prove to be important in selected patient-groups and is ideal to evaluate e.g. new surgical techniques or anesthetic agents or procedures. The physiological effects on systolic and diastolic function reported in this study will be useful reference data for future studies in patients with depressed LV function undergoing cardiac surgery.

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LETTER TO THE EDITOR

Left ventricular function after cardiopulmonary bypass is related to the length-dependent regulation of myocardial function

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We read with interest the paper of Tulner and colleagues, in which they reported, in eight coronary surgery patients, the use of the conductance catheter method for the peri-operative assessment of left ventricular (LV) function.[1] After cardiopulmonary bypass (CPB), the authors observed a preserved systolic function, an acceleration of LV pressure fall, and an increase in end-diastolic pressure (EDP). They suggested that these data may constitute useful reference values for further studies in patients undergoing cardiac surgery. We think that some caution is indicated with respect to this statement.

Recovery of LV function after CPB is a complex phenomenon and various patterns have been described over the years, most of them reporting a transient decrease in cardiac function. Different factors may be responsible for this variability. Apart from differences in patient population and cardioprotective strategies, specific weaning procedures and the choice of the anesthetic regimen may also influence post-CPB myocardial recovery. For instance, early restoration of preload conditions can prevent the transient depression of both systolic and diastolic dysfunction after weaning from CPB (ref. 30 in the article by Tulner et al.).[2] Similarly, the use of a volatile anesthetic regimen was associated with a better early recovery of myocardial function than a total intravenous regimen.[3,4]

More important however is the individual variability in cardiac functional reserve. It has been shown in coronary surgery patients that an increase in cardiac load resulted in a variable hemodynamic response that could not be explained by differences in preoperative variables. Some patients showed an improvement, whereas other patients showed either no change or even an impairment of LV function. These patients developed a decrease in maximal rate of pressure development (dP/dt_{max}), a delayed myocardial relaxation (increase in tau) with enhanced load dependence of LV pressure fall, and a major increase in EDP. These patients showed systolic and diastolic

dysfunction post-CPB, and necessitated inotropic support to be weaned from CPB.[5] This latter response has been attributed to a deficient length-dependent regulation of myocardial function.[6] On the other hand, patients who developed improvement of myocardial function with an increase in cardiac load (manifested by an increase in dP/dt_{max}, an acceleration of LV pressure fall with a decrease in tau, less load dependence of LV pressure fall and a minor change in EDP), typically showed no (or only minor) decrease in myocardial function post-CPB.[5]

In view of these data, it seems that the results reported by Tulner et al. concern a subgroup of patients with good cardiac functional reserve and an adequate length-dependent regulation of myocardial function, resulting in a preserved myocardial function post-CPB. Therefore, this particular response, although present in some patients, cannot be withheld as the sole reference for the patient population undergoing coronary surgery with CPB.

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IN RESPONSE

We thank De Hert and Van der Linden for their insightful comments on our paper and we would like to respond on some of the issues brought forward.[1] The aim of our study was two-fold: First to describe our approach to quantify peri-operative LV function, and second to obtain a reference data set for future studies in patients undergoing cardiac surgery. The comments of De Hert and Van der Linden focus on the latter aspect of our study.

We fully agree that the published literature indicates a substantial variability in recovery of LV function after cardiopulmonary bypass and we acknowledge the extensive list of possible factors influencing this variable outcome. In fact, this is exactly the reason why we felt it was necessary to generate a data set that would be applicable to the anesthetic and cardioprotective approach followed in our institute. Specifically, we use low-dose target-controlled infusion of propofol, remifentanil and sufentanil, and intermittent antegrade warm-blood cardioplegic arrest during normothermic cardiopulmonary bypass. The metabolic advantages of this approach have already been published, but few data are available on the acute hemodynamic effects. Our study was performed in patients with relatively preserved LV function undergoing elective CABG, to ensure that the possible changes in LV function could be contributed mainly to the effects of anesthesia and cardioplegic arrest, rather than to the surgical intervention. This selection may partly explain the preserved post-operative systolic function in our patient group. However, De Hert et al. studied a similar patient group and reported a more variable outcome that could not be explained by pre-operative LV function.[2] Therefore differences in anesthesia and cardioplegic approaches between our study and the studies by De Hert et al. may need to be considered. One such difference is the use of normothermic arrest with blood cardioplegia in our study, whereas the studies of de Hert et al. included the use of hypothermia and crystalloid cardioplegia. This may be important because recent studies indicate less myocardial cell damage after normothermic blood cardioplegia.[3] Furthermore, the use of propofol in both studies may not be comparable because hypothermia has an important influence on propofol pharmacokinetics.[4] However, we certainly agree that extrapolation of our findings to patients with poor baseline LV function and prolonged cardiac arrest should be done with caution. But despite this, we would still conclude that the new data provided by our study constitute valuable background information when interpreting the acute

hemodynamic effects of complex surgical interventions such as LV reconstruction in heart failure patients in whom the same anesthesia and cardioplegia approach is used.

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CHAPTER 3

Quantification of left ventricular mechanical dyssynchrony by conductance catheter in heart failure patients

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ABSTRACT

Mechanical dyssynchrony is an important co-determinant of cardiac dysfunction in heart failure. Treatment, either medical, surgical, or by pacing, may improve cardiac function to a large extent by improving mechanical synchrony. Consequently the quantification of ventricular mechanical dyssynchrony may have important diagnostic and prognostic value and may help to determine optimal therapy. Therefore we introduced new indices to quantify temporal and spatial aspects of mechanical dyssynchrony derived from on-line segmental conductance catheter signals obtained during diagnostic cardiac catheterization.

To test the feasibility and usefulness of our approach we determined cardiac function and left ventricular mechanical dyssynchrony by the conductance catheter in heart failure patients with intraventricular conduction delay (n=12) and in patients with coronary artery disease (n=6) and relatively preserved left ventricular function.

The heart failure patients showed depressed systolic and diastolic function. However, the most marked hemodynamic differences between the groups were found for mechanical dyssynchrony indicating a high sensitivity and specificity of the new indices. Comparison of conductance catheter derived indices with septal-to-lateral dyssynchrony derived by tissue-Doppler velocity imaging showed highly significant correlations.

The proposed indices provide additional, new and quantitative information on temporal and spatial aspects of mechanical dyssynchrony. They may refine diagnosis of cardiac dysfunction and evaluation of interventions, and ultimately help to select optimal therapy.

INTRODUCTION

In addition to intrinsic myocardial abnormalities and abnormal loading conditions, cardiac dysfunction in heart failure patients is determined by mechanical nonuniformities (dyssynchrony), which lead to inefficient pump performance and energy expenditure. There is increasing evidence that pharmacological, surgical and pacemaker therapies of heart failure partly exert their beneficial effects by reducing left ventricular (LV) dyssynchrony. Consequently, quantification of LV dyssynchrony will provide diagnostic and prognostic data, which should help to select and guide therapy.

Currently, various indices based on magnetic resonance imaging or echocardiographic measurements are being used. In the present study we introduce indices, which quantify temporal and spatial aspects of dyssynchrony based on measurements obtained during cardiac catheterization using conductance catheter methodology. To test the feasibility and usefulness of our approach we compared data from congestive heart failure (CHF) patients with left bundle branch block (LBBB) with those from patients with coronary artery disease (CAD) who had relatively preserved LV function. In addition we compared the conductance catheter derived dyssynchrony indices with septal to lateral delay in peak systolic velocity as obtained by tissue-Doppler imaging.

METHODS

Patients

All patients gave informed consent and procedures were conducted in accordance with institutional guidelines. The investigation conforms with the principles outlined in the Declaration of Helsinki.[1] Twelve CHF patients (NYHA class III/IV) with LBBB were studied during diagnostic catheterization. Six CAD patients were studied in the operating room prior to coronary artery bypass grafting.

Protocol

CHF patients underwent diagnostic catheterization including thermodilution cardiac output, left ventriculography and coronary angiography. In addition, a conductance catheter was placed in the LV via the femoral artery, and a temporary pacing lead was positioned in the right atrium.

Prior to catheterization the CHF patients were studied by echocardiography. We performed tissue-Doppler imaging as described in detail elsewhere[2] to determine myocardial velocities in basal septal and lateral segments. The time delay between peak systolic velocity in the septum and the lateral wall was determined as an index of mechanical dyssynchrony.

CAD patients received total intravenous anesthesia with target-controlled infusion of propofol and remifentanyl (1.5-2μg/ml, resp. 5-10ng/ml blood concentration). A continuous cardiac output catheter was placed in the pulmonary artery via the jugular vein. Following midline sternotomy and before starting cardiopulmonary bypass a

conductance catheter was placed in the LV via a purse-string suture on the ascending aorta. External pacing leads were placed on the right atrium.

Measurements: The conductance catheter enables on-line measurement of 5 segmental volume ($V_{SEG,i}$) slices perpendicular to the LV long axis. We used 7F combined pressure-conductance catheters with 1-cm interelectrode spacing (CD Leycom, Zoetermeer, The Netherlands). The catheter was connected to a Cardiac Function Lab (CD Leycom) for on-line display and acquisition (sample frequency 250Hz) of segmental and total LV volumes, LV pressure and ECG. Total LV volume (V_{LV}) is obtained as the instantaneous sum of the segmental volumes. V_{LV} was calibrated using thermodilution and hypertonic saline dilution as previously described.[3] Periods of approximately 10s at a paced heart rate of 80bpm were selected for off-line analysis using custom-made software.

Global cardiac function and nonuniform mechanical performance

Global LV function was measured by cardiac index (CI), end-diastolic and end-systolic volume index (EDVI, ESVI), ejection fraction (EF), end-systolic and end-diastolic pressure (ESP, EDP), maximal and minimal rate of pressure change (dP/dt_{MAX}, dP/dt_{MIN}), and the time constant of relaxation (Tau). LV systolic elastance was estimated by ESP/ESVI, and in addition (dP/dt_{MAX})/EDVI was calculated as relatively load-independent index of systolic function.

Nonuniform LV performance was determined from the segmental LV conductance signals and characterized by the following indices:

Mechanical dyssynchrony (DYS): At each time-point a segmental signal was defined as dyssynchronous if its change (i.e. dV_{SEG}/dt) was opposite to simultaneous change in the total LV volume (dV_{LV}/dt). Segmental dyssynchrony is quantified by calculating the percentage of time within the cardiac cycle that a segment is dyssynchronous. Overall LV dyssynchrony (DYS) was calculated as the mean of the segmental dyssynchronies.[4] DYS may be calculated within each specified time-interval: We determined DYS during systole (DYS_S) and diastole (DYS_D), with systole defined as the period between the moments of dP/dt_{MAX} and dP/dt_{MIN}.

Internal flow (IF): Nonuniform contraction and filling is associated with ineffective shifting of blood volume within the LV. This 'internal flow' is quantified by calculating the sum of the *absolute* volume changes of all segments and subtracting the absolute total volume change: $IF(t) = (\Sigma|dV_{SEG,i}(t)/dt| - |dV_{LV}(t)/dt|)/2$. Note that $dV_{LV}(t)/dt$ represents the effective flow into or out of the LV. Thus, IF measures segment-to-

segment blood volume shifts which do not result in effective filling or ejection. Division by 2 takes into account that any 'non-effective' segmental volume change is balanced by an equal but opposite volume change in the remaining segments. Internal Flow Fraction (IFF) is calculated by integrating IF(t) over the full cardiac cycle and dividing by the integrated absolute effective flow.

Mechanical dispersion (DISP): In the CHF patients we expected a substantial dispersion in the onset of contraction between the segments. This dispersion was assessed by segmental lag-times, $t_{LAG,i}$, which were determined by calculating the cross-correlations between $V_{LV}(t)$ and $V_{SEG,i}(t+t_{LAG,i})$ for all systolic time-points (i.e. between dP/dt_{MAX} and dP/dt_{MIN}). For each segment we determined the $t_{LAG,i}$ which produced the highest linear correlation. Thus if $t_{LAG,i}<0$, segment *i* precedes the global ejection, and vice versa. Mechanical dispersion (DISP) was defined as 2·SD of the segmental lag-times.

Statistical analysis

All data are presented as mean±SD. Comparisons between the CAD and CHF groups were performed by unpaired t-tests. We performed receiver-operating characteristic (ROC) curve analysis to test the diagnostic performance of the various indices to discriminate the patient groups.[5] Sensitivities and specificities at the optimal cut-off point were determined. Comparison between conductance-derived and tissue-Doppler derived dyssynchrony indices was made by linear regression analysis.

RESULTS

Typical pressure-volume loops from a CAD and a CHF patient are shown in Figure 1. The bottom panel shows the global LV pressure-volume loops clearly illustrating enlarged volumes and increased end-diastolic pressure in the CHF patient. Furthermore, whereas the CAD patient displays normal isovolumic trajectories during the contraction and relaxation phases, the loops from the CHF patient show a continued decrease in volume during these phases presumably reflecting mitral insufficiency. The segmental pressure-volume loops displayed in the top panels illustrate the inefficient ventricular pump behavior of the CHF patient especially in the apical segments.

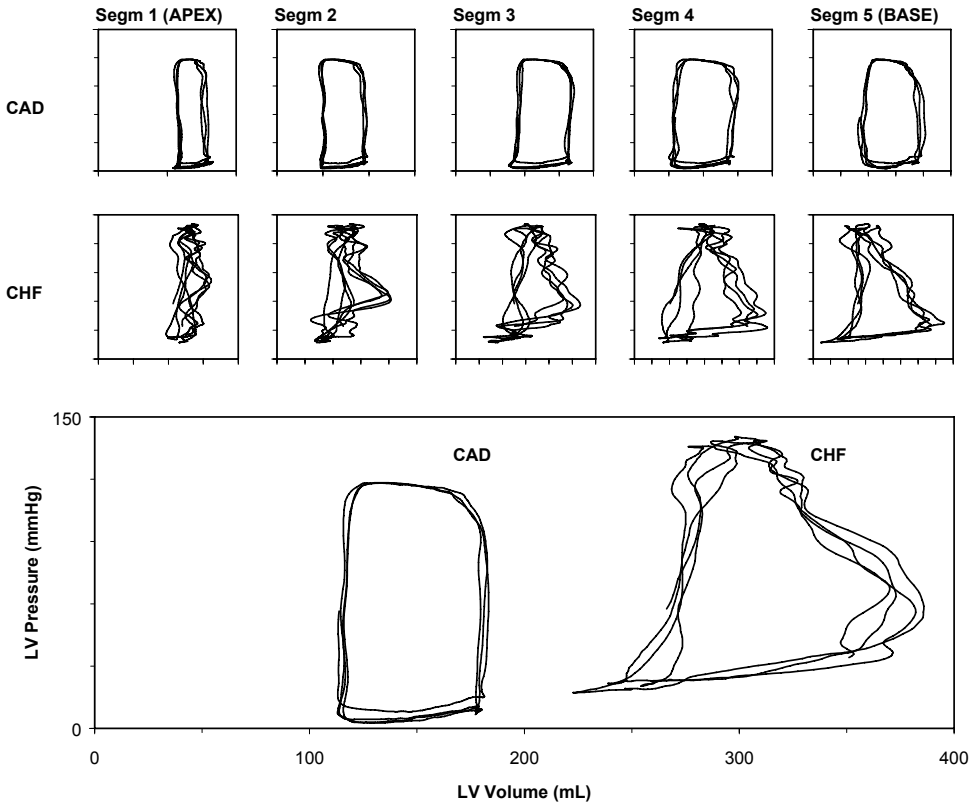

Figure 1. Segmental and global LV pressure-volume loops in typical CAD and CHF patients

The same signals are also displayed as a function of time in Figure 2. The top panels show the segmental and total LV volumes, and LV pressure. The bottom panels show calculated internal flows. Contraction and filling patterns are substantially more dyssynchronous in the CHF patient compared to the CAD patient. In the CAD patient internal flow is largely restricted to the isovolumic contraction and relaxation periods, which is consistent with normal physiology since, with mitral and aortic valves closed, LV shape changes result in internal segment-to-segment flow. In contrast, in the CHF patient substantial ineffective internal flow is present throughout the cardiac cycle.

Hemodynamic data are summarized in Table 1. EF and dP/dt_{MAX} indicate more pronounced systolic dysfunction while ESP/ESVI and (dP/dt_{MAX})/EDVI show depressed contractile state, whereas Tau and EDP indicate impaired diastolic function in CHF. Differences in EDVI, ESVI and CI were present but did not reach statistical significance. Pronounced differences between CAD and CHF were found in DYS, IFF and DISP.

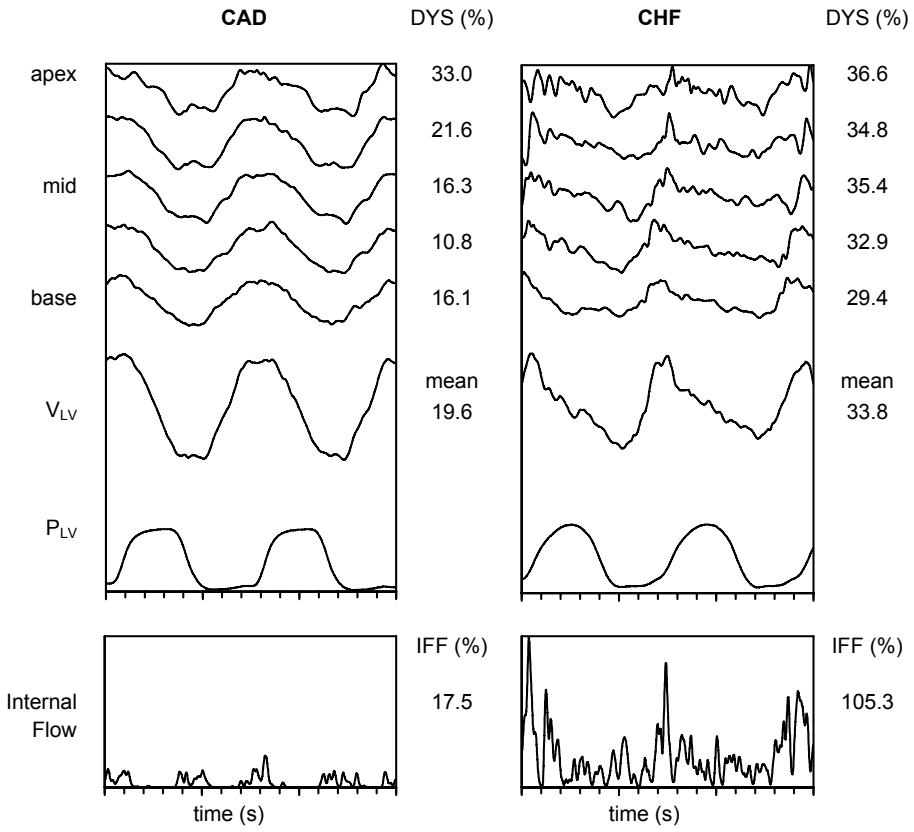

Figure 2. Typical examples of segmental and total LV volume signals and calculated internal flow in CAD and CHF patients. DYS: mechanical dyssynchrony; IFF: internal flow fraction

For both groups dyssynchrony and internal flows were highest in diastole, and the apical segments were the most affected (Figure 3). In both groups mechanical dispersion in the long-axis direction was present, but it was twice as large in CHF. Figure 3 (right panel) shows that contraction started in the basal segment and, on the average, subsequent segments (1cm-slices) followed after 5.9ms for CAD and after 12.4ms in CHF patients.

The diagnostic value of the various indices to discriminate the two patient groups was tested using ROC analysis. Table 1 shows the results with the optimal cut-off values, and corresponding sensitivities and specificities. As expected QRS duration accurately delineates the groups with a cut-off value of 107ms. The dyssynchrony indices DYS and IFF show excellent sensitivity/specificity values, which are higher than the best hemodynamic indices EF and dP/dt_{MAX}. The other hemodynamic indices show lower sensitivity/specificity reflecting a substantial overlap of the values between the two groups.

Table 1. Cardiac function, left ventricular mechanical dyssynchrony and receiver-operating characteristic (ROC) curve analysis in CAD (n=6) and CHF (n=12) patients

	Cardiac function and mechanical dyssynchrony			ROC curve analysis		
	CAD	CHF	p	cut-off	sensitivity	specificity
Gender (M/F)	5/1	9/3	.709			
Age (years)	63±7	67±9	.399			
QRS duration (ms)	86±16	186±24	<.001	107	100%	100%
CI (L/min/m^2)	2.6±0.8	2.0±0.5	.099	1.88	58.3%	100%
EDVI (mL/m^2)	73±33	107±37	.077	89	58.3%	83.3%
ESVI (mL/m^2)	45±25	74±32	.068	58	66.7%	66.7%
EF (%)	48±16	26±9	.001	37.6	91.7%	83.3%
dP/dt_{MAX} (mmHg/s)	1106±160	764±228	.005	928	83.3%	100%
$-dP/dt_{MIN}$ (mmHg/s)	1012±229	827±263	.164	797	58.3%	100%
Tau (ms)	58±9	77±16	.017	66.5	75%	100%
ESP (mmHg)	86±18	106±32	.167	91	75%	83.3%
EDP (mmHg)	9±5	18±8	.024	11.4	75%	83.3%
ESP/ESVI (mmHg/mL/m^2)	2.7±1.9	1.8±1.0	.183	1.89	66.7%	66.7%
dP/dt_{MAX}/EDVI(mmHg/s/mL/m^2)	17±7	8±4	.002	11.3	75%	83.3%
DYS (%)	19±8	32±3	<.001	19.6	100%	83.3%
DYS_S (%)	11±11	30±6	<.001	13.9	100%	83.3%
DYS_D (%)	24±6	34±2	<.001	25.7	100%	83.3%
IFF (%)	20±14	78±24	<.001	47.0	91.7%	100%
IFF_S (%)	13±19	63±30	.002	11.3	100%	83.3%
IFF_D (%)	25±12	90±29	<.001	33.1	100%	100%
DISP (%)	33±13	75±37	.026	39.9	83.3%	80%

Values given as mean±SD, p-values determined by unpaired t-tests. CI: cardiac index; EDVI, ESVI: end-diastolic and end-systolic volume index; EF: ejection fraction; dP/dt_{MAX} and $_{MIN}$: maximal and minimal rate of LV pressure change; Tau: time constant of relaxation; ESP, EDP: end-systolic and end-diastolic pressure; DYS: mechanical dyssynchrony; DYS_S, DYS_D: systolic and diastolic DYS; IFF: internal flow fraction; IFF_S, IFF_D: systolic and diastolic IFF, DISP: mechanical dispersion

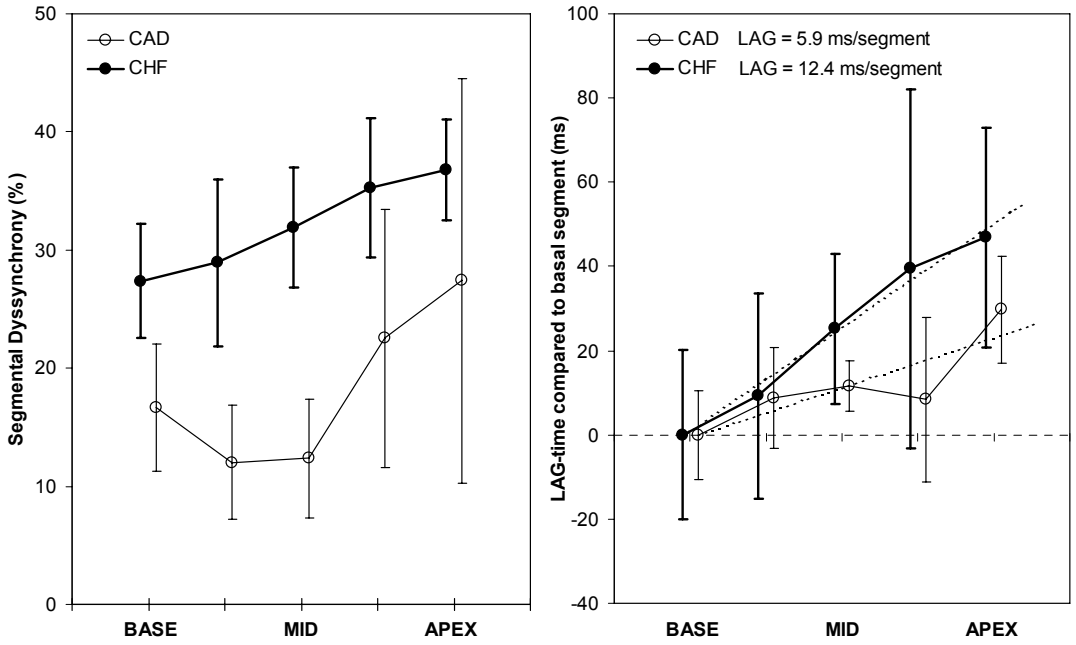

Figure 3. Average segmental dyssynchrony and dispersion lag-times in CAD and CHF patients. The inset shows the conductance catheter positioned in the LV and the division in 5 segments from apex to base

Tissue-Doppler measurements were performed in the CHF patients and revealed a significant difference in the timing of peak systolic velocities of the septum and the lateral wall. The average septal-to-lateral delay was 89±43 ms, indicating a dyssynchronous intraventricular contraction pattern. We compared the septal-to-lateral delay times with the conductance derived dyssynchrony indices using linear regression analysis. The results (Figure 4) show highly significant correlations with DYS (r^2=0.59, p=0.003) and IFF (r^2=0.63, p=0.002). The relation with DISP did not reach statistical significance (r^2=0.26, p=0.089).

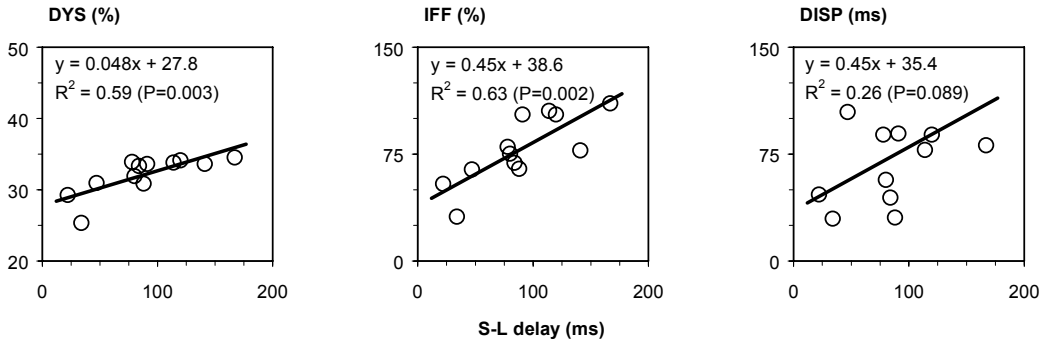

Figure 4. Linear regression of conductance catheter derived indices of mechanical dyssynchrony (DYS: mechanical dyssynchrony; IFF: internal flow fraction; DISP: mechanical dispersion) versus septal-to-lateral (S-L) delay in the timing of peak systolic myocardial velocity as obtained by tissue-Doppler echocardiography

DISCUSSION

Dyssynchrony plays a regulating role already in normal physiology, but is especially important in pathological conditions such as hypertrophy, ischemia, infarction, or heart failure.[6,7,8,9,10] Currently, cardiac resynchronization by biventricular pacing is emerging as an important therapy for heart failure.[11,12] Recently, MRI and echocardiography have been used to visualize mechanical dyssynchrony, further emphasizing the important role of mechanical dyssynchrony in cardiac dysfunction.[10,13,14-18] However, these methods are laborious and require substantial operator interaction and expertise.

We introduce novel indices to quantify dyssynchrony based on volume signals acquired with the conductance catheter during cardiac catheterization. The conductance catheter was validated previously and the segmental signals reflect instantaneous volume slices perpendicular to the LV long-axis as obtained by cine-CT.[3,19] Currently, the conductance catheter is used mainly to assess global systolic and diastolic function.[20-23] Quantification of nonuniform mechanical function and dyssynchrony may lead to a more complete diagnosis of ventricular dysfunction.[24,25] Moreover, it may guide therapy, since patients with extensive dyssynchrony are likely to benefit from resynchronization therapy.[26]

We compared CHF versus CAD patients. The groups show pronounced differences for DYS, IFF and DISP, which indicates a high sensitivity and specificity of these dyssynchrony indices. QRS duration, dP/dt_{MAX} and Tau show a similar discrimination between the groups and may also partly reflect dyssynchrony. However, whereas the conductance catheter derived indices directly measure regional mechanical events throughout the cardiac cycle, QRS duration reflects the underlying electrical activation and studies indicate that mechanical and electrical synchrony may diverge.[27] Tau and dP/dt_{MAX} have also been shown to be markers of dyssynchrony but they more indirectly reflect the integrated effects of spatially dispersed mechanical (de)activation during the isovolumic relaxation and contraction periods. Dyssynchrony is likely to be most pronounced in the isovolumic phases, which explains the sensitivity of parameters that reflect these periods. However, the consequences of dyssynchrony on the effectiveness of ejection and filling are important for cardiac pump performance, so that indices selectively reflecting those cardiac phases may be of high value.

In the CHF patients we compared the conductance derived dyssynchrony indices with the delay in timing of peak systolic velocity between the septal and lateral wall as obtained by tissue-Doppler echocardiography. Septal-to-lateral delay has recently been introduced as an index of mechanical dyssynchrony. We found a significant correlation for both DYS and IFF, but DISP did not reach a statistically significant correlation. The various indices measure different characteristics. Whereas the tissue-Doppler method compares the timing of peak velocity between two regions that are likely to show the largest phase shift, the conductance-derived indices are based on a comparison of the volume changes of short axis slices and global LV volume changes. Apparently patients with a larger septal-to-lateral delay also show more segmental dyssynchrony as reflected by DISP and IFF. Whether this correspondence is specific for LBBB-CHF patients or is more generally valid requires further study. The lack of correlation with DISP is unclear. It may be because the index is less sensitive than DISP or IFF as shown in the comparison between CAD and CHF patients, or the index may inherently be more prone to errors. Interestingly, within the group of CHF patients neither septal-to-lateral delay nor the conductance derived indices showed a significant correlation with QRS duration (Figure 5). This finding is consistent with other reports indicating that electrical dyssynchrony does not necessarily predict mechanical dyssynchrony, which prompts a need for methods to accurately detect mechanical dyssynchrony.[10,28]

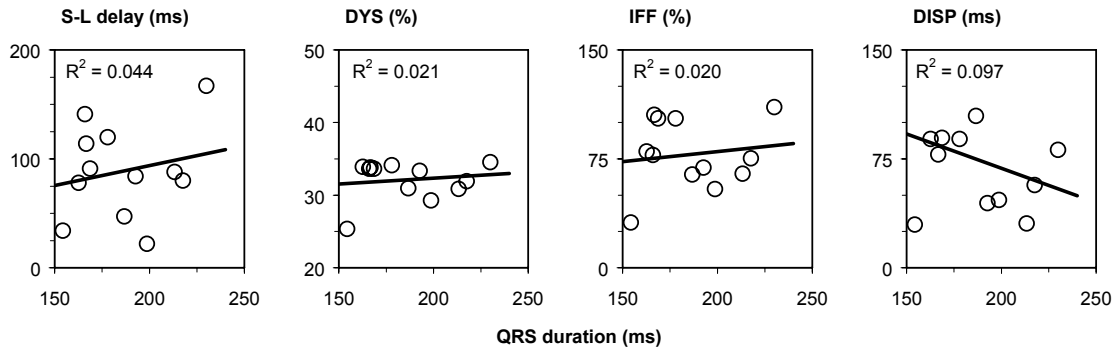

Figure 5. Linear regression of indices of mechanical dyssynchrony (S-L delay: septal-to-lateral delay of peak systolic velocity obtained by tissue-Doppler echocardiography; DYS: mechanical dyssynchrony; IFF: internal flow fraction; DISP: mechanical dispersion) vs QRS duration as index of electrical dyssynchrony

Our approach may offer several technical advantages. After catheter placement, the signals are obtained continuously without operator interaction. In the present study the analysis was performed off-line, but real-time display of dyssynchrony indices is technically feasible and should enable immediate quantification of the effects of

interventions and, e.g., effects of changes in pacemaker settings. The method is invasive, but positioning of the catheter in the LV largely eliminates problems with through-plane motion inherent in most imaging methods. Heart failure is often associated with substantial beat-to-beat hemodynamic variations due to changes in cycle length, cardio-pulmonary interaction and conduction disturbances. Thus, techniques - like MRI- that require hemodynamic steady state and beat-averaging to increase signal-to-noise may filter out important components of dyssynchrony. Furthermore, the temporal resolution of the conductance signals (4ms) is relatively high.

Determination of *absolute* LV volume from the conductance catheter requires careful calibration.[3] In the present study calibration factor parallel conductance was obtained by the hypertonic saline method and slope factor alpha by thermodilution. Slope factor alpha was significantly lower in the CHF patients than in the CAD patients (0.38±0.22 vs 0.67±0.08, $p<0.01$) and parallel conductance was significantly higher (214±60 vs 131±48mL, $p<0.01$). These findings are consistent with previous studies and reflect more electrical field inhomogeneity in the enlarged hearts in the CHF group. However, the conductance catheter has been used extensively in enlarged hearts and validation studies show that accurate volumes estimates can be obtained provided that appropriate calibration is performed.[29] As an advantage the dyssynchrony indices can be calculated from the raw segmental conductance signals and do not require calibration. Correction for parallel conductance (offset factor) is not required because the calculations are based on volume changes, and correction for slope factor alpha is not required because segmental volume changes are judged relative to the global LV volume changes. The latter however implicitly assumes that the segmental slope factors are all the same (and thus equal to the slope factor for global volume). This assumption may be a concern because theoretical studies indicate that volume in the segments closest to the current electrodes may be relatively underestimated due to electric field inhomogeneity especially in enlarged hearts.[30-32] To test the effects of such underestimations, if present, on our dyssynchrony indices we recalculated DYS, IFF and DISP after correcting segments 1 and 5 for an assumed underestimation of 20% and segments 2 and 4 for an assumed underestimation of 10%. Theoretical studies indicate that underestimation in this order of magnitude may be present.[30,32] The results were compared with the original data using Bland-Altman analysis (Figure 6).[33]

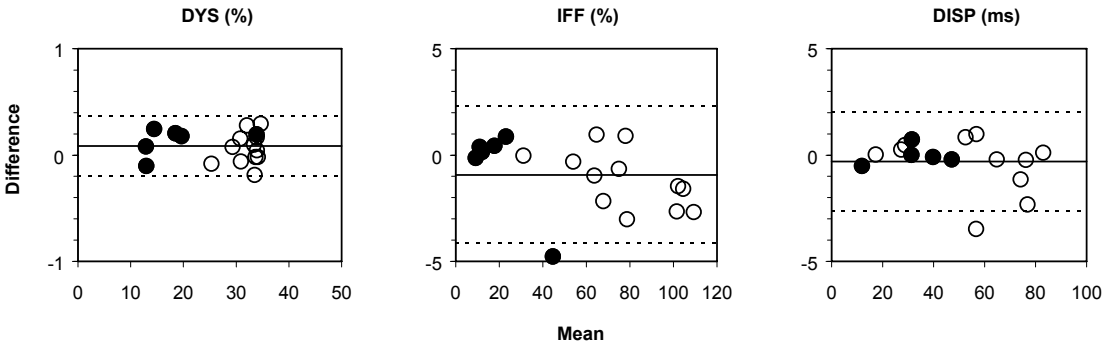

Figure 6. Bland-Altman analysis comparing conductance catheter derived indices of mechanical dyssynchrony before and after correction of assumed underestimation of segmental volumes due to electric field inhomogeneity. Open circles represent CHF patients, closed circles CAD patients

The analysis shows no significant bias and fairly narrow limits of agreement for each of the indices indicating that the influence of a potential underestimation of the outer segments on the dyssynchrony indices is relatively small. Although the mean dyssynchronies were higher in the CHF patients the differences as detected by the Bland-Altman analysis were not systematically different between the two groups.

The methods for quantifying dyssynchrony presented in this study show similarities with an approach previously published by Strum et al.[34] They used segmental volume signals obtained from conductance catheters to quantify regional wall motion abnormalities and referenced amplitudes and phase angles of the segmental signals to the global LV volume signal. The phase angle analysis is comparable to our DISP index. However, Strum et al measured (in degrees) the relative distances between time-points of regional minimal volume and global end-systole, whereas we used the entire systolic wave forms and used cross-correlation to determine the lag-time between segmental and global volume signals. In addition, they compared regional maximal stroke volume with effective stroke volume. The latter was measured using maximums and minimums of the total LV volume as gated markers of the time when regional contraction would contribute to total LV ejection. This effective stroke volume analysis is comparable to our internal flow calculation (IFF index), which determines at each time point throughout the cardiac cycle whether segmental volume changes are effective (i.e. contributing to global volume changes) or lead to ineffective (segment-to-segment) internal flow. Strum et al applied these concepts in animal studies where reversible regional myocardial dysfunction was induced by intracoronary infusion of esmolol and global inotropy was modulated by dobutamine infusions.[35,36]

Limitations

Optimally the conductance catheter is placed in a straight position from the aortic valve to the LV apex. In the operating room we used transesophageal echocardiography and in the catheterization laboratory we used angiography to guide positioning.[37] However occasionally arrhythmias necessitate pulling back the catheter slightly from the apical position. In addition the distance from the pigtail to the first measurement electrode is approximately 2 cm. Thus volume changes in the most apical part of the LV are not measured. If this region is highly dyssynchronous, as might be the case in patients with apical infarcts, underestimation of dyssynchrony by our methodology may be expected.

The patient groups in our study were investigated under different conditions. For practical purposes we studied the CAD patients in the operating room during anesthesia and after sternotomy, whereas the CHF patients were awake and studied in the catheterization laboratory. These differences may have affected the comparisons between the two groups. Propofol-remifentanyl anesthesia is known to have myocardial depressant and vasodilating properties, whereas sternotomy and pericardiotomy are associated with alterations in loading conditions.[38,39,40] Given the anesthesia-related cardiodepression in the CAD patients, one may expect that the differences in the hemodynamic indices would have been more pronounced in case both groups had been studied awake. Whether these changes affect the level of dyssynchrony is not well known, but studies in dogs with regional stunning show unchanged LV wall asynchrony after systemic inotropic stimulation.[41] Thus we do not expect that the differences in mechanical dyssynchrony between the groups were importantly influenced by the different experimental conditions.

Furthermore, we did not study normal subjects. Thus, future studies are required to establish a 'normal' range for the dyssynchrony indices.

Finally, the segmental conductance catheter signals do not provide an anatomical view but represent the total volume of slices perpendicular to the LV long-axis. Thus, e.g. in CAD patients, abnormal regional wall motion might be obscured by compensatory wall motions within the same circumferential segment. The proposed dyssynchrony indices therefore reflect intersegmental differences in contraction and filling and may underestimate phase changes obtained by comparing regional lateral and septal wall motions, e.g. using tissue Doppler imaging.

In conclusion, the proposed indices quantify various aspects of mechanical dyssynchrony using conductance catheter methodology which, at the same time, can be used for assessment of global systolic and diastolic (dys)function. Diagnostic and prognostic value of the dyssynchrony indices requires further investigation.

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CHAPTER 4

Left ventricular function and chronotropic responses after normothermic cardiopulmonary bypass with intermittent antegrade warm blood cardioplegia in patients undergoing coronary artery bypass grafting

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ABSTRACT

Background. Recent studies indicate that normothermic cardiopulmonary bypass (CPB) with intermittent antegrade warm blood cardioplegia (IAWBC) may have metabolic and clinical advantages, but limited data exist on its effects on myocardial function. Therefore, we investigated the acute effects of this approach on systolic and diastolic left ventricular function and on chronotropic responses.

Methods. In 10 patients undergoing isolated CABG we obtained on-line left ventricular pressure-volume loops using the conductance catheter before and after normothermic CPB with IAWBC. Steady state and load-independent indices of left ventricular function derived from pressure-volume relations were obtained during right atrial pacing (80-100-120 beats/min) to determine baseline systolic and diastolic function and chronotropic responses.

Results. The mean time of CPB was 105±36 min (median 103, range 60-167 min) with a mean aortic cross-clamp time of 75±27 min (median 69, range 43-129 min). Baseline (80 beats/min) end-systolic elastance (E_{ES}) did not change after CPB (1.22±0.53 to 1.12±0.28 mmHg/ml, P>0.2), while the diastolic chamber stiffness constant (k_{ED}) significantly increased (0.014±0.005 to 0.040±0.007 ml^{-1}, p=0.018) and relaxation time constant (τ) significantly decreased (61±3 to 49±2 ms, p=0.004). Before CPB, incremental atrial pacing had no significant effects on E_{ES} and τ but significant negative effects on k_{ED} (0.014±0.005 to 0.045±0.012 ml^{-1}, p=0.013). After CPB, atrial pacing had significant positive effects on E_{ES}, τ and k_{ED} (E_{ES}: 1.12±0.28 to 2.60±1.54 mmHg/ml, p=0.021; τ: 49±2 to 45±2 ms, p=0.009; k_{ED}: 0.040±0.007 to 0.026±0.005 mmHg, p=0.010), indicating improved systolic and diastolic chronotropic responses.

Conclusion. On-pump normothermic CABG with IAWBC preserved systolic function, increased diastolic stiffness, and improved systolic and diastolic chronotropic responses. Normalization of the chronotropic responses post-CPB is likely due to effects of successful revascularization and subsequent relief of ischemia.

INTRODUCTION

Coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB) is a routine and safe procedure with a mortality rate of approximately 2% in elective cases. As traditional cold heart and cold cardioplegic arrest have been shown to reduce post-operative myocardial function, improvements in cardioplegic approaches are still valuable.[1] Moreover, the number of patients with heart failure who are eligible for surgical intervention is rapidly increasing and preservation of left ventricular function by cardioprotection in these patients should be optimal. Warm blood cardioplegia represents an accepted alternative method for myocardial protection. Recent studies indicate that warm blood cardioplegia results in less myocardial damage than cold crystalloid cardioplegia, whereas comparisons against cold blood cardioplegia indicated metabolic advantages, a reduced rate of low output syndrome, and improved post-operative LV function.[2,3,4,5] To facilitate construction of distal coronary anastomoses *intermittent* antegrade warm blood cardioplegia (IAWBC) is currently used by many surgeons and has shown to be a safe approach with potentially important metabolic advantages.[6,7,8,9] However, the acute effects of IAWBC on post-operative myocardial function have not been studied extensively. With on-pump CABG, postoperative myocardial function may be affected by at least three factors: the extracorporal circulation, the revascularization and the cardioplegic cardiac arrest. In addition, the interpretation of postoperative hemodynamic measurements is complicated by possible alterations in loading conditions and heart rate in comparison to preoperative values. The aim of the present study was to quantify the physiological effects of on-pump CABG using IAWBC on systolic and diastolic left ventricular function. To this end, we measured pressure-volume loops by conductance catheter and quantified systolic and diastolic left ventricular function by load-independent parameters derived from pressure-volume relations. To assess chronotropic responses the measurements pre- and post-CPB were performed during right atrial pacing at 80, 100 and 120 beats/min.

METHODS

Patients

Patients undergoing elective isolated CABG were studied pre- and post-CPB. All patients had multi-vessel coronary artery disease and a relatively normal left ventricular ejection fraction (> 40%). The ejection fraction was derived from preoperative echocardiography. Patients included in the study had regular sinus rhythm and none of them had significant valvular disease. The study protocol was reviewed and approved by the medical ethics committee of our institute board and all included patients gave informed consent.

Anaesthesia

Patients received premedication (2 mg Lorazepam, sublingual) two hours before surgery. All patients received total intravenous anesthesia with target-controlled infusion of propofol, remifentanyl and sufentanyl. Pancuronium bromide 0.1 mg/kg was given to facilitate intubation. No further muscle relaxation was used. To monitor cardiac function and facilitate positioning of the conductance catheter a transesophageal multiplane echo (TEE) probe was inserted after induction of anesthesia. Subsequently, a thermal filament catheter was placed in the pulmonary artery via the right internal jugular vein for semi-continuous cardiac output "stat" measurements (Edwards Lifesciences, Uden, The Netherlands). 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 arterial CO_2 tension between 3.5 and 4 kPa.

Cardiopulmonary bypass and cardioplegic arrest

The cardiopulmonary bypass system consisted of a centrifugal pump (Stockert SIII, Stockert instrumente GmbH, Munchen, Germany), a closed venous reservoir, a Trillium coated Affinity hollow fiber oxygenator (Medtronic Cardiac Surgery, Kerkrade, The Netherlands), a cardiotomy reservoir, and an arterial filter (Dideco, Mirandola Italy). The systems were primed with 1300 ml Ringer solution, 200 ml 20% Human albumin Cealb®solution (Sanquin, Amsterdam, The Netherlands), 100 ml 20% Mannitol and 5000 IU of heparin. CPB was performed with a nonpulsatile flow of 2.4 L/min/m^2 and the core temperature was maintained at 35 ^{0}C. Heparin (300 IU/kg) was administered before cannulation. Additional heparin was administered if the activating clotting time (ACT, Hemochron, Edison, USA) was less than 400 seconds. After cessation of CPB

protamine sulfate was administered (1 mg/ 100 IU heparin). All patients received intermittent antegrade warm blood cardioplegia as described by Calafiore et al.[6] Normothermic blood (temperature 35-37°C) was collected from the oxygenator and was infused into the aortic root using a roller pump with a mean mean flow of 280 ml/min. The tubing was connected to a syringe pump containing potassium in a concentration of 2 mmol/ml. The first dose (2 min duration, or longer if necessary to obtain a flat ECG) was given immediately after aorta cross-clamping and subsequent doses (2 min duration) after construction of each distal anastomosis or after 15 minutes. During the first dose an initial 2 ml bolus of potassium solution was given and subsequently the syringe pump was set to 150 ml/hr. During the second dose the syringe pump speed was set to 120 ml/hr, and to 60 ml/hr during all subsequent doses. Consequently, 14 mmol potassium was given during the first infusion, 8 mmol during the second, and 4 mmol in all subsequent infusions.

Study protocol

Before and directly after CPB, conductance catheter measurements were performed as described previously: Briefly, temporary epicardial pacemaker wires were placed on the right atrium to enable measurement at fixed heart rates.[10] 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 left ventricle. 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.[11,12] Continuous left ventricular pressure and volume signals derived from the conductance catheter were displayed and acquired at a 250 Hz sampling rate using a Leycom CFL (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 repeated at atrial pacing rates (80, 100 and 120 beats/min). From these signals hemodynamic indices were derived as described below.

Pressure-volume analysis

Post-process data analysis was performed by custom-made software. Indices of global, systolic and diastolic left ventricular function (heart rate, cardiac output, stroke volume,

stroke work, ejection fraction, dP/dt_{MAX}, dP/dt_{MIN}, end-diastolic volume, end-systolic volume, end-diastolic pressure, end-systolic pressure, relaxation time constant τ) were calculated from steady state pressure-volume loops at 80, 100 and 120 beats/min. Systolic and diastolic pressure-volume relations were derived from pressure-volume loops acquired during caval vein occlusion at heart rates of 80, 100 and 120 beats/min. The slope of the end-systolic pressure-volume relationship (end-systolic elastance, E_{ES}) was used as relatively load-independent index of systolic left ventricular contractility.[13] Exponential regression of the end-diastolic pressure-volume relationship was used to determine the stiffness constant k_{ED} as a measure of diastolic chamber stiffness.[14]

Ischemic markers

We evaluated post-operative troponin T levels at regular intervals up to 48 hours (1, 3, 6, 12, 24 and 48 hours). Twelve-lead electrocardiographic recordings before and after CPB were routinely performed and assessed by the cardiologist for signs of myocardial infarction. Peri- and postoperative myocardial ischemia or infarction was defined as serum troponin T levels above 1 μg/l, ECG changes suspective for myocardial infarction, and new echocardiographic regional left ventricular wall motion abnormalities.

Statistical analysis

The pre- and post-CPB data were compared with paired t-tests and we used a multiple linear regression implementation of repeated measures analysis of variance to analyze the effects of chronotropic stimulation pre-CPB and post-CPB, respectively.[15] Data are presented as mean ± SEM. A p-value less than 0.05 was considered statistically significant.

RESULTS

Ten patients (9 men; age 62±10 years) were enrolled in this study. All patients had multi-vessel disease (mean number of affected vessels 2.7±0.5) and four had previous myocardial infarction. The mean pre-operative echocardiographic left ventricular ejection fraction was 58±9%. Mean CPB-time was 105±36 min (median 103, range 60-167 min) with a mean aortic cross-clamp time of 75±27 min (median 69, range 43-129 min). Note that the actual ischemic time is less because approximately 15% of cross-

clamp time is used for cardioplegic delivery. The mean number of anastomoses was 4±1; the left internal thoracic artery was anastomosed to the left anterior descending artery in all cases and used as a jump-graft to the diagonal artery in 6 cases. The right internal thoracic artery was anastomosed to the obtuse marginal artery in three cases, while it was used as a free graft off the left internal thoracic artery and anastomosed to both obtuse marginal and right descending posterior arteries in 5 cases. In two patients venous bypass grafts were used for revascularization of both these vessels.

Weaning from CPB was uneventful: four patients received low dosages of dobutamine post-CPB (≤ 5 µg/kg/min). There were no peri-operative myocardial infarctions. Troponin-T concentrations remained below the diagnostic criteria in all patients 48 hours postoperatively (Figure 1). The hospital stay was uncomplicated in all patients except in one patient who developed mediastinitis and stayed in the hospital for 35 days. The mean length of hospital stay was 11 days (range 6-35 days, median 8 days). The mean length of stay in the intensive care unit was 1.9 days (range 1-3, median 2 days).

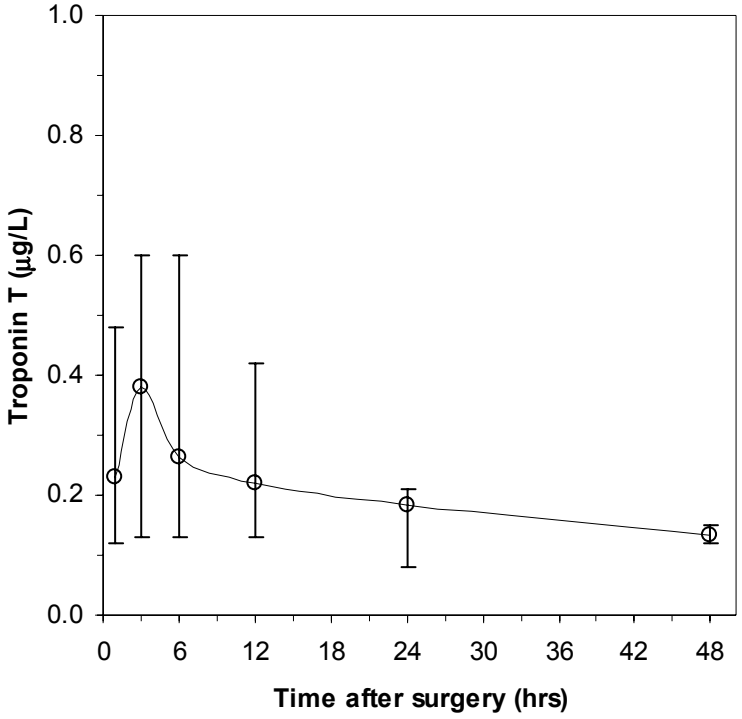

Figure 1. Postoperative troponin T plasma levels. The concentration of troponin T (TnT) remained below the diagnostic criteria for myocardial infarction in all patients in the post-operative period up to 48 hrs. Symbols show median values, error bars indicate ranges

Pressure-volume data

Hemodynamic data from pre- and post-CPB at paced heart rates of 80 (baseline), 100 and 120 beats/min are summarized in Table 1. Figure 2 shows pressure and volume

signals and corresponding pressure-volume loops during preload reduction at paced heart rate of 80 beats/min before and after CPB in a typical patient. The effects of pacing pre- and post-CPB on the main systolic and diastolic function indices are presented in Figure 3.

Table 1. Hemodynamic data obtained at incremental paced heart rate, pre- and post CPB

	Pre-CPB			Post-CPB		
	pre-80	pre-100	pre-120	post-80	post-100	post-120
HR (beats/min)	81.5±1.6	101.1±0.6 *	120.0±1.4 *	86.2±3.9 $^{\&}$	102.5±1.3 $^{\#}$	121.2±0.3 $^{\#}$
CO (l/min)	6.0±0.6	5.9±0.7	6.0±0.7	5.6±0.3	5.9±0.3	6.2±0.3 $^{\#}$
SV (ml)	73±7	58±6 *	50±5 *	66±3	58±3 $^{\#}$	51±2 $^{\#}$
EF (%)	45±7	41±6 *	38±6 *	50±8 $^{\&}$	47±8	47±9
ESV (ml)	123±38	118±37 *	112±36 *	93±27	93±27	87±27
EDV (ml)	191±41	171±41 *	159±40 *	152±26	149±28	137±28 $^{\#}$
ESP (mmHg)	80±5	77±6	72±5 *	78±6	76±3	70±5 $^{\#}$
EDP (mmHg)	10.1±1.2	7.2±0.7 *	9.0±1.1	16.3±2.8 $^{\&}$	14.9±2.7	11.5±1.9 $^{\#}$
SW (mmHg.ml)	5,584±729	4,630±645 *	3,567±455 *	4,471±383	4,007±367 $^{\#}$	3,312±260 $^{\#}$
dP/dt_{MAX}(mmHg/s)	981±90	1,004±102	1,014±123	991±84	985±64	997±64
dP/dt_{MIN} (mmHg/s)	-937±94	-956±110	-896±88	-923±67	-936±59	-903±70
τ (ms)	61±3	58±3	57±3	49±2 $^{\&}$	49±3	45±2 $^{\#}$
E_{ES} (mmHg/ml)	1.22±0.53	1.21±0.43	1.43±0.61	1.12±0.28	1.76±0.92	2.60±1.54 $^{\#}$
k_{ED} (ml^{-1})	0.014±0.005	0.015±0.008	0.045±0.012*	0.040±0.007$^{\&}$	0.023±0.005$^{\#}$	0.026±0.005$^{\#}$

*pre-80, pre-100, pre-120: paced heart rate 80 beats/min (respectively 100, 120 beats/min) pre-CPB; post-80, post-100, post-120: paced heart rate 80 beats/min (respectively 100, 120 beats/min) post-CPB. HR = heart rate, CO = cardiac output, SV = stroke volume, EF = ejection fraction, ESV = end-systolic volume, EDV = end-diastolic volume, ESP = end-systolic pressure, EDP = end-diastolic pressure, SW = stroke work, dP/dt_{MAX} maximal rate of pressure change during contraction; dP/dt_{MIN} maximal rate of pressure change during relaxation; τ = relaxation time constant, E_{ES} = end-systolic elastance, k_{ED} = diastolic chamber stiffness constant. Significances: * : $p<0.05$ vs pre-80; $^{\#}$ $p<0.05$ vs post-80; $^{\&}$ $p<0.05$ post-80 vs pre-80*

Baseline data. Hemodynamic data at baseline (i.e. at 80 beats/min) pre- and post-CPB are included in Table 1 and Figure 3. Cardiac output and stroke volume remained unchanged after CPB, while left ventricular ejection fraction improved significantly.

End-diastolic volume (EDV) and end-systolic volume (ESV) had a clear tendency to decrease post-CPB (EDV: -39 ml; ESV: -30 ml), but these changes did not reach statistical significance. Both end-diastolic pressure and diastolic chamber stiffness increased significantly after CPB, while the relaxation time constant τ decreased significantly. End-systolic elastance (E_{ES}) remained unchanged after CPB.

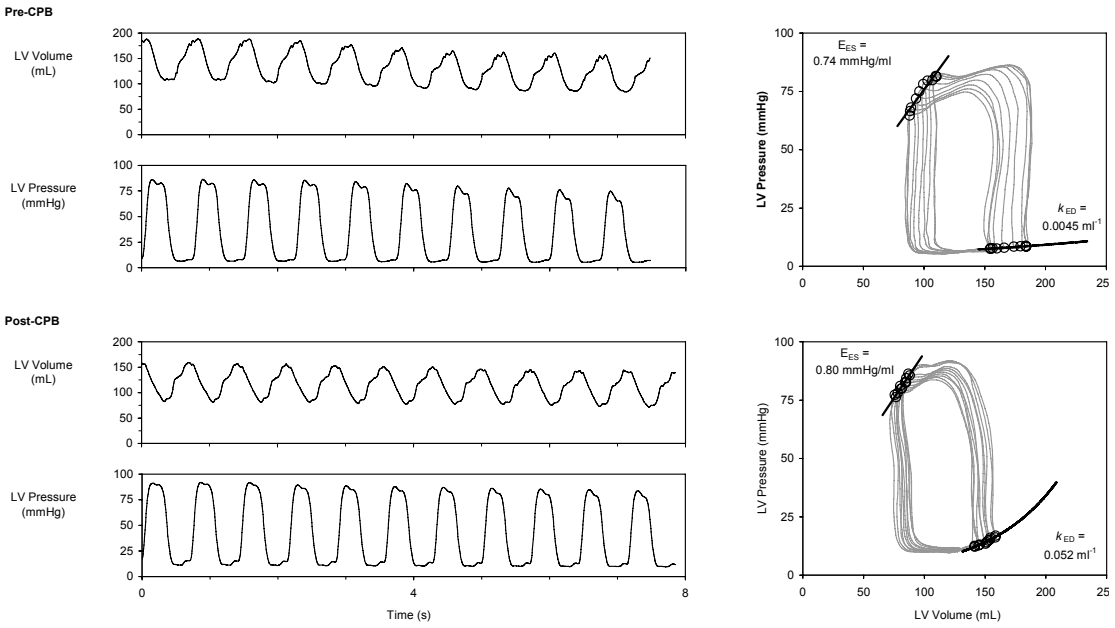

Figure 2. Typical LV pressure and volume signals and pressure-volume loops during preload reduction by transient vena cava occlusion, pre- and post-CPB, at paced heart rate of 80 beats/min

Effects of pacing. Hemodynamic data pre- and post-CPB at 80, 100, and 120 beats/min are given in Table 1 and Figure 3. Note that post-CPB the mean baseline heart rate was 86±4 beats/min because in some patients sinus rhythm exceeded the target pacing rate of 80 beats/min. Cardiac output increased with incremental pacing post-CPB, while pre-CPB pacing did not affect cardiac output. Stroke volume decreased both before and after CPB with pacing, but this decrease was less pronounced after CPB (-24 ml pre-CPB vs -14 ml post-CPB). The smaller reduction in stroke volume with pacing post-CPB was the result of a less pronounced reduction in end-diastolic volume (pre-CPB: -33 ml; post-CPB: -15 ml), since end-systolic volume decreased by 11 ml pre-CPB and by 6 ml post-CPB. Apparently, the capability of the ventricle to fill despite a high heart rate is relatively improved post-CPB. This is supported by the results for the diastolic indices. Active relaxation, τ, improved during pacing post-CPB, while it remained unchanged during pacing pre-CPB. Furthermore, the end-diastolic chamber stiffness constant increased significantly during pacing pre-CPB, whereas it decreased during pacing post-CPB. It should be mentioned that baseline diastolic stiffness (i.e. at 80

beats/min) was higher post-CPB as compared to pre-CPB, but with pacing at 120 beat/min the post-CPB values dropped below the pre-CPB values.

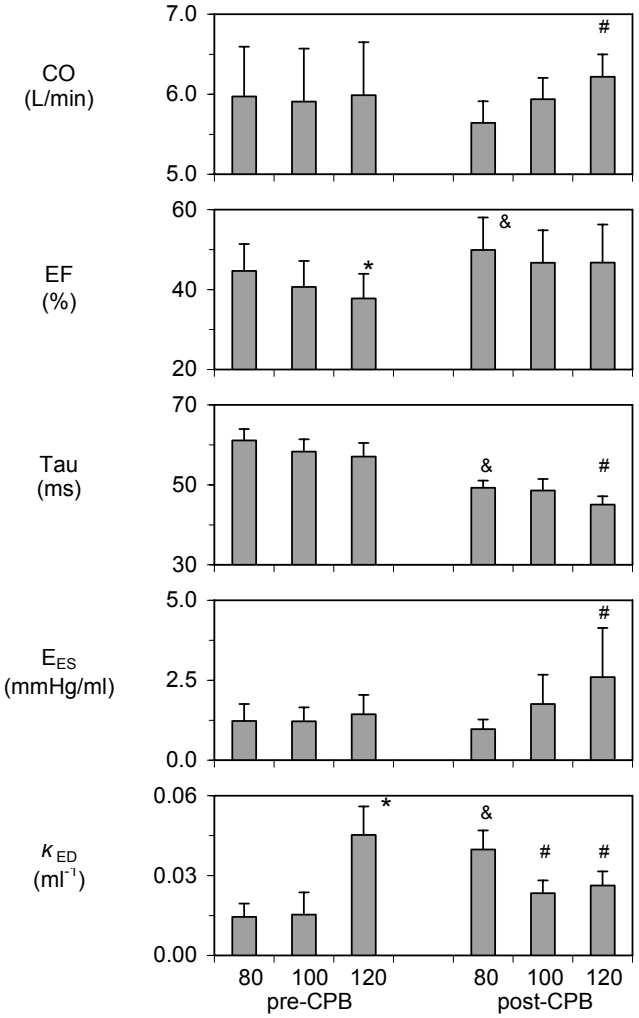

*Figure 3. Main systolic and diastolic hemodynamic indices pre-and post-CPB at paced heart rates of 80, 100 and 120 beats/min. Significances: * : p<0.05 vs pre-80; # : p<0.05 vs post-80; & : p<0.05 post-80 vs pre-80*

During pacing end-diastolic pressure remained constant pre-CPB, which is the result of a reduced end-diastolic volume (which should lower end-diastolic pressure) combined with an increased diastolic stiffness (which increases end-diastolic pressure). However, post-CPB end-diastolic pressure gradually dropped with incremental pacing, since both end-diastolic volume and stiffness decreased. With regard to systolic function, pre-CPB EF decreased significantly at 120 beats/min, whereas it was unchanged post-CPB. dP/dt_{MAX} was unchanged both before and after CPB. Furthermore, no systematic effects were seen on E_{ES} during pacing pre-CPB, but post-CPB E_{ES} increased significantly at 120 beats/min indicating an improvement in systolic function (Figure 3).

DISCUSSION

CABG is increasingly performed in heart failure patients with concomitant surgical valvular repair and/or left ventricular restoration. Optimal preservation of myocardial function is important to facilitate these surgical procedures. Traditional cold heart and cold cardioplegic arrest may have negative effects on post-operative myocardial function and currently normothermic procedures are increasingly used as an alternative.[1] Previous studies indicate that normothermic arrest with warm blood cardioplegia provides metabolic benefits and less cell damage, possibly mediated by a better protection from from ischemia-reperfusion injury.[2,3,9] However, few data are available on the acute effects on ventricular function. The aim of our study was therefore to quantify the effects of normothermic on-pump CABG and IAWBC on systolic and diastolic left ventricular function. In brief, our results show that this approach has no negative effects on baseline systolic function, whereas it tended to improve the response of systolic function during incremental pacing. With regard to diastolic function we found an improved early relaxation, but the end-diastolic stiffness was increased at baseline. However, incremental pacing revealed improved relaxation and filling characteristics post-CPB, whereas pre-CPB the diastolic indices remained constant or worsened during pacing.

Baseline hemodynamic changes

The baseline hemodynamic results (i.e. comparing pre- vs. post-CPB at 80 beats/min) show a slight but significant increase of ejection fraction after CPB, which is due to a marked decrease in end-diastolic volume (-39 ml) with a relatively unchanged stroke volume. Stroke volume remained largely unchanged due to a similar decrease of end-systolic volume (-30 ml) after CPB. Note that, except for EF, none of these volumetric changes reached statistical significance. The effect on EDV is the result of impairment of late passive diastolic function (k_{ED} and EDP increased significantly after CPB), despite the fact that active relaxation (τ) significantly improved after CPB. The improved ejection fraction and the finding of a reduced end-systolic volume with maintained end-systolic pressure both point towards an improved systolic function. However, the load-independent contractility index E_{ES} did not change significantly. Therefore, we would conclude that normothermic CPB with IAWBC at least preserves systolic function in this patient group. This is in contrast with studies using cold blood

cardioplegia during hypothermia in which a reduced systolic left ventricular function after CPB was reported.[1]

With respect to diastolic function we found a somewhat prolonged τ at baseline pre-CPB, which has already been shown to be representative for patients with coronary artery disease.[16,17] In our study τ decreased significantly after CPB with warm blood cardioplegia indicating an improved early, active relaxation. This normalization of τ after revascularization is consistent with previous studies regardless of the use of cold or warm blood cardioplegia and is most likely related to enhancement of the, highly oxygen-dependent, calcium re-uptake process by the sarcoplasmic reticulum after revascularization, and not due to effects of CPB.[18] After CPB increased circulating catecholamines resulting from CPB and ischemia may influence active relaxation. However, the unchanged systolic pressure and heart rate after CPB indicate that this effect is unlikely to be very prominent in our study. In contrast to the improvement in τ, the diastolic chamber stiffness constant, which represents passive late diastolic function was significantly increased post-CPB. This increased stiffness (thus reduced diastolic compliance) is likely due to temporary myocardial edema and increased water content after CPB.[19,20] This finding is important when interpreting changes in diastolic function after surgical interventions such as ventricular restoration and other procedures.[21] Apparently, part of the changes in diastolic function, at least in the acute phase, are related to the cardioplegic arrest and CPB, and should not be attributed to the surgical procedure per se.

Chronotropic responses

We found a significant improvement of cardiac output during incremental atrial pacing post-CPB, whereas cardiac output remained constant pre-CPB. This effect reflected a more pronounced decrease in stroke volume with pacing pre-CPB, compared to post-CPB. In normal physiology maintained stroke volume (or a limited reduction) during increased heart rate is obtained by a combination of increased systolic function (Bowditch effect), which reduces or maintains end-systolic volume, and an improved relaxation, which limits the reduction in end-diastolic volume resulting from the reduced diastolic filling time. Our results indicate that neither of these mechanisms is operative in patients with coronary artery disease (CAD) pre-CPB and consequently cardiac output did not increase during incremental pacing. Moreover, diastolic stiffness substantially increased during pacing which further limited filling. The finding that systolic function does not improve or even decreases with increased heart rate in CAD

patients is consistent with previous studies.[22] A recent echocardiographic study in patients undergoing CABG indicates an increased diastolic stiffness during pacing very similar to our findings.[23] Numerous studies have documented increased diastolic pressure, increased stiffness and upward shifts of the diastolic pressure-volume relation with pacing angina, however our study shows that more subtle increases in diastolic stiffness are obtained with a relatively small increase in heart rate in CAD patients with relatively preserved EF.[24]

After CPB, diastolic chamber stiffness, end-diastolic pressure and τ all significantly decreased during pacing which may explain the improvement of cardiac output at higher heart rates. In addition, E_{ES} gradually increased with incremental pacing post-CPB, whereas it remained constant pre-CPB, indicating that improvement in systolic function contributed to the increase in cardiac output.

The effects of pacing pre- vs. post-CPB in our study largely mimic the effects of exercise before and after revascularization surgery as described in a study by Caroll et al.[25] After surgery, but not before, both pacing and exercise induced improvements in systolic and diastolic function, which enable the required increase in cardiac output. However, during exercise end-diastolic pressure and volume increased whereas during pacing in our study these indices decreased. These differences are presumably due to recruitment of blood volume during exercise leading to increased preload, which does not occur during pacing.

The impaired chronotropic responses pre-CPB as found in our study are presumably due to coronary artery disease and the normalization of these responses post-CPB due to effects of successful revascularization and subsequent relief of ischemia.

Limitations

We did not include a control group with a cold cardioplegic approach. However, this approach is well documented in the literature and we compared our results against those reports. Furthermore, our study was performed in patients with relatively normal LV function, whereas the advantages of IAWBC are presumably most important for patients with poor LV function. However, in heart failure patients the effects of IAWBC would be difficult to assess separately because the surgical interventions (CABG and additional procedures like mitral annuloplasty and/or surgical restoration) may importantly affect post-operative LV function.

In conclusion, this study shows that intermittent antegrade warm blood cardioplegia during normothermic cardiopulmonary bypass provides excellent myocardial protection

of systolic properties, whereas improved diastolic and systolic left ventricular chronotropic responses were found acutely after surgery. This cardioprotective stategy may be particularly advantageous in patients with heart failure who undergo complex surgical procedures with long procedure times.

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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).

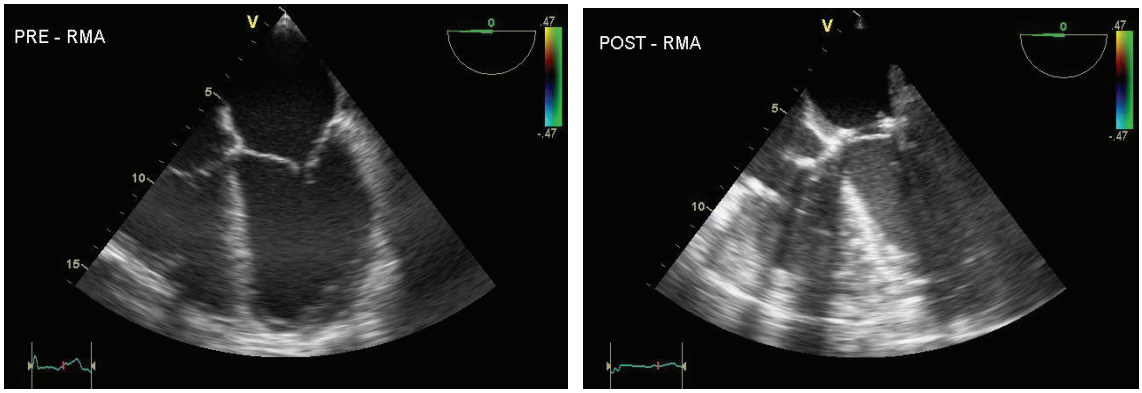

Figure 1. Transesophageal echocardiographic long-axis view before and after restrictive mitral annuloplasty in a 41 year-old patient with ischemic dilated cardiomyopathy (LVEF: 20%) and severe mitral regurgitation (grade 4). Mitral annular dilatation was demonstrated as the relative ratio between the 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.

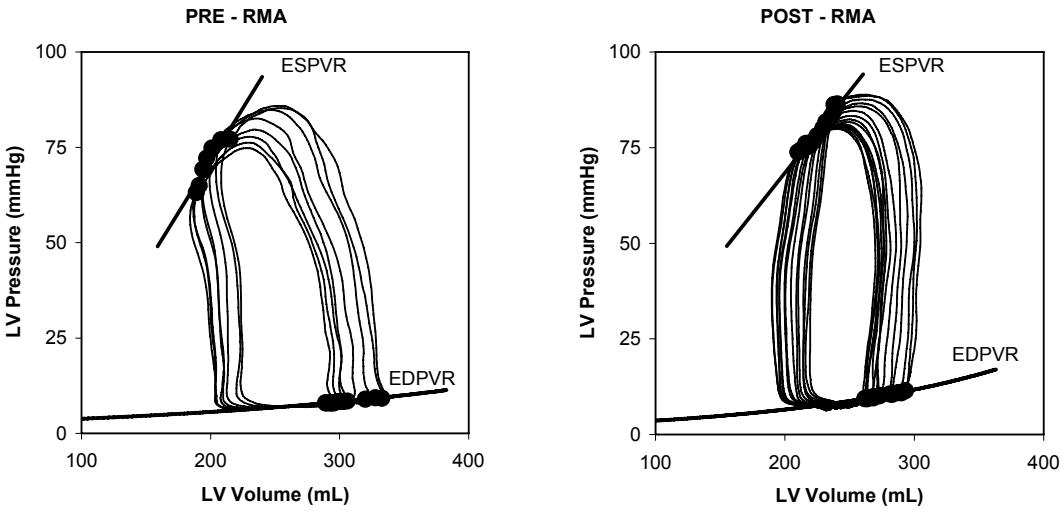

Figure 2. Pressure-volume relations before and after RMA in a patient with end-stage heart failure. In this patient the end-diastolic pressure-volume relation (EDPVR) demonstrates an increased diastolic stiffness. This was also found in the group as a whole, but the effect was not statistically significant. 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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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]

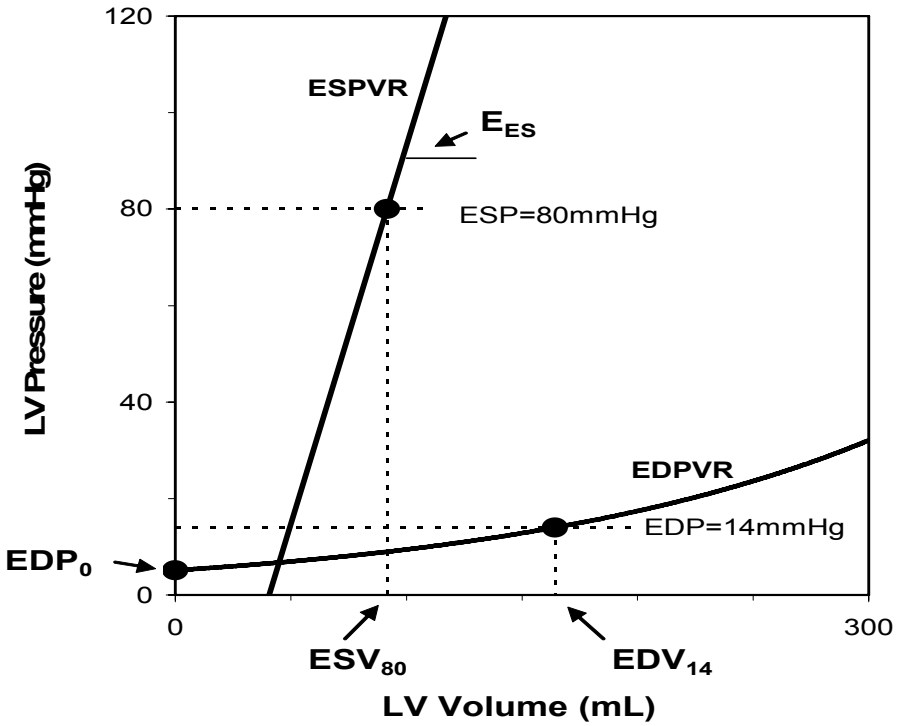

Figure 1. The end-systolic pressure-volume relation (ESPVR) and the end-diastolic pressure-volume relation (EDPVR) in the pressure-volume diagram. The linear ESPVR is characterized by its slope, end-systolic elastance (E_{ES}), and its volume intercept at an end-systolic pressure of 80 mmHg (ESV_{80}). 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.

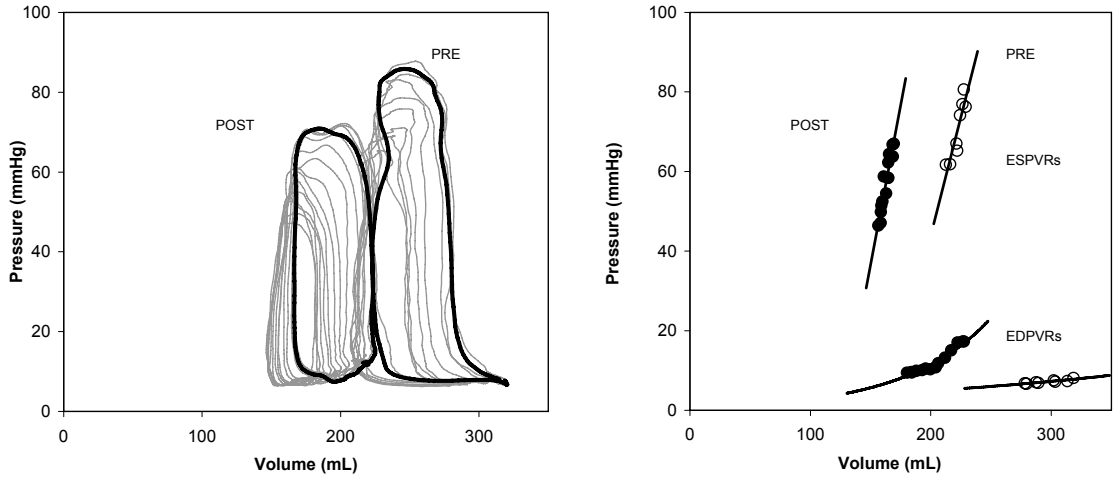

Figure 2. Typical example of pressure-volume relations in a patient with ischemic dilated cardiomyopathy before (PRE) and after (POST) surgical ventricular restoration. The steady state pressure-volume loops show a significant reduction in end-diastolic and end-systolic volumes with unchanged stroke 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).

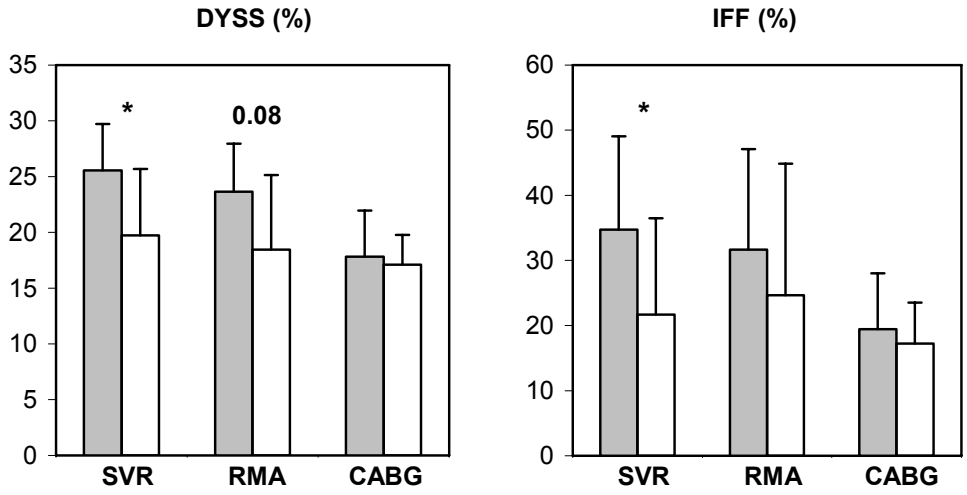

*Figure 3. Acute effects of surgery on mechanical dyssynchrony indexes in the SVR-, RMA and CABG-groups. DYSS indicates mechanical dyssynchrony; IFF, internal flow fraction. * indicates p<0.05. Marginal significances (p<0.10) are tabulated*

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)

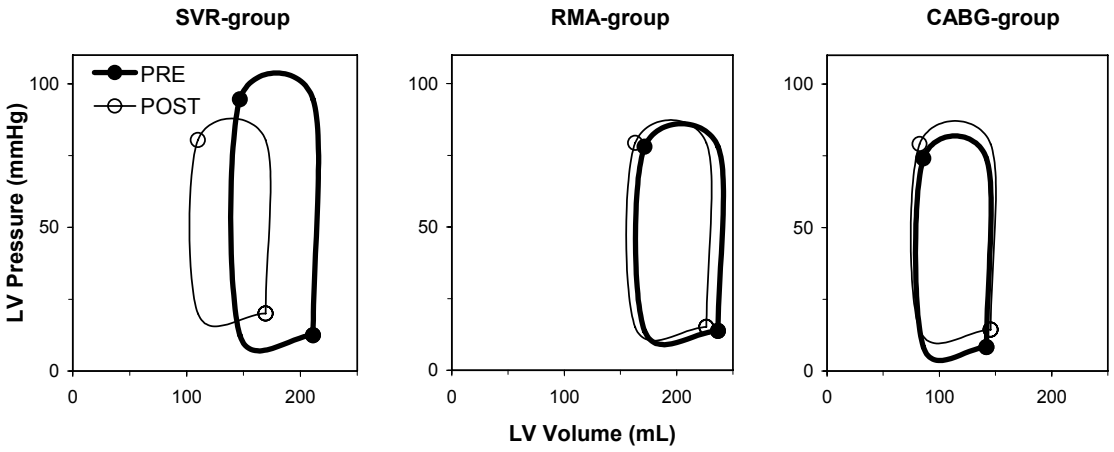

Figure 4. Average steady state pressure-volume loops before (PRE) and after (POST) SVR (surgical ventricular restoration), isolated RMA (restrictive mitral annuloplasty), and CABG (coronary artery bypass grafting). The average loops (based on mean end-systolic and end-diastolic volumes and pressure) 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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CHAPTER 7

Pressure-volume measurements by conductance catheter during cardiac resynchronization therapy

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INTRODUCTION

The conductance catheter developed by Baan et al. enables continuous on-line measurements of left ventricular (LV) volume and pressure.[1,2] This method has been used extensively to assess global systolic and diastolic ventricular function and more recently the ability of this instrument to pick-up multiple segmental volume signals has been used to quantify mechanical ventricular dyssynchrony.[3-13,14,15] These characteristics offer interesting possibilities to apply this technique in patients considered for or treated with cardiac resynchronization therapy (CRT). The aim of the present review is therefore to give an overview of the (potential) applications of pressure-volume measurements by conductance catheter in relation to CRT, and discuss the possibilities and limitations of this approach.

METHODS

The conductance catheter method

The method has been described extensively in previous publications.[2,16,17] Briefly, the conductance methodology is based on the measurement of the electrical conductance of the blood contained in the LV cavity. To this end the catheter contains multiple electrodes to generate an intra-cavitary electric field and pick-up the resulting voltage gradients. In its present form the catheter has 12 electrodes and should be positioned along the long axis of the LV as depicted in figure 1. The two most distal and two most proximal electrodes are employed to generate an electrical field. This dual pair of current electrodes enables the use of a dual excitation mode, which has been shown to improve the accuracy of the method especially in dilated hearts.[16] The remaining 8 electrodes are used pair wise to measure up to 7 segmental conductance signals (G_i) which represent the instantaneous volumes of corresponding slices (note that the figure shows only 5 segments).

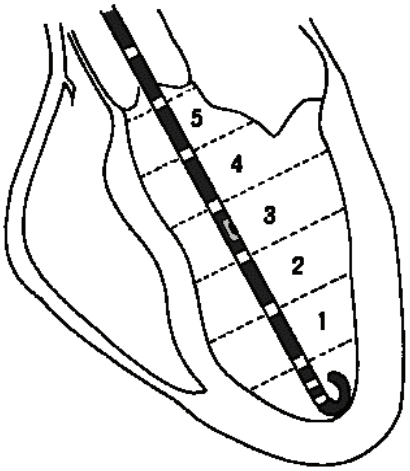

Figure 1. The combined pressure-conductance catheter positioned in the left ventricle. The electrodes are used to setup an intracavitary electric field and measure segmental conductances. Note the pressure sensor positioned in segment 3

To convert the measured conductance (i.e. applied current divided by the measured voltage gradient) to an absolute volume signal the specific conductivity of blood (σ) and the electrode spacing (L) have to be taken into account. In addition, the measured conductance contains an offset factor, which is due to the conductance of the structures surrounding the cavity. This so-called parallel conductance (G^p) may be determined by the hypertonic saline dilution method and subsequently subtracted.[2,17] Finally, the conductance-derived stroke volume generally underestimates actual stroke volume due to electrical field inhomogeneity and because the segments do not fully cover the LV long axis. This underestimation is corrected by introducing a slope factor (α), which may determined by comparing conductance-derived stroke volume with an independent estimate of stroke volume (e.g. determined by thermodilution). Consequently, absolute LV volume (V_{LV}) is derived from measured conductance $G(t)$ as:

$$V_{LV}(t) = (1/\alpha) \cdot (L^2/\sigma) \cdot [G(t) - G^P]$$

Note that $G(t)$ is the instantaneous sum of the segmental conductances:

$$G(t) = \Sigma\, G_i(t)$$

The equation also holds at a segmental level:

$$V_{seg,i}(t) = (1/\alpha) \cdot (L^2/\sigma) \cdot [G_i(t) - G_i^P]$$

As shown in figure 1 the conductance catheter also contains a solid-state, high-fidelity pressure sensor to measure instantaneous LV pressure.

Catheters, equipment and software

Currently, most pressure-volume studies performed in humans use combined pressure-conductance catheters. Typically, these catheters are 7F, over-the-wire, pigtail catheters and are produced by several companies (e.g. CDLeycom, Zoetermeer, The Netherlands; Millar Instruments, Houston, Texas). To generate the electric field, measure the resulting voltages, acquire and handle the various signals the catheter must be connected to dedicated equipment. For this purpose all studies presented and discussed in this review used the Cardiac Function Lab CFL-512 or the Sigma 5 DF (CDLeycom, Zoetermeer, The Netherlands). Data analysis is generally performed with software installed on the CFL-512 or by using other commercially available physiological data-analysis software, or software that is custom-made by the various research groups.

Pressure-volume signals, loops and relations

When positioned in the LV, the combined pressure-conductance catheter yields continuous segmental volume signals and LV pressure. Total LV volume is calculated as the instantaneous sum of the segmental signals. An example of these signals obtained in a patient with coronary artery disease and relatively normal LV function and contraction pattern is shown in figure 2. The temporal resolution in this example is 4 ms. The volume signals show a normal ejection during systole and a biphasic filling pattern during diastole reflecting early rapid filling, diastasis and the atrial contribution to filling.

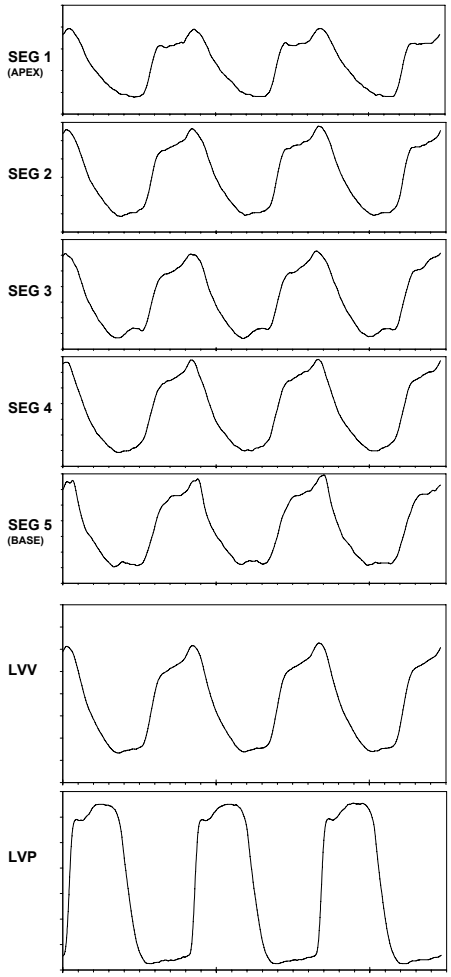

Figure 2. Typical left ventricular segmental (SEG 1 to SEG 5) and total LV volume (LVV) signals and left ventricular pressure (LVP). Corresponding pressure-volume loops are shown in Figure 3

To characterize pump-function of the LV, pressure and volume signals may be combined to construct pressure-volume loops as depicted in figure 3. Each loop represents one cardiac cycle. The distinct cardiac phases, filling, isovolumic contraction, ejection and isovolumic relaxation, are indicated in the figure. The phases are separated by opening and closure of mitral and aortic valves, which moments coincide with the 'corners' of the pressure-volume loop. Important parameters characterizing LV function can be directly determined from the pressure-volume loops, or from the pressure and volume-time curves and their derivatives. Such parameters include indices of pump function (stroke volume, cardiac output, and stroke work), systolic function (end-systolic pressure, end-systolic volume, ejection fraction, peak ejection rate (dV/dt_{MAX}), and dP/dt_{MAX}) and diastolic function (end-diastolic volume, end-diastolic pressure, peak filling rate (dV/dt_{MIN}), dP/dt_{MIN}, and relaxation time constant τ).

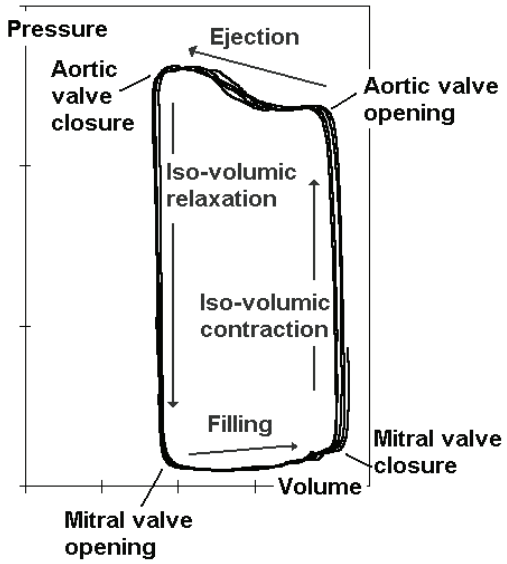

Figure 3. Pressure-volume loops. Cardiac phases and time-points of opening and closure of mitral and aortic valves are indicated

An important limitation of all of the above mentioned indices is that they are, more-or-less, load dependent. A possible approach to amend this is to construct pressure-volume relations from which indices can be derived which are less load-dependent and therefore better measures of *intrinsic* systolic or diastolic ventricular function. Construction of pressure-volume relations requires pressure-volume loops obtained at different loading conditions. Importantly, such alteration in loading should be induced by interventions that minimally affect intrinsic myocardial function. An elegant way to achieve this is to use a balloon occlusion of the inferior vena cava. This procedure enables a rapid, purely mechanical, reduction in preload, which prevents reflex mechanisms and is easily reversed by deflation of the balloon. This method has been described in detail in several publications.[5,6] A typical example of pressure-volume loops acquired during caval occlusion is shown in figure 4.

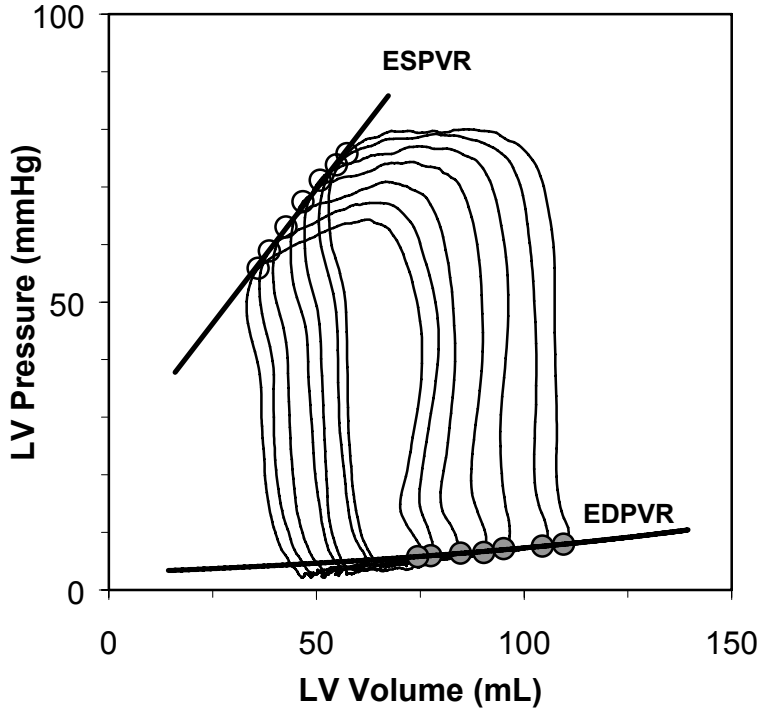

Figure 4. Pressure-volume loops during preload reduction by vena cava occlusion. Systolic and diastolic function indices are derived from the curves fitted to the end-systolic and end-diastolic pressure-volume points, respectively

The relation between the pressure-volume points at end-systole, the end-systolic pressure-volume relation (ESPVR) has been shown a sensitive and relatively load-independent description of LV systolic function.[18] Both the slope of the ESPVR, which determines end-systolic elastance (E_{ES}) and the position of the ESPVR (in recent generally papers characterized by the volume-intercept at a fixed pressure, e.g. end-systolic volume at 100 mmHg, ESV_{100}) are used as indices of systolic function.[19-21] The relation between the end-diastolic pressure-volume points, the end-diastolic pressure-volume relation (EDPVR), may be fitted with a linear curve. The slope of this curve (dEDP/dEDV) represents diastolic stiffness. More commonly, the term diastolic compliance is used, which is the inverse of this slope (dEDV/dEDP). If the EDPVR is constructed over a wider range it is generally clear that this relation is non-linear and better approximated by an exponential fit, such as $EDP = A \cdot \exp(k \cdot EDV)$ and diastolic function characterized by the diastolic stiffness constant (k).[7] In addition, several other relations, which may be derived from pressure-volume loops during a loading interventions have been used to quantify LV function, such as the relation between dP/dt_{MAX} and end-diastolic volume and the preload recruitable stroke work relation (i.e. SW vs EDV).[18,20,22-24]

Mechanical dyssynchrony

Several studies have confirmed the hypothesis that baseline dyssynchrony (i.e. pre-implantation) is an important determinant of the success of CRT in individual patients.[25-27] Currently the primary variable to identify patients that are most likely to benefit is QRS duration. However, electrical and mechanical dyssynchrony may diverge and recent studies indicate that direct analysis of mechanical dyssynchrony may have higher predictive value.[25,28] Mechanical dyssynchrony may be quantified by means of MRI, echocardiographic or tissue Doppler techniques.[26,29,30,31,32] Recently, we introduced indices of mechanical dyssynchrony derived from the segmental volume signals obtained with the conductance catheter.[33,34] The methods and indices are described and validated in detail elsewhere.[35] Briefly, a segmental volume signal is compared with the simultaneous global volume signal and a segment is marked as dyssynchronous at time-point *t* if the instantaneous change in the segmental volume signal is opposite to the change in the global volume signal at that same time-point. An index of regional dyssynchrony is obtained by calculation the percentage of time during the cardiac cycle that a specific segment is dyssynchronous. A global index of mechanical dyssynchrony is subsequently derived by calculating the mean value over all segments. Furthermore, nonuniform contraction and filling is associated with ineffective movements of blood volume within the LV. This 'internal flow' may be quantified by calculating segment-to-segment flow (i.e. segmental volume changes that do not result in effective changes in total LV volume). An internal flow fraction (IFF) is obtained by dividing the average internal flow by effective global LV flow. A comparative study in heart failure patients with LBBB showed good correlation between these conductance derived dyssynchrony indices and tissue-Doppler derived septal-to-lateral delay in peak systolic velocity.[31,36]

PRESSURE-VOLUME MEASUREMENTS DURING CRT

We may distinguish several fields of application where pressure-volume measurements by conductance catheter may play a role in the context of CRT. In principle, the methodology can be applied to study the basic physiological mechanisms involved, as a tool to select patients that might benefit from CRT, to optimize the therapy, and to evaluate the treatment effects of CRT. In the following we will briefly review several

applications of pressure-volume measurements, and discuss the possibilities and limitations in these four fields.

Mechanisms

We and several other groups have used pressure-volume analysis to investigate the physiological mechanisms of CRT. The two primary targets of CRT are normalization of the pattern of LV activation and optimization of the atrial-ventricular delay.[37] In patients with intraventricular conduction delay mechanical synchrony can be improved by pre-excitation of the otherwise late-activated region. As shown in figure 5 (unpublished data) this may result in dramatic acute systolic improvements evident from increased stroke volume and increased stroke work. In this case the improvements are obtained largely from a reduced end-systolic volume, whereas end-diastolic volume is unaltered. Similar results were presented by Nelson et al. who very elegantly demonstrated that the improvement in systolic function is achieved with a minimal change or even a reduction in myocardial oxygen consumption. [38]

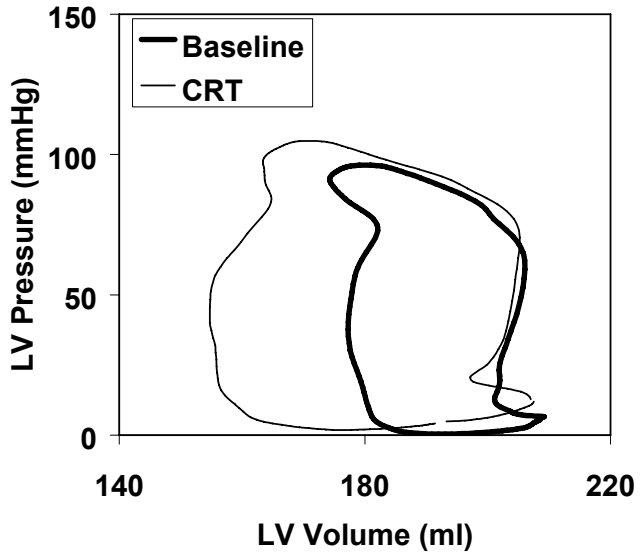

Figure 5. Acute effects of biventricular pacing on LV pressure-volume loops. Note the increased stroke volume (width of pressure-volume loops) and stroke work (area of pressure volume loop) during CRT

A nice demonstration of the influence of asynchronous activation on LV function was presented by Simantirakis et al.[39] They determined systolic and diastolic LV function by pressure-volume loops in patients with long-term right ventricular apical pacing. Restoration of normal activation was achieved by switching from DDD to AAI pacing mode. The results indicate an acute improvement in systolic function evident from an increased end-systolic elastance, preload recruitable stroke work and dP/dt_{MAX}-EDV

slope. Diastolic function was unaltered. Similar to the study by Nelson et al. it was found that myocardial oxygen consumption was unchanged and therefore the improvement in contractility must be attributed to a more economic functioning of the heart.[38] Although mechanical dysfunction arising from right ventricular apex pacing is not necessarily equivalent to that found in patients with intrinsic conduction delay (such as LBBB), this study clearly illustrates the acute improvements that can be obtained after restoration of normal activation.[40]

Pressure-volume loop analysis has been applied to study the influence of pacing site and AV-delay in an experimental animal model of left bundle branch block (LBBB) by Verbeek et al.[41] They show that experimental LBBB acutely induces inter- and intraventricular electrical asynchrony which is reflected in reductions in dP/dt_{MAX}, stroke volume and stroke work. LV pacing recovered LV function and maximal improvement was obtained with intra-ventricular resynchronization of activation, which depended on LV pacing site and required optimalization of the AV-delay.

An interesting alternative hypothesis regarding the working mechanism of CRT has been put forward by the group of Frenneaux.[42] They hypothesized that the mechanism of response may be an improvement in LV filling as well as ventricular systolic resynchronization. This hypothesis is based on the finding that patients with heart failure and high end-diastolic pressure (>15mmHg) often exhibit so-called diastolic ventricular interaction indicating that filling of the LV is constrained (external constraint) by the stretched pericardium and the pressure and volume overloaded the right ventricle.[43] In this condition LV pacing may advance LV filling relative to right ventricular filling and thereby delay the onset of diastolic ventricular interaction and improve LV filling. Recently, they have employed conductance catheter derived pressure-volume measurements during unloading by vena cava occlusion to assess external constraint (example is shown in figure 6) with and without LV pacing.[44] The results indicate a reduction in external constraint during LV pacing. The resulting increase in the effective filling pressure is followed by an increase in LV end-diastolic volume and a subsequent increase in stroke volume and stroke work via the Starling mechanism.

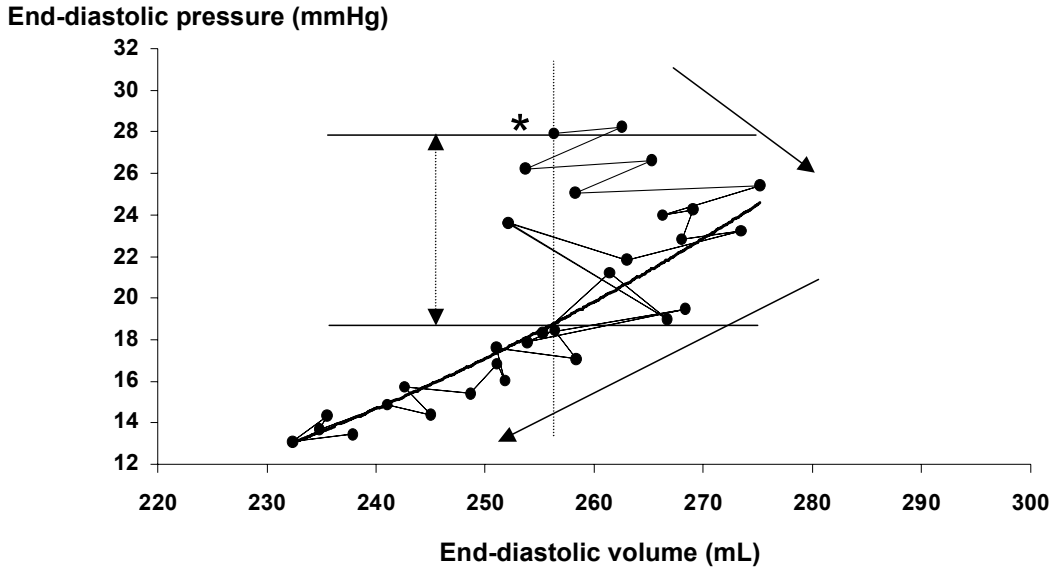

Figure 6. An example of the end-diastolic pressure-volume relation during inferior vena caval occlusion of a patient with significant external constraint. The baseline end-diastolic pressure-volume point is marked with an asterix. During vena cava occlusion LV end-diastolic pressure decreases but initially LV end-diastolic volume increases as represented by the initial right- and downward shift the pressure-volume points. Then LV end-diastolic volume also starts to decrease as indicated by the left- and downward movement of the pressure-volume points. A quadratic regression has been fitted to the subsequent points. External constraint was defined as the pressure difference between the baseline point and the regression line (distance between the two thin horizontal lines) indicated by the dotted vertical arrow

Patient selection

Currently, selection criteria for CRT are typically NYHA III-IV, poor LV function (LVEF < 30-35%) and a wide QRS (> 120-150 ms) with LBBB configuration. However a substantial percentage of patients that fulfill the traditional inclusion criteria do not benefit from CRT.[45] Several approaches to amend this problem have been used or suggested. E.g. the MIRACLE trial used two additional selection criteria: LV end-diastolic dimension of 55 mm or more and a six-minute walking distance of 450 m or less.[46] Recent studies indicate that acute hemodynamic improvement may be predicted by baseline mechanical dyssynchrony, therefore the number of nonresponders may be reduced by adding a pre-implantation assessment of mechanical dyssynchrony and exclude patients who do not show important dyssynchrony.[25-27] An alternative approach is followed by the group in Bad Oeynhausen by performing an invasive pre-implantation test procedure in all CRT candidates to identify responders, and optimize lead position and pacing mode: Temporary pacing electrodes are placed in the right atrium and the right ventricle, and the LV is paced through a temporary lead in a lateral cardiac vein.[47] Various pacing modes are tested and acute hemodynamic benefit is

quantified by measuring femoral artery pulse pressure as a surrogate for stroke volume. Subsequent permanent implantation of a CRT device is only considered in patients showing an increase in pulse pressure greater than 10%. In on-going studies measurements of pressure-volume signals have been added to this protocol. Figure 7 shows a typical example.

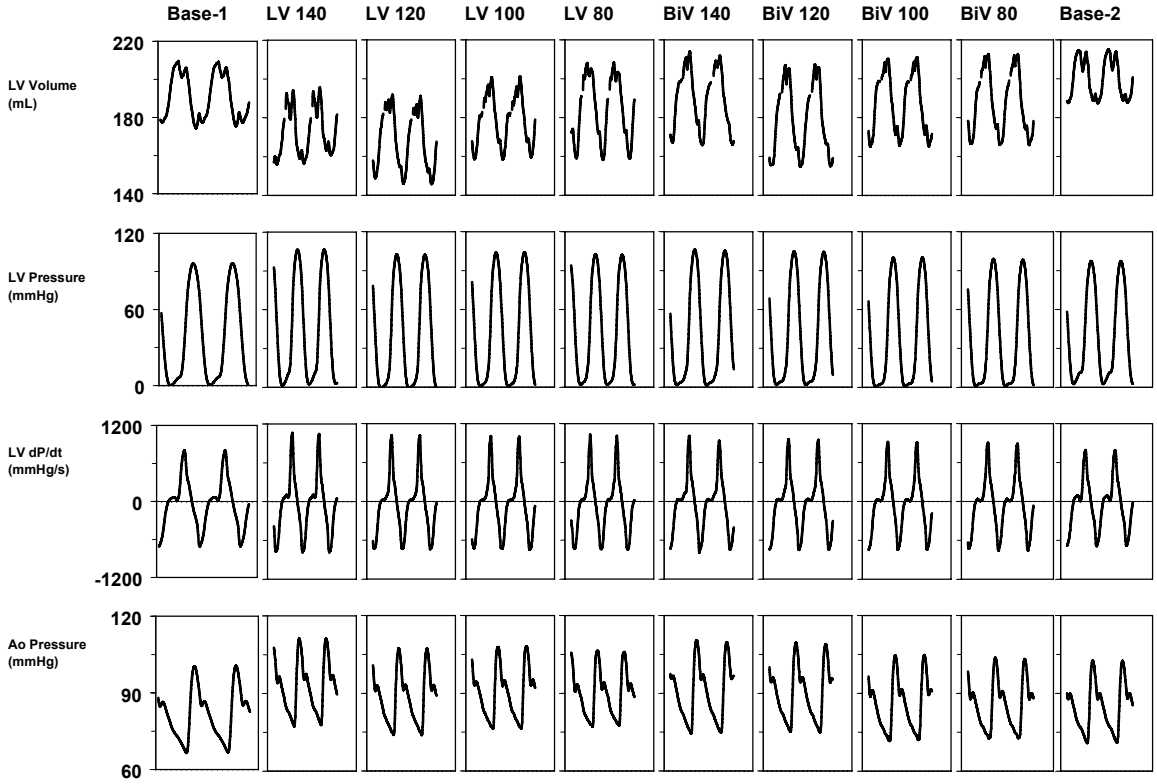

Figure 7. Pre-implantation hemodynamic testing. LV volume, LV pressure, LV dP/dt and femoral artery pressure at baseline and during CRT with LV pacing and biventricular pacing with AV delays set at 140, 120, 100 and 80 ms. Note that the optimal stroke volume (amplitude of LV volume signal) with a reduction in end-diastolic volume is obtained during LV pacing with an AV delay of 120 ms. Similar effects, but with a less pronounced reduction in end-diastolic volume are obtained in this example with biventricular pacing

Optimization

Current CRT involves atrial synchronized ventricular pacing to optimize AV timing, and biventricular pacing to improve intraventricular and interventricular synchrony. Acute hemodynamic studies indicate that optimal contractility and stroke volume requires a patient-specific AV interval[48,49], whereas an optimal RV-LV timing may contribute to a further improvement in synchrony and ejection fraction.[32] Comparison between LV and biventricular pacing has been the subject of several studies[50] but this issue remains unresolved.[37] With regard to lead position the best hemodynamic

response of LV pacing is generally obtained through pacing in the mid-lateral or posterior LV[51-53], which is achieved with leads placed in the posterior or lateral branches of the coronary sinus. Despite advances in percutaneous techniques, special guiding sheaths and improved lead design[47,54], suboptimal lead positioning may still be an important cause of non-response to CRT. Intraoperative epicardial lead placement is currently mainly used as rescue in patients with failed endocardial leads, but may provide an alternative approach with possibilities for optimal lead placement.[55,56] Finally some studies suggest that multiple LV sites may be required for optimal hemodynamic results.[57] Despite a large number of studies many questions regarding optimization of CRT remain disputed. Conceivably studies with the conductance catheter may resolve some of these issues by providing on-line pressure-volume loops which may guide optimization of CRT.

Evaluation

Studies have demonstrated acute hemodynamic improvement after CRT, followed by improvement in symptoms, quality of life and exercise capacity.[46,48,58] More recent studies have provided objective evidence for improved systolic performance and reversed remodeling during long-term CRT which may provide the basis for the clinical improvements.[27,59] The evaluation of long-term hemodynamic effects is complex because it involves alterations in both systolic and diastolic function, and in loading conditions. Although initially the improved systolic function most likely largely reflects improved contraction synchrony, long-term alternation in intrinsic myocardial function may be present e.g. due to alterations in wall stress or sympathetic activity.[60] Interpretation of traditional diastolic indices is complicated because alterations in filling time and mitral insufficiency are present and may interact with changes in intrinsic myocardial function. Analysis in terms of pressure-volume loops and pressure-volume relations is attractive because it provides relatively load-independent indices of systolic and diastolic function. In on-going studies we investigate patients before pacemaker implantation and after 6 months of CRT. The example shown in Figure 8 illustrates reversed remodeling with improved systolic and diastolic function and reduction in mitral regurgitation. Analysis of the segmental conductance signals yielded improved systolic and diastolic mechanical synchrony and reduced internal flow.[61]

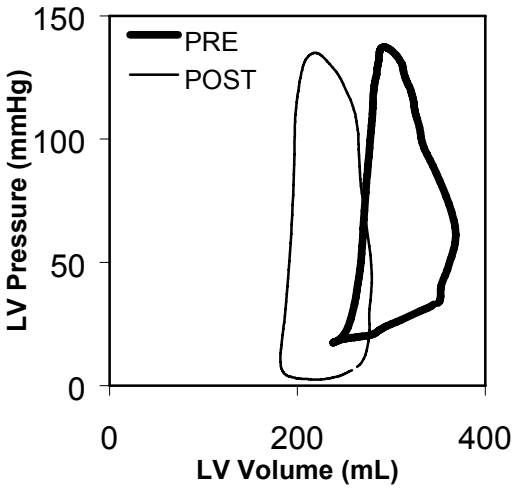

Figure 8. Effects of chronic CRT. Pressure-volume loops at baseline (PRE) and after 6 months of chronic CRT (POST). Note the left ward shift of the pressure-volume loop indicating substantial reversed remodeling. Diastolic pressure decreased and the diastolic part of the pressure-volume loop indicates improved diastolic compliance

CONCLUSION

We conclude that, in the context of CRT, pressure-volume measurements by conductance catheter have been mainly applied to study the basic mechanisms of dyssynchronous and resynchronized cardiac contraction. In this field important new insights were obtained from pressure-volume measurements. There are certainly possibilities and distinct advantages in the field of patient selection but this application will remain limited by the invasive character of the conductance method. Currently, ongoing studies apply pressure-volume measurements to optimize CRT in individual patients and evaluate the long-term hemodynamic effects of CRT. The possibility to assess cardiac function and mechanical dyssynchrony during implantation and study the immediate effects of changes in lead position, AV and VV-delay, in an on-line and quantitative fashion makes this a promising tool to optimize CRT. Load-independent quantitative parameters of systolic and diastolic function derived from pressure-volume relations should provide more insight in the working mechanisms of chronic CRT.

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CHAPTER 8

Hemodynamic effects of long-term cardiac resynchronization therapy -Analysis by pressure-volume loops-

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ABSTRACT

Background. Acute hemodynamic effects of cardiac resynchronization therapy (CRT) have been reported previously, but detailed invasive studies showing hemodynamic consequences of long-term CRT are not available.

Methods and Results. We studied 22 patients scheduled for implantation of a CRT device based on conventional criteria (NYHA class III or IV, left ventricular (LV) ejection fraction <35%, left bundle-branch block, QRS duration >120ms). During diagnostic catheterization prior to CRT we acquired pressure-volume loops using conductance catheters during right atrial pacing at 80, 100, 120 and 140 beats/min. These studies were repeated during biventricular pacing at the same heart rates after 6 months of CRT. Our data show significant clinical benefit of CRT (NYHA class: 3.1±0.5 to 2.1±0.8; Quality-of-Life score: 44±12 to 31±16; 6-min hall-walk: 260±149 to 396±129m; all $p<0.001$), improved LV ejection fraction (29±10 to 40±13%, $p<0.01$), decreased diastolic pressure (18±8 to 13±6mmHg, $p<0.05$), and reverse remodeling (end-diastolic volume: 257±67 to 205±54mL, $p<0.01$). Previously reported acute improvements in LV function remained present at 6 months: dP/dt_{MAX} (+18%, $p<0.01$), dP/dt_{MIN} (+13%, $p<0.01$), stroke work (+34%, $p<0.01$). Effects of increased heart rate were improved towards more physiological responses for LV ejection fraction, cardiac output and dP/dt_{MAX}. Moreover, our study shows improved ventricular-arterial coupling (+69%, $p<0.01$) and improved mechanical efficiency (+44%, $p<0.01$).

Conclusions. Hemodynamic improvements with CRT, which were previously shown in acute invasive studies, are maintained long-term. In addition, ventricular-arterial coupling, mechanical efficiency, and chronotropic responses are improved after 6 months of CRT. These findings may help to explain the improved functional status and exercise tolerance in heart failure patients treated with CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) improves quality of life, symptoms, and exercise capacity in patients with heart failure and intraventricular conduction delay.[1] A recent study confirmed these favorable effects and also demonstrated that CRT significantly reduced the risk of death.[2] Whereas previous randomized controlled trials have clearly demonstrated beneficial clinical effects over a period of up to 6 months,

small-scaled studies suggest that these clinical improvements are maintained long-term.[3-5] The primary working mechanism of CRT is the optimization of the mechanical activation pattern of the left ventricle (LV), which is achieved by pre-excitation of the region which is otherwise activated late due to delayed intrinsic conduction.[6] In addition to this intraventricular resynchronization, additional benefit may be obtained by optimizing the delay between atrial and ventricular systole, and the timing of LV and right ventricle (RV) stimulation. Acute improvements in mechanical dyssynchrony resulting in enhanced systolic function have been demonstrated by various studies.[7-10] Invasive studies have shown increased LV ejection fraction and stroke volume, accompanied by increased systolic pressure, dP/dt_{MAX}, and stroke work, and reduced diastolic pressure.[9,11] Interestingly, these improvements in cardiac function are obtained at diminished energy cost.[12] In the long-term, CRT is associated with LV reversed remodeling[13] and improved myocardial efficiency.[14] However, currently no invasive studies are available regarding the effects of long-term CRT on systolic and diastolic hemodynamic parameters. In this study we assessed the long-term hemodynamic effects of CRT, and investigated the underlying mechanisms. To this end, we acquired pressure-volume loops prior to CRT during right atrial pacing at 80, 100, 120 and 140 beats/min, and these studies were repeated during biventricular pacing at the same heart rates after 6 months of CRT.

METHODS

Patients

Twenty-two patients (mean age, 66±11 years; 17 men) with NYHA class III or IV heart failure despite optimized medical treatment, echocardiographic LV ejection fraction <35% and QRS duration >120ms scheduled for implantation of a CRT device were included. The protocol was approved by our institutional review committee and all patients gave informed consent. The etiology of heart failure was ischemic in 14 and non-ischemic in 8 patients. All patients received stable medical therapy for chronic heart failure, including diuretics (n=19), spironolactone (n=8), β-blockers (n=10), ACE inhibitors (n=20), and amiodarone (n=6). Medication was unchanged and no new therapies were installed during the 6-months follow-up period. In addition to the invasive studies described in detail below, we performed echocardiography, 6-minute

hall-walk tests, and quality of life assessments by the Minnesota Living with Heart Failure Questionnaire at baseline and after 6 months of CRT.

Protocol

Baseline (i.e. pre-CRT) hemodynamic data were obtained during routine diagnostic right and left heart catheterization, including thermodilution cardiac output, left ventriculography and coronary angiography. To acquire pressure-volume loops at incremental heart rates, a 7F combined pressure-conductance catheter (CD Leycom, Zoetermeer, The Netherlands) was placed in the LV via the femoral artery, and a temporary pacing lead was placed in the right atrium. Pressure-volume signals were displayed on-line and digitized at a sample frequency of 250Hz (Leycom CFL, CD Leycom). LV volume was calibrated using thermodilution and hypertonic saline dilution as previously described.[15,16] Right atrial pacing was performed at 80, 100, 120 and 140 beats/min. Data were acquired consecutively approximately 60s after changing to a higher rate, and periods of at least 20s were selected for off-line analysis. All measurements were repeated during recatheterization after at least 6 months of chronic CRT. During this session biventricular pacing was performed at 80, 100, 120 and 140 beats/min by reprogramming the CRT device. The atrioventricular (AV) delay was kept fixed at the optimal clinical setting based on Doppler mitral flow velocity recordings obtained previously at the outpatient clinic.

Data analysis

Analysis of the steady state pressure-volume loops was performed using custom software as previously described.[17] Briefly, for each patient and each pacing rate hemodynamic indexes were calculated as the mean of all beats during a steady state period of approximately 20s. LV function was quantified by cardiac output and stroke volume, end-diastolic and end-systolic volume, LV ejection fraction, end-systolic and end-diastolic pressure, maximal and minimal rate of LV pressure change (dP/dt_{MAX}, dP/dt_{MIN}). The time constant of relaxation (τ) was determined using phase-plot analysis.[18] Stroke work was calculated as the area of the pressure-volume loop. LV end-systolic elastance (E_{ES}) was estimated by end-systolic pressure divided by end-systolic volume, and end-diastolic stiffness (E_{ED}) by end-diastolic pressure divided by end-diastolic volume. Effective arterial elastance (E_A) was calculated as end-systolic pressure divided by stroke volume.[19] Ventricular-arterial coupling was quantified as E_{ES}/E_A,[20] and mechanical efficiency was calculated as the ratio of external stroke work

and pressure-volume area (a measure of total mechanical work).[21] Nonuniform LV performance 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 shifting of blood volume within the LV due to nonuniform contraction and filling. This approach was described and validated in a previous study.[17] Time-varying wall stress, WS(t), was calculated from the instantaneous LV pressure and volume signals (P(t) and V(t), respectively) as described by Arts et al.[22]: $WS(t) = P(t)\cdot(1+3\cdot V(t) / LVM)$. LV mass (LVM) was calculated from M-mode echocardiography according to the conventions proposed by the American Society of Echocardiography.[23] Atrioventricular delay was determined as the time between the right atrial pacing and the start of left ventricular contraction.[24]

Statistical analysis

We used a linear mixed-effects model to account for repeated measurements on each patient. In this model, patients were included as random effects and conditions (baseline, CRT), pacing (80, 100, 120, and 140 beats/min), and their interaction as fixed effects.[25] To assess statistical significances between pacing levels and conditions, appropriate contrasts were selected. Data are presented as mean±SD. A p-value <0.05 was considered statistically significant.

RESULTS

Clinical assessment and atrioventricular delay

All patients were successfully implanted with a CRT device (Contac Renewal, Guidant (n=21), or InSync III, Medtronic (n=1)). All patients received CRT for at least 6 months (7.2±1.6 months). Table 1 shows the clinical parameters which all improved significantly, consistent with previous reports[1]. AV delay was optimized based on Doppler mitral flow velocity recordings at our outpatient clinic shortly after pacemaker implantation: The AV delay was set to achieve the longest left ventricular filling time without premature truncation of the A-wave by mitral valve closure.[26] Baseline AV delay (during right atrial pacing at 80 beats/min) was 184±96 ms and tended to decrease

at higher pacing rates. Mean optimized AV delay with biventricular pacing was 97±15 ms and was unchanged at the higher pacing rates (Table 2).

Table 1. Clinical parameters at baseline (pre-CRT) and after 6 months of CRT

	Baseline	6-mo CRT
NYHA class	3.05±0.49	2.05±0.79 ****
Quality of life score	44±12	31±16 ****
6-min hall-walk, m	260±149	396±129 ****

** p<0.05, ** p<0.01, *** p<0.005, **** p<0.001 vs. baseline by paired t-tests*

Left ventricular function

Figure 1 shows typical examples of pressure-volume loops at 80 beats/min at baseline and after 6 months of CRT from two patients. Full hemodynamic data including the effects of increased pacing rate from all patients are summarized in Table 2. Comparison of 6 months of CRT vs. baseline at the lowest pacing rate (80 beats/min, p80) shows that cardiac output and LV ejection fraction improved significantly, whereas end-diastolic volume and end-systolic volume were significantly reduced. The latter indicates substantial reversed remodeling consistent with previous reports.[13] Improved systolic function was evidenced by a significantly increased dP/dt_{MAX}, E_{ES} and stroke work. In addition, end-diastolic pressure was significantly reduced. Diastolic stiffness E_{ED} and τ showed a non-significant tendency to reduce. dP/dt_{MIN} was significantly improved indicating improved active relaxation. The increase in E_{ES} combined with a modest decrease in E_A resulted in a significantly improved ventricular-arterial coupling ratio (E_{ES}/E_A). The significant increase in external stroke work with unchanged total mechanical work resulted in a significantly improved mechanical efficiency.

*Legends of table 2. p80..p140 indicates paced at 80..140 beats/min; BL, baseline (i.e. pre-CRT) ; CRT, 6-months cardiac resynchronization therapy; Condition effect, BL vs. CRT; Pacing effect, effect of incremental paced heart rate; Interaction effect, condition-pacing interaction; HR, heart rate; AVD, atrioventricular delay; CO, cardiac output; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; SW, stroke work; ESP, end-systolic pressure; EDP, end-diastolic pressure; τ, relaxation time constant; PWS, peak wall stress; WS_{ED}, end-diastolic wall stress; DYS, mechanical dyssynchrony; IFF, internal flow fraction; E_A, effective arterial elastance; E_{ES}, end-systolic elastance; E_{ED}, end-diastolic stiffness; PVA, pressure-volume area; ME = SW/PVA, mechanical efficiency; and E_{ES}/E_A, ventricular-arterial coupling. Statistical significances and contrasts (changes vs. p80) were determined by using a linear mixed-effects model (see text for details). CRT-p80 vs. BL-p80: # p<0.05, ## p<0.01. Changes vs. p80 at same condition (BL or CRT): * p<0.05, ** p<0.01*

Table 2. Left ventricular function indexes at baseline (pre-CRT) and at 6 months of CRT

			Changes vs. p80			P-values of Effects		
		p80	p100	p120	p140	Condition	Pacing	Interaction
HR (beats/min)	BL	78.6±4.4	21.6±0.7**	43.8±0.8**	62.7±0.8**	0.308	<0.001	0.093
	CRT	80.1±2.2	20.6±0.7**	41.1±0.7**	61.8±0.8**			
AVD (ms)	BL	184±96	-12±16	-20±16	-28±17	<0.001	0.832	0.472
	CRT	97±15##	0.4±12	2±12	3±13			
CO (L/min)	BL	4.36±0.70	0.09±0.17	-0.25±0.19	-1.14±0.20**	<0.001	<0.001	0.026
	CRT	4.98±0.86##	0.45±0.17**	0.08±0.17	-0.32±0.19			
ESV (ml)	BL	195±72	4.1±13.6	-5.3±14.7	-15.0±15.9	<0.001	0.615	0.947
	CRT	137±52##	-2.6±12.4	-5.6±12.4	-9.5±14.1			
EDV (mL)	BL	257±67	0.6±15.2	-25.7±16.5*	-44.9±17.8**	<0.001	0.005	0.814
	CRT	205±54##	-4.3±14.0	-14.2±14.0	-21.9±15.8*			
EF (%)	BL	29.1±10.4	-3.5±2.4	-8.9±2.6**	-12.6±2.8**	<0.001	<0.001	0.235
	CRT	39.5±12.8##	-0.2±2.2	-2.3±2.2	-7.4±2.5**			
SW (mmHg·L)	BL	4.37±2.07	-0.82±0.39*	-1.91±0.42**	-2.62±0.49**	<0.001	<0.001	0.468
	CRT	5.87±2.26##	-0.43±0.35	-1.06±0.35**	-2.24±0.39**			
ESP (mmHg)	BL	105±29	-1.2±3.5	-7.0±3.8	-17.6±4.1**	<0.001	<0.001	0.701
	CRT	108±22	-1.8±3.3	-5.7±3.3	-12.1±3.7**			
EDP (mmHg)	BL	17.9±8.2	0.9±1.9	1.7±2.0	3.0±2.2	<0.001	0.013	0.614
	CRT	13.2±6.4#	-0.4±1.8	2.1±1.8	5.7±2.1**			
dP/dt_{MAX} (mmHg/s)	BL	807±264	51±42	39±45	-42±48	<0.001	0.045	0.296
	CRT	953±287##	79±39*	98±39*	77±44			
$-dP/dt_{MIN}$ (mmHg/s)	BL	829±237	5±34	-36±37	-84±40	<0.001	0.105	0.650
	CRT	936±281##	17±32	6±32	-25±37			
τ (ms)	BL	83.1±12.6	-7.0±2.9*	-7.5±3.1*	-13.2±3.3**	0.637	<0.001	0.653
	CRT	81.4±12.7	-3.2±2.7	-8.0±2.7**	-10.7±3.0**			
PWS (mmHg)	BL	342±89	-2.5±20	-22±21	-54±23*	0.149	0.012	0.940
	CRT	331±99	-9.5±18	-19±18	-43±21*			
WS_{ED} (mmHg)	BL	61±26	1.4±8.0	-3.1±8.6	-3.5±9.3	0.142	0.323	0.105
	CRT	47±31	-2.5±7.3	8.5±7.3	19.7±8.2*			
DYS (%)	BL	31.4±3.2	-0.2±1.1	-0.5±1.2	-1.4±1.3	<0.001	0.960	0.346
	CRT	27.4±4.5##	-0.5±1.0	-0.1±1.0	1.2±1.2			
IFF (%)	BL	71±23	-0.7±6.4	-1.0±6.8	-3.2±7.3	<0.001	0.979	0.959
	CRT	42±23##	-0.8±6.0	-2.5±6.0	-0.6±6.7			
E_A (mmHg/mL)	BL	1.94±0.33	0.43±0.11**	1.03±0.12**	2.06±0.12**	<0.001	<0.001	<0.001
	CRT	1.78±0.41	0.25±0.10**	0.74±0.10**	1.29±0.11**			
E_{ES} (mmHg/ml)	BL	0.67±0.43	-0.03±0.10	-0.04±0.11	-0.11±0.12	<0.001	0.902	0.936
	CRT	1.00±0.67##	-0.02±0.09	-0.03±0.09	-0.02±0.10			
E_{ED} (mmHg/mL)	BL	0.074±0.038	0.002±0.011	0.014±0.012	0.035±0.014*	0.777	<0.001	0.810
	CRT	0.067±0.029	0.001±0.010	0.020±0.010	0.050±0.012**			
PVA (mmHg·L)	BL	14.5±4.4	-1.50±0.79	-2.90±0.85**	-5.20±1.06**	0.056	<0.001	0.505
	CRT	13.1±3.2	-0.62±0.71	-1.64±0.71*	-3.44±0.78**			
ME	BL	0.31±0.14	-0.03±0.03	-0.09±0.03**	-0.09±0.04*	<0.001	<0.001	0.470
	CRT	0.45±0.15##	-0.02±0.02	-0.03±0.02	-0.08±0.03**			
E_{ES}/E_A	BL	0.34±0.21	-0.08±0.04	-0.14±0.04**	-0.22±0.05**	<0.001	<0.001	0.841
	CRT	0.57±0.39##	-0.09±0.04*	-0.19±0.04**	-0.23±0.04**			

Mechanical dyssynchrony and internal flow fraction were significantly reduced. Mechanical dyssynchrony was improved at all segmental levels except for the apical segment (Figure 2). Despite the significant reduction in LV volumes, LV wall stress was not significantly reduced. This was due to a concomitant significant reduction in LV mass from 324±92g at baseline to 290±107g ($p<0.001$) after 6 months of CRT.

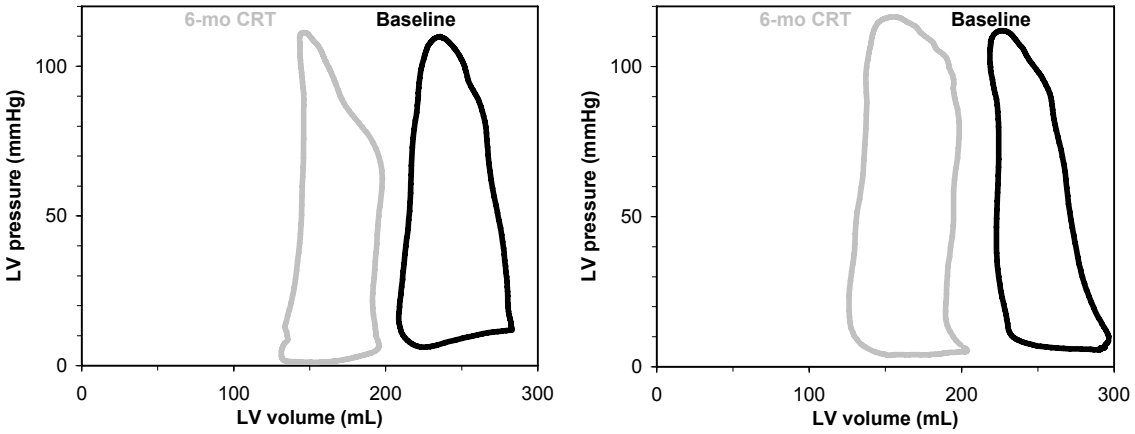

Figure 1. Effects of chronic CRT in two patients. Typical pressure-volume loops at baseline (grey) and after 6 months of chronic CRT (black) are shown (in all cases at a heart rate of 80 beats/min). Note the left ward shift of the pressure-volume loops indicating substantial reversed remodeling

Responses to increased heart rate

Table 2 shows mean values at baseline and 6-months CRT for all hemodynamic indexes at 80 beats/min, and the related changes during pacing at 100, 120 and 140 beats/min. The mean values of the main indexes are also graphically displayed in Figure 3. At baseline, cardiac output did not increase with incremental pacing, but rather cardiac output was significantly reduced at 140 beats/min, indicating an exhausted chronotropic reserve in these heart failure patients. In contrast, at 6 months follow-up, cardiac output, which was significantly higher at 80 beats/min compared to the same heart rate at baseline, increased further at 100 beats/min and remained stable at higher rates (Figure 3A). Similarly, at follow-up, LV ejection fraction was significantly higher at 80 beats/min, and the reduction in LV ejection fraction at incremental pacing was substantially less pronounced than at baseline (Figure 3B). The negative chronotropic responses at baseline mainly resulted from a rapid decrease in end-diastolic volume with incremental pacing, with a less pronounced drop in end-systolic volume. After 6 months of CRT, the reduction in end-diastolic volume was more limited (only significant at 140 beats/min) whereas end-systolic volume remained unchanged (Figure 3C).

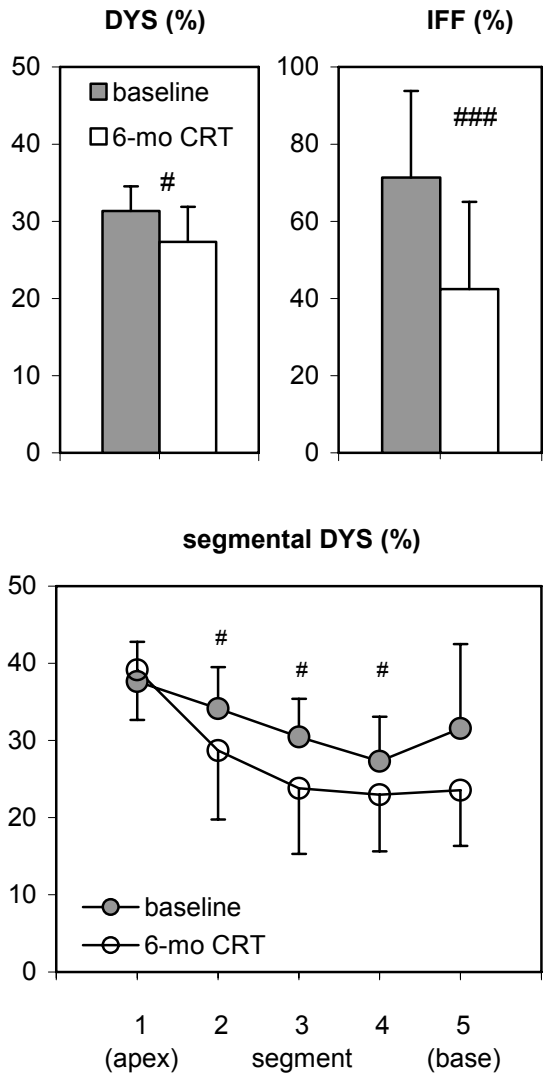

Figure 2. Mechanical dyssynchrony (DYS) and internal flow fraction (IFF) at baseline and after 6 months of CRT (at 80 beats/min). DYS is also shown per segment. Significances vs. baseline: # p<0.05, ## p<0.01, ### p<0.005, #### p<0.001

At the same time systolic pressure dropped significantly at 140 beats/min both at baseline and at 6 months of CRT, and diastolic pressure tended to increase with pacing rate at both time-points. These effects are clearly shown by the average (i.e. based on mean end-systolic and end-diastolic pressures and volumes) pressure-volume loops in Figure 4. Note the substantial reverse remodeling evidenced by the leftward shift of all pressure-volume loops at 6 months of CRT, and the fact that stroke volume (the width of the pressure-volume loops) was better maintained during increased heart rate after 6 months of CRT.

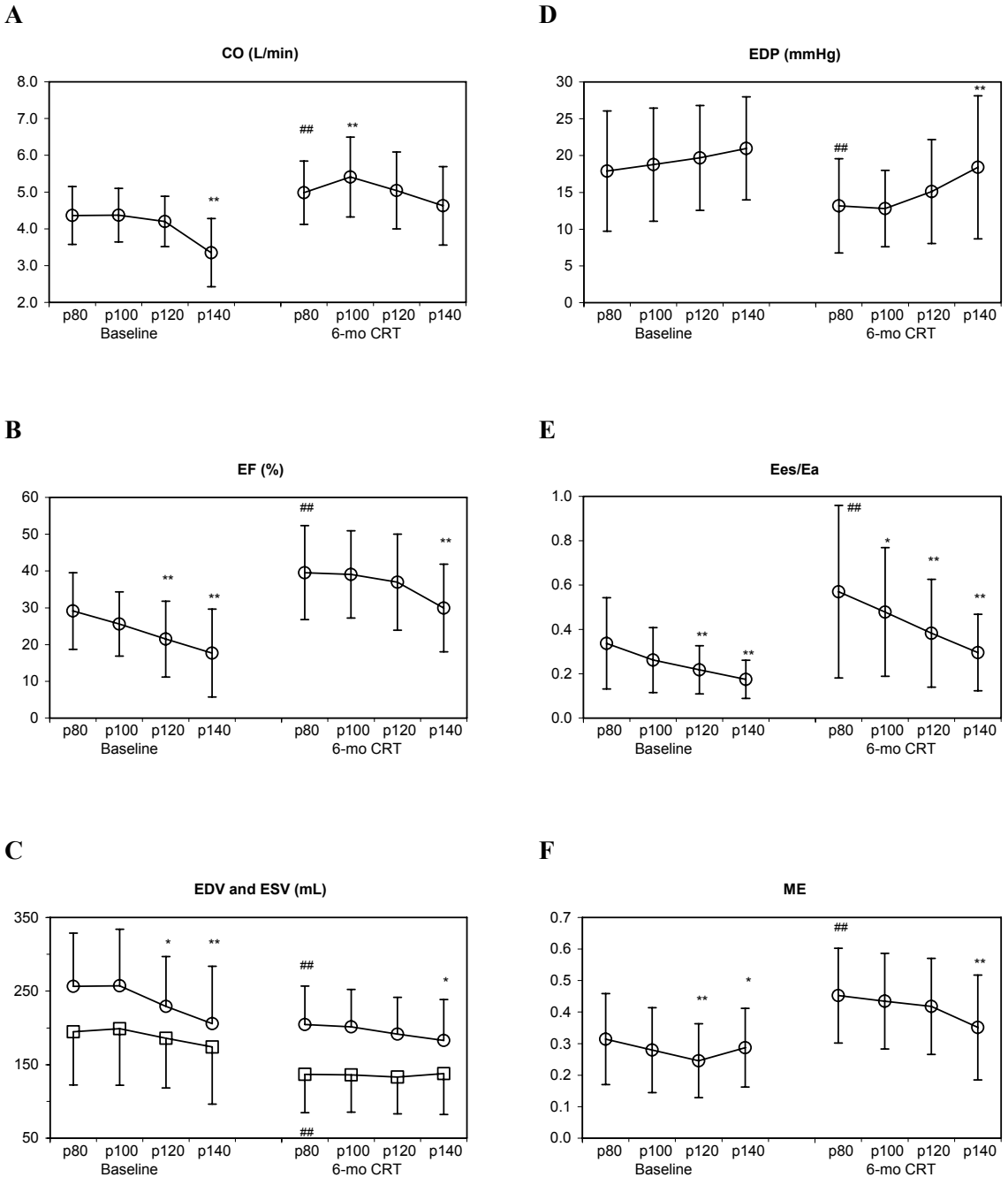

*Figure 3. Main hemodynamic indexes at baseline and after 6 months of CRT. CO indicates cardiac output; EDP, end-diastolic pressure; EF, LV ejection fraction; E_{ES}, end-systolic elastance; E_A, arterial elastance; EDV, end-diastolic volume; ESV, end-systolic volume; ME, mechanical efficiency. The Figures show mean±SD at 80, 100, 120 and 140 beats/min (p80, p100, p120 and p140). Significances vs. p80 at the same condition (baseline or CRT): * p<0.05, ** p<0.01. Significances at p80 for CRT vs. baseline: # p<0.05, ## p<0.01*

Interestingly, after 6 months of CRT, dP/dt_{MAX} showed a significant increase at higher pacing levels as compared to the value at 80 beats/min, whereas at baseline no significant increases were found during incremental pacing. This indicates a more

physiological response after 6 months of CRT. This is illustrated in Figure 5, which shows LV pressure and LV dP/dt for the different heart rates at baseline and after 6 months of CRT in a typical patient. Note the higher dP/dt_{MAX} after 6 months of CRT and the gradual increase in dP/dt_{MAX} with increased pacing rate, which was absent at baseline. This change towards normalization of chronotropic response was not found for dP/dt_{MIN}. Ventricular-arterial coupling, quantified by the ratio of ventricular and arterial elastance, was highly abnormal in the heart failure patients, but improved significantly after 6 months of CRT. The drop in E_{ES}/E_A with increased heart rate was still present after CRT (Figure 3E). Likewise, mechanical efficiency was improved at follow-up, but dropped significantly at 140 beats/min both at baseline and after 6 months of CRT (Figure 3F).

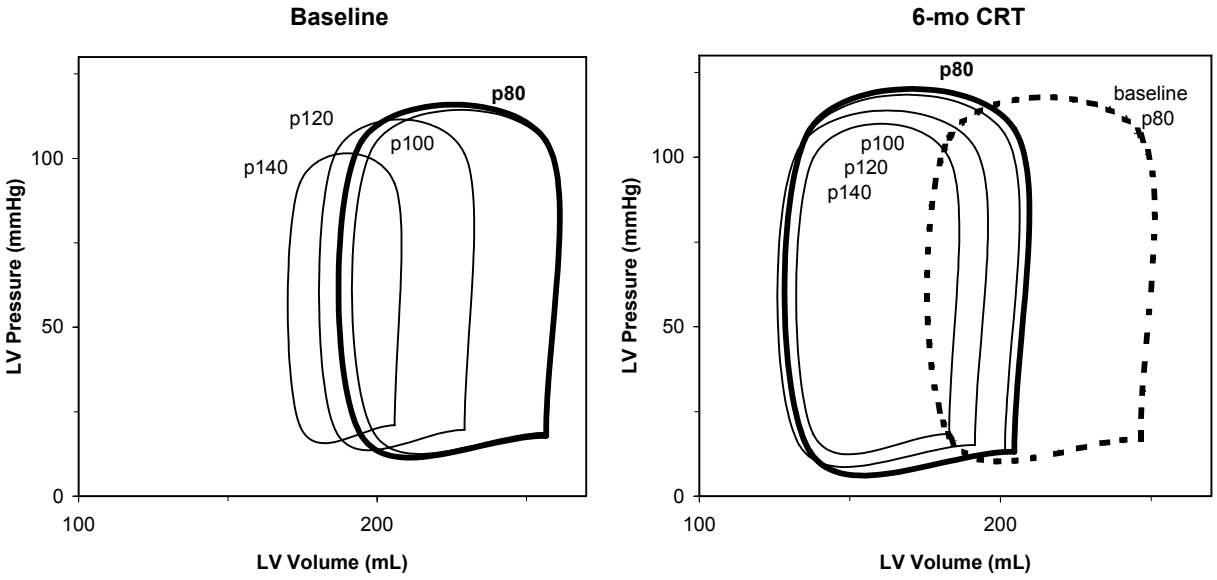

Figure 4. Mean pressure-volume loops at baseline and after 6 months of CRT. Mean pressure-volume loops are based on mean end-systolic and end-diastolic pressures and volumes and are shown at heart rates 80, 100, 120 and 140 beats/min. At baseline we used right atrial pacing via a temporary pacing lead; at follow-up biventricular pacing was performed by reprogramming the CRT device

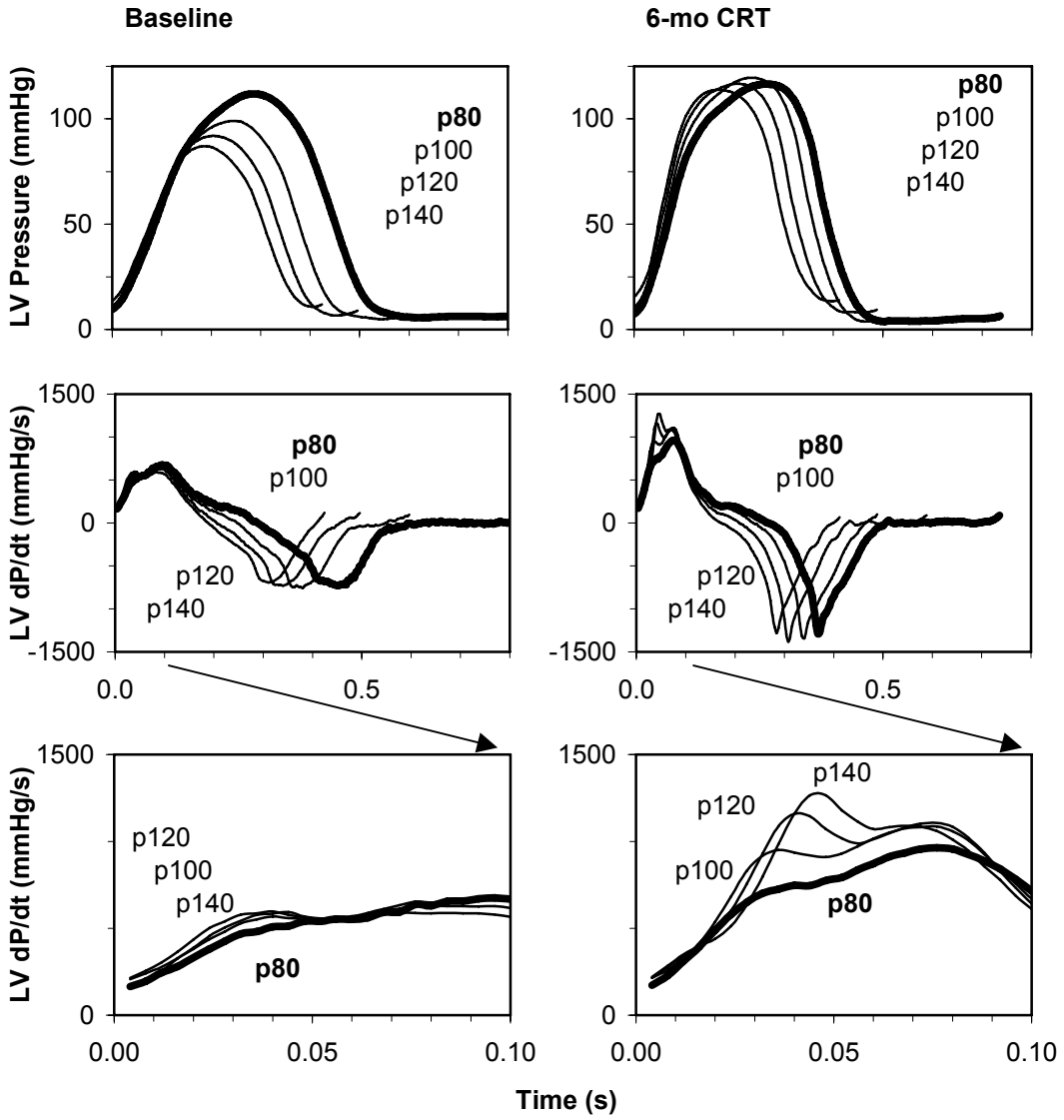

Figure 5. Typical examples of LV pressure and LV dP/dt during incremental pacing rate at baseline and after 6 months of CRT. Note that dP/dt_{MAX} was unchanged with increasing heart rate at baseline, whereas dP/dt_{MAX} substantially increased after CRT (See the bottom panels which extent the first 100ms of the dP/dt tracings)

DISCUSSION

CRT is a highly effective new therapy in patients with left bundle-branch block and severe heart failure. Large-scale studies have reported long-term clinical benefit with improved LV function and reverse LV remodeling.[1,6,13,27] In these studies, follow-up is generally performed with echocardiography, and improvements in LV function are reported mainly in terms of increased ejection fraction. Detailed invasive hemodynamic studies of the acute effects of CRT, including analyses with pressure-volume loops[12,28], have been published previously, but to our best knowledge no such data are available

for chronic CRT. In the present study we obtained invasive hemodynamics by pressure-volume loops at baseline and after 6 months of CRT. Our data confirm previous findings regarding clinical benefit, improved LV ejection fraction and reverse remodeling. In addition, it shows that hemodynamic improvements in terms of increased dP/dt_{MAX}, dP/dt_{MIN} and stroke work, and reduced end-diastolic pressure, previously found in acute studies[6,11,28,29], are still present at 6 months follow-up.

Moreover, our study shows improved ventricular-arterial coupling and improved mechanical efficiency. These hemodynamic findings are consistent with the observed improvements in clinical and functional status. The altered responses to increased heart rate may partly explain the improved exercise capacity of patients treated with CRT. At baseline, cardiac output was unchanged when heart rate was increased illustrating the exhausted LV function reserve of these patients. At follow-up this is converted to a more physiological response although the capacity to increase cardiac output is still limited. The latter presumably is partly due to an abnormal relaxation reflected by a relatively long isovolumic relaxation time (τ), which did not improve after CRT. In the normal heart, τ substantially shortens at higher heart rate, which enables adequate filling despite a shortened diastolic period. This response is largely lost in heart failure, and did not normalize after 6 months of CRT in our patients. Consistent with our findings, previous studies failed to show improvements in isovolumic relaxation neither with acute biventricular pacing[29,30] nor at long-term.[13] A theoretical model by Hay et al.[31] shows a close correlation between increased τ and increased diastolic pressure, which is most evident at high heart rates. Our data are consistent with this prediction and show that the phenomenon is still present after 6 months of CRT. The improved mechanical efficiency found in our study is in line with previous studies on acute effects of CRT by Nelson et al.[12] and is consistent with studies by, e.g., Sundell et al.[14] in patients treated long-term. Most likely, the improved mechanical intraventricular synchrony underlies the more efficient conversion of total mechanical energy to external stroke work. This is most evident from a highly significant reduction in internal flow fraction from 71 to 42%, which indicates that segmental volume changes are more efficiently used for effective ejection rather than for energy-wasting shifting of blood volumes between segments within the ventricle. In addition, ventricular-arterial coupling was significantly improved which further optimizes production of external work.[32,33] However, whereas in the normal heart optimal ventricular-arterial coupling is maintained with increased heart rate[34], E_{ES}/E_A significantly dropped in our patients and this abnormal response was still present after long-term CRT. The baseline values for mechanical efficiency and

ventricular-arterial coupling found in our study (0.31 and 0.34, respectively) were in the same range but somewhat lower than values reported by Kim et al.[35]: 0.38 and 0.42, respectively. However, the patients in their study had less severe heart failure evidenced by an average NYHA classification of 1.8±0.7 and an LV ejection fraction of 37±13%. Asanoi et al.[36] reported that in the failing heart homeostatic mechanisms maintain arterial blood pressure within the normal range, but that this blood pressure level causes a deviation from energetically optimal conditions in hearts with a severely reduced contractile state. This discrepancy results from worsening of ventricular-arterial coupling and decreased mechanical efficiency. Conversely, the improved ventricular-arterial coupling and mechanical efficiency after 6 months of CRT, as found in our study, constitutes a more optimal energetic condition. Interestingly, despite the substantial reverse remodeling in our study, wall stress was not significantly reduced after 6 months of CRT. This was due to a concomitant reduction in LV mass. We would hypothesize that the regression in LV volumes initially leads to a reduction in wall stress, which then in turn may cause a reduction in LV hypertrophy. Note however that, although not statistically significant, diastolic wall stress was reduced by 23% at 80 beats/min and by 30% at 100 beats/min. At higher heart rates, wall stress was virtually unchanged or even increased compared to baseline (-5% at 120 beat/min, and +24% at 140 beats/min). This finding is explained by the fact that at baseline end-diastolic volume drops substantially at the high heart rates (which also limits the increase in end-diastolic pressure), whereas end-diastolic volume is better maintained at 6-months follow-up. Furthermore, the global model to calculate wall stress does not take into account spatial dyssynchrony, and conversion to a more uniform contraction pattern at 6-months follow-up may lead to reductions in wall stress at a regional level.

In our study we used simultaneous biventricular pacing in all patients. Sequential biventricular pacing has been proposed to optimize CRT, and either right ventricular or left ventricular pre-excitation may optimize hemodynamics in individual patients.[8,37] However, Hay et al.[28] demonstrated that sequential biventricular stimulation offered minimal benefit and that, on the average, most systolic and diastolic function parameters reached a maximum with simultaneous pacing. In addition to improvement of intra- and interventricular dyssynchrony, the patients may also have benefited from optimization of the AV delay. In our study the AV delay was reduced from a baseline value of 184±96 ms to a mean value of 97±15 ms during CRT. Studies by Auricchio et al.[24] showed that the maximal increases in pulse pressure and dP/dt_{MAX} were obtained at

45% of the intrinsic AV interval. Consistently, most studies report optimal AV delays of 100-120 ms, but small differences in delay have far less influence than pacing site.[29] Because our baseline studies were performed prior to implantation of the CRT device we could not assess the acute hemodynamic effects of CRT. However, these effects were documented in previous studies. Acute improvements in CO or SV, in most studies assessed by changes in aortic pulse pressure, were reported to be in the range of 7 to 15% [3,11,24,28,29,38,39], which is comparable to the 14% increase found at 6-months in our study. Previous studies show an acute reduction of 10 to 18% in end-systolic volume, and a relatively smaller reduction in end-diastolic volume of 5 to 9% [8,30,39] , which lead to 15 to 33% relative improvement in EF. The reductions in end-systolic and end-diastolic volume at 6 months in our study were 30 and 20%, respectively. Apparently, the acute improvement in cardiac output is maintained long-term, but both end-systolic and end-diastolic volume show a gradual, more or less parallel, further reversed remodeling, as previously documented over a 3-months period by Yu et al.[27] With regard to dP/dt_{MAX}, previous studies fairly consistently showed an acute increase of 13 to 21% [3,7,11,24,28,29,38], which is close to the 18% increase found in our study at 6-months follow-up. Yu's study revealed that more than 60% of the gain in dP/dt_{MAX} obtained after 3 months CRT is lost immediately after turning off the pacemaker, whereas 4 weeks after cessation of CRT dP/dt_{MAX} had completely returned to pre-CRT values. Their study also showed that left ventricular volumes increased and other echocardiographic benefits were gradually lost over the 4-week period. We did not systematically investigate the effects of turning off the pacemaker, but in a few patients we registered pressure-volume loops during temporary cessation of pacing in the follow-up study. Figure 6 shows two typical examples: The pressure-volume loops show an immediate reduction in stroke volume, whereas dP/dt_{MAX} was decreased by 20 and 7%, respectively. These immediate on-off responses are very similar to those registered previously in acute studies.[29]

Limitations

The sample size in our study was too small to justify a meaningful responder/non-responder analysis. Only 4 patients did not show an improved clinical status: 3 patients with NYHA class III remained in class III, one class III patient deteriorated to class IV. All other patients improved by 1 or 2 NYHA classes. In the 'non-responder' group the baseline end-diastolic volume and end-systolic volume (282±73 and 228±70 mL,

respectively) appeared to be somewhat higher than in the group as a whole, and ejection fraction somewhat lower (21±6%).

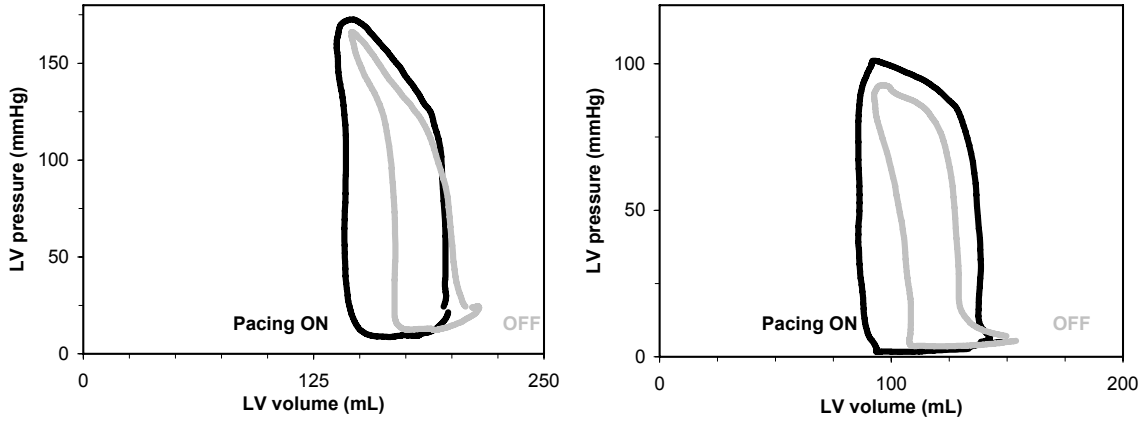

Figure 6. Immediate effects of cessation of biventricular pacing after 6-months CRT in two patients. Typical pressure-volume loops during pacing ON (black) and OFF (grey). Note the immediate reduction in stroke volume

In conclusion, our study shows that hemodynamic improvements that were previously shown in acute studies are maintained with long-term CRT. In addition, ventricular-arterial coupling, mechanical efficiency, and chronotropic responses are improved after 6 months of CRT. These findings may help to explain the improved functional status and exercise tolerance in heart failure patients treated with cardiac resynchronization.

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CHAPTER 9

Clinical efficacy of surgical ventricular restoration and restrictive mitral annuloplasty in patients with end-stage heart failure

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ABSTRACT

Background. Surgical ventricular restoration (SVR) and restrictive mitral annuloplasty (RMA) are increasingly performed for end-stage heart failure. We studied their clinical efficacy in patients with end-stage heart failure.

Methods. We included 33 patients with NYHA class III/IV and left ventricular ejection fraction ≤ 35%. In this group, patients with moderate to severe mitral regurgitation (grade ≥ 2) underwent RMA and patients with anteroseptal aneurysm underwent SVR. A combined procedure (SVR and RMA) was performed in 12 patients, isolated SVR in 5 patients and isolated RMA in 16 patients. Additional coronary artery bypass grafting was done in 27 patients. Clinical parameters, including NYHA classification, Minnesota Quality of Life (QoL) questionnaire, and 6-minute walking distance, were assessed at baseline and 6 months after surgery.

Results. In the total group, operative mortality was 3% (n=1), in-hospital mortality was 9% (n=3), and there was no late mortality. Four patients (12%) needed post-operative intra-aortic balloon pump support. The median duration at intensive care was 4 days (range: 2-28) with a median hospital stay of 13 days (range: 7-49). All clinical parameters were significantly improved at 6 months follow-up ($p<0.001$); NYHA classification was improved from 3.4±0.5 to 1.5±0.5, QoL questionnaire score was improved from 44±22 to 16±12, and 6-minute walking distance was increased from 248±134 to 422±113 m.

Conclusions. Surgical treatment of end-stage heart failure by SVR and/or RMA was associated with 12% mortality at 6 months. Surviving patients showed a highly significant clinical improvement.

INTRODUCTION

Chronic heart failure is one of the major healthcare problems in the world both in terms of patient numbers, hospitalizations, and economic costs. In the United States, 4 to 5 million people have chronic heart failure, which leads to more than 2 million hospitalizations each year.[1] Despite optimal medical therapy, many patients remain severely symptomatic. In these patients, cardiac transplantation remains the most effective surgical therapy with 1-, 5- and 10-year survival rates of 94, 78, and 46%,

respectively.[2,3] Although effective, heart transplantation is importantly hindered by donor shortage, chronic rejection, and complications related to medication.

Given the limitations of medical therapy and cardiac transplantation, alternative surgical therapies such as surgical ventricular restoration (SVR) and restrictive mitral annuloplasty (RMA) have been introduced and are currently widely performed in patients with end-stage heart failure.[4,5] These therapies aim to correct frequently observed end-stage complications as left ventricular aneurysm and mitral regurgitation.[6,7] If not treated, these complications usually have important adverse effects on long-term morbidity and survival.[8-10]

A long-term study by the RESTORE-group has demonstrated that SVR is safe and highly effective in the treatment of ischemic cardiomyopathy with a reduction of end-systolic volume and a five-year survival of 69%.[11] Several studies reported promising results in patients with heart failure treated with RMA with one- and two-year survival rates of 86% and 84%, respectively.[12,13]

In the present study, clinical efficacy was evaluated six months after surgery in a cohort of patients with end-stage heart failure who underwent combined SVR and RMA, isolated SVR or isolated RMA.

METHODS

Patients

We included 33 patients with end-stage heart failure, NYHA classification III or IV with left ventricular ejection fraction ≤ 35%. These patients underwent heart failure surgery for anteroseptal aneurysm and/or moderate to severe mitral regurgitation. Twelve patients had both anteroseptal aneurysm and moderate to severe mitral regurgitation (grade ≥ 2) and they underwent combined SVR and RMA; 5 patients had an anteroseptal aneurysm and underwent isolated SVR (SVR group, n=17). Another 16 patients had severe mitral regurgitation (grade > 2) and no aneurysm and thus underwent isolated restrictive mitral annuloplasty (RMA group, n=16). All patients received stable medical therapy for chronic heart failure, including diuretics, spironolactone, β-blockers, and ACE-inhibitors. The institutional review board approved the study protocol and all patients provided informed consent. Patient characteristics are summarized in table 1.

Table 1. Patient characteristics

Variable	N=33
Gender (M/F)	20/13
Age, yrs	64±12
Etiology (ischemic vs non-ischemic)	29/4
NYHA class	3.4±0.5
Duration of symptoms (median, months)	8 (2-62)
LVEF, %	27±8
Medication:	
- Diuretics/spironolactone	25 (76%)
- Nitrates	7 (21%)
- ACE-inhibitors/A-II antagonists	26 (79%)
- β-blockers	21 (64%)
- Anticoagulants/aspirin	22 (67%)

NYHA, New York Heart Association. LVEF, left ventricular ejection fraction, ACE, Angiotensin Converting Enzyme; A-II, Angiotensin II

Evaluation of mitral regurgitation

In patients with moderate to severe mitral regurgitation (grade ≥2) on transthoracic echocardiography (TTE), additional transesophageal echocardiography (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 regurgitation. The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images. Mitral regurgitation was 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%).[14,15] The severity and precise mechanism of mitral regurgitation was confirmed from the TEE images.

When the severity of mitral regurgitation was grade 2, an intraoperative loading test (as described previously) was performed.[16,17] Briefly, a preload test is performed by rapid infusion of volume through the aortic cannula until the pulmonary artery capillary wedge pressure increases by 15 mmHg. During this provocative test, the severity of mitral regurgitation is continuously monitored, and patients who deteriorated to grade 3 or 4 mitral regurgitation underwent RMA. Immediately after surgery, TEE was repeated to assess residual mitral regurgitation, transmitral diastolic gradient (determined from continuous-wave Doppler), and length of coaptation of the mitral leaflets.

Surgical procedures

SVR was performed by the endoventricular circular patch plasty as previously described by Dor.[18,19] Briefly, the left ventricle 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 55mL/m^2 body surface area saline was introduced into the left ventricle 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 septal scar and to delineate a new apex with the goal to restore the normal elliptical shape.

Stringent restrictive mitral annuloplasty (2 sizes smaller than measured) was performed via an atrial transseptal approach using a Carpentier Edwards Physio ring (Edwards Lifesciences, USA) as previously described.[20] Additional coronary artery bypass grafting was performed, if indicated.

Clinical evaluation

Patients were evaluated at the outpatient clinic at baseline and at 6 months after surgery. Heart failure symptoms were classified using the NYHA score. Quality of Life score was assessed using the Minnesota Living with Heart Failure questionnaire.[21] This questionnaire contains 21 questions concerning the patient's perception of the effects of heart failure on daily life activities. Questions are scored from 0 to 5, resulting in a total score from 0 to 105, with the highest score reflecting the worst quality of life. Exercise tolerance was evaluated using 6-minute hall-walk tests at both visits.[22]

Statistics

Baseline and follow-up data were compared with paired t-tests. Statistical significance was assumed at $p < 0.05$. All data are presented as the mean value ± SD.

RESULTS

Mean cardiopulmonary bypass (CPB)-time was 192±64 minutes with a mean aortic cross-clamp time of 132±49 minutes. Weaning from CPB was uneventful in almost all patients. However, in one case a patient developed an irreversible vasoplegic shock after weaning from CPB and died during surgery (3% operative mortality) and four patients

(12%) needed post-operative intra-aortic balloon pump support. There were no peri-operative myocardial infarctions. Three additional patients died in the hospital (9%); one patient who underwent combined SVR/RMA died 30 days postoperatively due to a cerebrovascular accident, one patient (isolated SVR) died 5h postoperatively due to left ventricular failure, and one patient (isolated RMA) died 7 days postoperatively due to left ventricular failure. Early non-fatal complications consisted of postoperative atrial fibrillation (3 patients), cerebrovascular accidents (1 patient), and renal failure (1 patient). One patient developed postoperative sepsis with an empyema in the pleural space, which required surgical evacuation and this patient stayed 54 days at ICU with a total hospital stay of 66 days. For the remaining patients, the median duration at intensive care was 4 days (range: 2-28) with a median hospital stay of 13 days (range: 7-49). In the total group, we had no late mortality during the 6 months follow-up period. Thus, overall mortality in our patient group was 12% at 6 months and complete clinical assessment was performed in the 29 surviving patients.

Mitral regurgitation

The mean grade of mitral regurgitation at baseline in the patients who underwent RMA was 3.0±0.6. The length of the anterior mitral leaflet (AML) was 2.88±0.30 cm with a mean mitral annular diameter (MAD) of 4.08±0.55 cm (mean ratio MAD/AML 1.42±0.18). After surgery, no recurrence of mitral regurgitation was observed in these patients (0.3±0.4) with restored length of leaflet coaptation of 0.82±0.19 cm and a mean gradient of 2.9±1.3 mmHg.

NYHA score

In the total group, the mean NYHA score improved from 3.4±0.5 at baseline to 1.5±0.5 at 6 months follow-up ($p< 0.001$) (Figure 1). In both the RMA and SVR patients the improvements in NYHA score was similar; in the RMA patients NYHA score improved from 3.4±0.5 at baseline to 1.5±0.5 at 6 months follow-up ($p< 0.001$) and in the SVR patients NYHA score improved from 3.5±0.5 at baseline to 1.5±0.5 at 6 months follow-up ($p< 0.001$).

Quality-of-Life Minnesota score

Quality of Life score in the total group at baseline was 44±22 and decreased by 64% to 16±12 at 6 months follow-up ($p< 0.001$) (Figure 1). The change in the total group was

similar to changes in the RMA (-63%) and SVR (-65%) subgroups. In the RMA patients Quality of Life score was decreased from 48±23 at baseline to 18±11 at 6 months follow-up ($p< 0.001$) and this score was decreased from 40±21 at baseline to 14±12 at 6 months follow-up ($p=0.002$) in the SVR patients.

Six-minute hall-walk test

The mean walking distance in the total group of patients was 248±134 m at baseline and improved by 70% to a mean walking distance of 422±113 m at 6 months follow-up ($p< 0.001$) (Figure 1). In the RMA patients the mean distance walked was 238±151 m at baseline and improved significantly ($p <0.001$) to 438±110 m at 6 months follow-up. In the SVR patients, the mean walking distance increased from 258±120 m at baseline to 406±117 m at 6 months follow-up ($p< 0.001$).

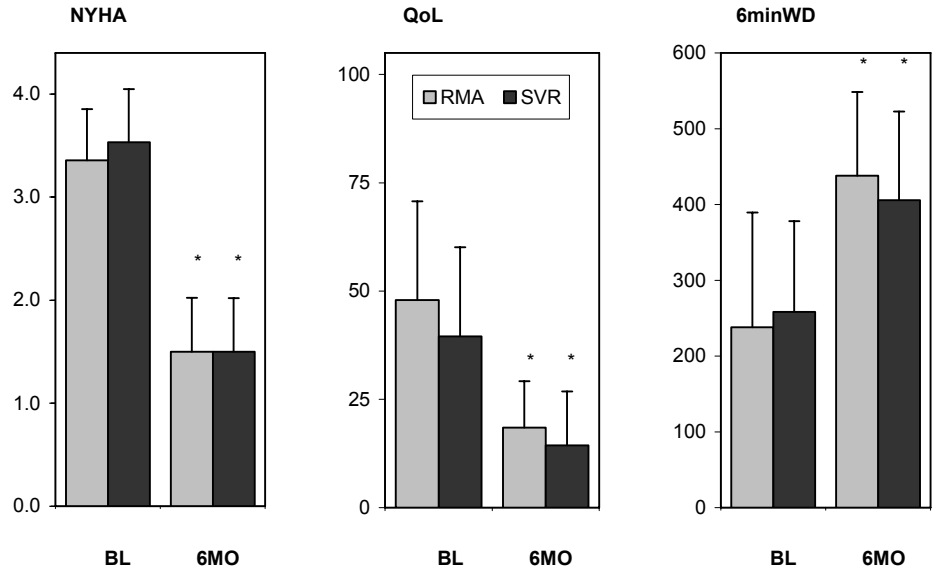

*Figure 1. NYHA classification, quality-of-life (QoL) score, and 6-minute walking distance (6minWD) at baseline (BL) and at 6 months follow-up (6MO) for the RMA and the SVR groups. Significant improvements were observed in all parameters at 6 months follow-up in both groups. No significant differences were found between groups. * p < 0.002 versus baseline*

DISCUSSION

Heart transplantation is now considered standard treatment for select patients with end-stage heart disease; but it is only applicable to a small number of patients. In an effort to address this problem, alternative surgical therapies are evolving, including SVR and

RMA, and other approaches. These operative techniques to alter the shape of the left ventricle, in combination with optimal medical management for heart failure, may improve survival. In some patients it may even avoid or postpone transplantation.

The purpose of the present study was to evaluate the clinical efficacy of these treatments using NYHA classification, Minnesota Living with Heart failure questionnaire, and 6-minute hall-walk test in a cohort of patients with end-stage heart failure who underwent SVR and/or RMA at our institution.

We found that the surgical treatment was associated with 12% mortality at 6 months and resulted in an improvement in symptoms (NYHA class), accompanied by improvement in 6-minute walking distance and Quality of Life score. Our results regarding mortality are in line with the results of Dor et al. who reported 12% operative mortality in 835 patients with end-stage heart failure.[23] Earlier studies by Di Donato et al. indicated a 19% in-hospital mortality and 26% mortality at one-year follow-up.[24] However, the mean left ventricular ejection fraction in Di Donato's group was 17±3%, while the mean ejection fraction in our series was 27±8% and in Dor's group only about 10% of the patients had an left ventricular ejection fraction < 20%. More recently, Qin et al. reported a lower rate of mortality at six months follow-up of 5% in 60 patients who underwent SVR with or without mitral valve repair.[25] Similar findings were reported by the RESTORE group with a 30-day mortality after SVR of 5.3% (8.7% with mitral repair vs. 4.0% without repair).[11] However, in this large patient population, also patients with NYHA classification I/II were included. In all these previous studies, a significant improvement in NYHA classification has been observed at long-term follow-up, which was similar to the improvement found in our series.

The aim of alternative surgical interventions (SVR and RMA) in patients with end-stage heart failure is to reduce left ventricular wall stress leading to reduced oxygen demand, improved mechanical dyssynchrony and mechanical efficiency. These effects may result in improvement of global and intrinsic systolic function. These theoretical assumptions were recently confirmed by hemodynamic studies in patients with end-stage heart failure.[26,27] Operative mortality of both SVR and RMA are acceptable, however long-term results are limited to survival rates, NYHA classification and hemodynamic parameters.[11,12,28] Therefore, it is still relatively unknown whether these therapies lead to improvement of clinical status of the patient. Although previous studies indicate improvement in NYHA classification, to our best knowledge, our study is the first to show that these interventions lead to clinical improvement using 6-minute walking distance and Quality of Life score at 6-months follow-up. Our study did not include a

control group. However, previous epidemiological studies indicate that 1-year mortality rate in class III/IV heart failure patients is around 50%. [29] In comparison, the clinical efficacy of our surgical approach in terms of Quality of Life and 6-minute walking distance appears to be similar to the outcome after biventricular pacing in patients with end-stage heart failure.[30-32]

Limitations

This study represents a single-center experience in a relatively small cohort of patients with a combined surgical approach of SVR and/or RMA. Subgroup analysis did not show statistical differences, but the groups were relatively small and treatment obviously was not randomized. Moreover, this comparison should be taken with caution because, despite similar baseline clinical parameters, the etiology was different between groups.

In conclusion, surgical treatment of end-stage heart failure by SVR and RMA seems relatively safe and surviving patients have clear clinical benefit at six months follow-up. Long-term prospective clinical randomized trials should be performed to assess benefit over optimal medical therapy.

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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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CHAPTER 11

Sustained left ventricular reverse remodeling, improved systolic function and unchanged diastolic function six months after surgical ventricular restoration
-Analysis by pressure-volume loops-

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ABSTRACT

Background. Previous studies have demonstrated that surgical ventricular restoration (SVR) has acute beneficial effects on mechanical dyssynchrony and left ventricular (LV) systolic function. However, chronic effects on systolic and diastolic function are largely unknown.

Methods. We studied 8 patients with ischemic dilated cardiomyopathy who underwent SVR, restrictive mitral annuloplasty and coronary artery bypass grafting. In all patients, invasive hemodynamic measurements by the conductance catheter were performed before and six months after surgery. In addition, NYHA classification, six-minute walk-test, Minnesota Living with Heart failure questionnaire were assessed at the same time-points.

Results. At six months follow-up, all patients were alive and clinically improved significantly (NYHA from 3.6±0.5 to 1.5±0.5, Minnesota-score from 45±23 to 16±16, and six-minute walking distance from 300±133 to 442±89 m). Hemodynamic data showed significantly improved LV ejection fraction (from 31±8 to 40±14%), LV reverse remodeling (end-diastolic volume from 214±57 to 173±46 mL, end-systolic volume from 146±46 to 100±41 mL), and significantly improved intrinsic systolic function (end-systolic elastance from 0.98±0.31 to 1.51±0.82 mmHg/mL). In addition, mechanical efficiency significantly improved (0.40±0.12 to 0.55±0.13) with significant reduction of mechanical dyssynchrony (30±4 to 26±3%). However, parameters of diastolic function were unchanged six months after surgery (end-diastolic pressure: 20±9 to 18±7 mmHg; dP/dt_{MIN}: -1149±233 to –1189±307 mmHg/s; tau: 80±14 to 81±17 ms; chamber stiffness constant: 0.097±0.037 to 0.104±0.037 mmHg/mL).

Conclusion. Surgical ventricular restoration leads to clinical improvement with sustained LV reverse remodeling, improved global and intrinsic systolic function and unchanged diastolic function. The improved clinical status after six months may be related to improved mechanical efficiency, intrinsic systolic function and reduced mechanical dyssynchrony.

INTRODUCTION

Chronic heart failure is one of the leading causes of morbidity and mortality in the Western world.[1] In the majority of cases, the etiology in these patients is ischemic heart disease. More specific in patients after anteroseptal infarction, left ventricular (LV) aneurysm is a frequently observed complication. It leads to ineffective wall motion during the cardiac cycle and LV geometric shape changes resulting in inefficient LV pump function and adverse effects on remote myocardium.[2] These changes will increase the systolic workload in the remote myocardium, which may contribute to progressive heart failure.[3] Despite optimal medical treatment, patients with LV aneurysm often remain symptomatic and surgery may be indicated. Surgical ventricular restoration (SVR) by endoventricular circular patch plasty is increasingly performed in these patients. This technique can exclude akinetic or dyskinetic portions of the anterior wall and septum, reshapes the LV by the use of a patch to re-establishes the ventricular wall continuity.[4] Long-term studies have been demonstrated that SVR is safe and highly effective in the treatment of ischemic cardiomyopathy with reduction of end-systolic volume and favorable five-year outcome.[5]

Currently, little is known about the mechanisms of SVR on long-term LV systolic and diastolic function. Recent hemodynamic studies have demonstrated that SVR acutely reduces LV mechanical dyssynchrony with acute improvement of intrinsic LV systolic function.[6,7] In these studies, no data is available about the acute effects on diastolic function while some studies suggest that SVR may induce diastolic dysfunction.[8,9] Furthermore, limited data are available regarding chronic hemodynamic effects of SVR on LV function. Therefore, the purpose of this study is to evaluate these effects by use of invasive hemodynamic measurements derived by the conductance catheter before and six months after surgery.

METHODS

Patients

In this study we included 8 patients with ischemic dilated cardiomyopathy (NYHA class III/IV, LVEF < 35%) who underwent SVR. All patients underwent restrictive mitral annuloplasty for at least moderate to severe mitral regurgitation (grade ≥ 2) and all underwent additional CABG. All patients received stable medical therapy for chronic

heart failure, including diuretics (n=7), spironolactone (n=5), β-blockers (n=6), and ACE inhibitors (n=6). All patients gave informed consent and procedures were conducted in accordance with institutional guidelines. Patient characteristics are summarized in table 1.

Table 1. Patient characteristics

Number of patients (n)	8
Male / Female	6/2
Age (years)	62±7
NYHA class	3.6± 0.5
LVEF (%)	27±8
Angina (n)	5
Mean stenosed coronary arteries	2.3±0.9
Duration of symptoms (median, months)	8 (2-14)
Post-MI time (median, months)	3 (8-144)

NYHA: New York Heart Association, MI: myocardial infarction

Study protocol

All patients underwent routine right and left heart catheterization at baseline (i.e. pre-surgery) and six months after surgery, including thermodilution cardiac output, left ventriculography, and coronary angiography. In addition, a conductance catheter was placed in the LV via the femoral artery, and a temporary pacing lead was positioned in the right atrium.

Hemodynamic measurements. The conductance catheter enables on-line measurement of multiple segmental volume slices perpendicular to the LV long axis. We used 7F combined pressure-conductance catheters with 1-cm interelectrode spacing (CD Leycom, Zoetermeer, The Netherlands). The catheter was connected to a Cardiac Function Lab (CD Leycom) for on-line display and acquisition (sample frequency 250Hz) of segmental and total LV volumes, LV pressure and ECG. Total LV volume (V_{LV}) is obtained as the instantaneous sum of the segmental volumes. V_{LV} was calibrated using thermodilution and hypertonic saline dilution as previously described.[10] Right atrial pacing was performed at 80 beats/min. All measurements were repeated during re-catheterization at least six months after surgery.

Clinical evaluation. Evaluation of clinical status included assessment of NYHA functional class, quality-of-life score (using the Minnesota quality-of-life questionnaire) and six-minute hall-walk test.

Echocardiography. In patients with moderate to severe mitral regurgitation (grade ≥2) on transthoracic echocardiography (TTE), additional transesophageal echocardiography (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 regurgitation. The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images.[11,12] When the severity of mitral regurgitation was less than 3+, a loading test (as described previously[13,14]) was performed during anesthesia just before surgery. During these provocative tests, the severity of mitral regurgitation is followed, and patients who deteriorate to grade 3 or 4+ mitral regurgitation underwent restrictive mitral annuloplasty. Immediately after surgery, TEE was repeated to assess residual mitral regurgitation, transmitral diastolic gradient (determined from continuous-wave Doppler), and length of coaptation of the mitral leaflets (ideally ≥ 8 mm). Six months after surgery, TTE was performed to assess the severity of mitral regurgitation. 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.

Surgical procedures

SVR was performed by the endoventricular circular patch plasty as previously described by Dor.[4,15] Briefly, the left ventricle 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 55mL/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. The excluded scar tissue was closed over the patch to ensure hemostasis. Care was taken to eliminate all septal scar and to delineate a new LV apex with the goal to restore the normal elliptical shape. After completion of the LV restoration, a stringent restrictive mitral annuloplasty (2 sizes smaller than measured) was performed in these patients via an atrial transseptal approach using a Carpentier Edwards Physio ring (Edwards Lifesciences, USA).

Data-analysis

LV function was quantified by cardiac output (CO), LV ejection fraction (LVEF) and stroke volume (SV), end-diastolic and end-systolic volume (EDV, ESV), end-systolic and end-diastolic pressure (ESP, EDP), maximal and minimal rate of LV pressure change (dP/dt_{MAX}, dP/dt_{MIN}). The time constant of relaxation (τ) was determined using phase-plot analysis.[16] Stroke work (SW) was calculated as the area of the pressure-volume loop. Mechanical efficiency (ME) was calculated as the ratio of external stroke work and pressure-volume area (PVA) as a measure of total mechanical work: ME=SW/PVA[17]. LV end-systolic elastance (Ees) was estimated by ESP/ESV as relatively load-independent indexes of systolic function. LV end-diastolic chamber stiffness (CS) was estimated by EDP/EDV to characterize passive late diastolic function. Nonuniform LV performance 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 dyssynchrony (DYS) was determined as the mean of the segmental dyssynchronies. In addition, we calculated the internal flow fraction (IFF), which quantifies the ineffective shifting of blood volume within the LV due to nonuniform contraction and filling[18].

Statistics

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

RESULTS

There were no peri-operative or hospital deaths and all patients were alive at six months follow-up. After surgery, two patients needed intra-aortic balloon pump to wean from cardiopulmonary bypass and six patients needed inotropic support (dobutamine > 2 µg/kg/min) more than 24 hours postoperatively. Immediate after surgery, transesophageal echocardiography was performed and showed restored leaflet coaptation with no residual mitral regurgitation. Surgical details are summarized in table 2.

Table 2. Surgical data

CPB (minutes)	228±46
Aox (minutes)	155±29
Number of distal anastomosis	3±1
Ring size	25± 1
Pre-operative TEE	
-MR-grade	2.5± 0.9
-AML (cm)	2.88± 0.11
-MA (cm)	3.81± 0.64
-MA/AML-ratio	1.32± 0.22
-Coaptation	0.21±0.07
Post-operative TEE	
-MR-grade	0.1±0.4
-Coaptation (cm)	0.78±0.13
-MV-gradient (mmHg)	2.57±1.02
ICU-stay (days)	5±2
Hospital stay (days)	16±5

CPB, Cardiopulmonary bypass; AoX, Aortic cross clamping time; TEE, Transesophageal echocardiography; MR, Mitral regurgitation; AML, Anterior mitral leaflet; MA, Mitral annulus MV, Mitral valve; ICU: Intensive care unit

Clinical and hemodynamic data. Clinical parameters as NYHA functional class, quality-of-life score (using the Minnesota quality-of-life questionnaire) and 6-minute hall-walk test significantly improved from baseline to six months follow-up (Table 3). QRS duration was unchanged and mitral valve repair was successful in all cases with no recurrence of mitral regurgitation at six months follow-up.

The chronic effects of surgery on LV function are summarized in detail in table 3. LVEF improved significantly, whereas EDV and ESV were significantly reduced at six months follow-up, indicating substantial reversed remodeling. Stroke volume was unchanged at six months follow-up. Improved intrinsic systolic function was evidenced by the significant increase in the end-systolic elastance (Ees). End-diastolic pressure, active relaxation (τ), dP/dt_{MIN}, and CS, all parameters of diastolic function, were unchanged, indicating unchanged LV diastolic function six months after SVR. Furthermore, at six month follow-up, mechanical dyssynchrony was reduced as shown by significantly reduced DYS, whereas IFF showed a clear tendency to be reduced. Mechanical efficiency was significantly improved at six months follow-up, resulting from a significant increase of SW in combination with a significant decrease of PVA.

Table 3. Clinical and hemodynamic data

Parameter	Baseline	6 months follow-up	P-value
NYHA class	3.6±0.5	1.5±0.5	<0.001
QoL-test	45±23	16±16	0.028
6-minute HWT (m)	300±133	442±89	0.003
QRS-duration (ms)	103± 19	109± 15	0.348
MR-TTE (grade)	2.1±0.7	0.4±0.5	0.001
HR (bpm)	80±2	83±2	0.059
SV (mL)	64±17	65±12	0.619
CO (L/min)	5±1	5±1	0.270
ESV (mL)	146±46	100±41	0.014
EDV (mL)	214±57	173±46	0.034
EF (%)	31±8	40±14	0.032
ESP (mmHg)	133±33	124±28	0.319
EDP (mmHg)	20±9	18±8	0.435
dPdtMax (mmHg/s)	1270±254	1283±240	0.906
dPdtMin (mmHg/s)	-1149±233	-1189±307	0.577
SW (mmHg.mL)	5971±1749	6878±1266	0.062
Tau (ms)	80±15	81±18	0.966
Ees (mmHg/mL)	0.98±0.31	1.51±0.82	0.049
CS (1/mmHg)	0.097±0.037	0.104±0.037	0.667
ME	0.40±0.12	0.55±0.13	0.020
PVA (mmHg.mL)	16000±5160	13047±3407	0.044
DYS (%)	30±5	26±3	0.058
IFF (%)	61±25	41±19	0.169

NYHA, New York Heart Association; QoL, Quality of life; HWT, Hall walk test; MR-TTE, Mitral regurgitation on transthoracic echocardiography; HR, Heart rate; CO, Cardiac output; ESV,End-systolic volume; EDV, End-diastolic volume; EF; Ejection fraction; ESP, End systolic pressure; EDP, End-diastolic pressure; SW, Stroke work; Ees, End-systolic elastance; CS, Chamber stiffness ;ME, Mechanical efficiency; DYS, Dyssynchrony; IFF, Internal flow fraction

DISCUSSION

SVR by endoventricular circular patch plasty has been applied in patients with ischemic dilated cardiomyopathy complicated by an apicoseptal LV aneurysm. The short-term effects of this procedure on LV function are beneficial and consists of acute LV volume reduction with a decrease of mechanical dyssynchrony and improved LV systolic

function.[6,19] The purpose of the present study was to quantify chronic hemodynamic effects of SVR and in particular the effects on diastolic function.

The results of this study demonstrate that SVR leads to clinical improvement with improved LV hemodynamics. At six months follow-up, sustained LV reverse remodeling and improved global and intrinsic systolic function were observed. Furthermore, mechanical dyssynchrony was significantly reduced with significantly improved mechanical efficiency of the LV. Parameters of early (dP/dtmin, tau) and late diastolic function (EDP, CS) were unchanged six months after surgery, indicating that volume reduction and patch insertion did not compromise LV diastolic function.

LV reverse remodeling. Our results demonstrated a 20% and 31% reduction of EDV and ESV respectively at six months follow-up. The observed decrease in EDV and ESV is consistent with the findings of Qin et al. showing similar reductions of EDV (25%) and ESV (35%) at six months follow-up in 30 patients who underwent SVR and mitral valve repair.[20]

Somewhat larger reductions in LV volumes were reported in studies by Schreuder et al. and Di Donato et al.[6,7] These larger reductions may be due to a more extensive surgical volume reduction related to larger pre-operative LV volumes. Alternatively, these differences may reflect redilation, because ours and Qin's studies were done at six months follow-up, whereas the studies by Schreuder and Di Donato were performed acutely after surgery. Findings of a later study by Di Donato et al., showing a reduction in EDV and ESV of 31% and 44% respectively at 12 months follow-up, may suggest some redilation at late follow-up.[21]

A possible explanation for redilation in the study of Di Donato is the high recurrence of mitral regurgitation (38%) at 12 months follow-up. Qin et al. emphasized the importance of effective mitral valve repair in SVR patients as a pronounced redilation was occurred in patients with recurrence of mitral regurgitation.[20] However, in our study no recurrence of mitral regurgitation occurred after six months follow-up. Therefore, it may be suggested that the smaller volume reduction at six months in our study may be result from less extensive resection in the acute phase due to smaller pre-operative LV volumes. Long-term sustained volume reduction has been confirmed by a recent study by Fujii et al. reporting 33% reduction in EDV after isolated SVR at 23 days, which was unchanged at 32 months follow-up.[22]

Systolic function. Our data confirm previous findings regarding improved LVEF, unchanged SV and reduced LV volumes after SVR.[23,24] However, to our best knowledge, the present study is the first study with invasive hemodynamic measurements before and six months after SVR. At six months follow-up, a significant increase in Ees (from 0.98±0.31 mmHg/mL to 1.51±0.82 mmHg/mL) was observed in our study, indicating improved long-term intrinsic systolic function. Furthermore, mechanical efficiency was significantly improved with a significant reduction in mechanical dyssynchrony. These results are in line with previous findings by Schreuder et al. reporting a significant acute increase in Ees (from 1.2±0.6 mmHg/mL to 2.2±1.0 mmHg/mL), reduced mechanical dyssynchrony and improved LV mechanical efficiency.[7] Similarly, Tanoue et al. reported a similar significant increase in Ees (from 1.15±0.6 mmHg/mL to 1.86±0.84 mmHg/mL) and improvement of ventricular efficiency derived by LV angiography 3 to 4 weeks postoperatively.[25] However, these previous findings merely reflect acute changes of SVR on LV systolic function. Our study demonstrated that the increase in Ees is sustained after six months follow-up. Therefore, the improvement of intrinsic systolic function immediate after SVR is sustained on the long-term. These chronic effects are possibly due to positive acute effects on the remote myocardium by reduction of mechanical dyssynchrony, improvement of mechanical efficiency and reduction in LV wall stress. Schreuder et al. found that changes in Ees are inversely related to parameters of mechanical dyssynchrony and energy efficiency. Presumably, the chronic beneficial effects on Ees found in our study are mainly related to acute beneficial effects.

Diastolic function. In this study, both early and late diastolic function were unchanged at six months follow-up. This is an important finding as endoventricular circular patch plasty may induce diastolic filling abnormalities with a restrictive pattern.[9]

Previous acute studies reported altered early diastolic function after SVR with improved active relaxation (τ).[6,7] These acute effects may be related to direct effects of revascularization[26,27] and effects of cardiopulmonary bypass.[28,29] Schreuder et al.[7] found an increase in EDP (from 9.4±3 to 13.8±3 mmHg) after SVR, however these changes may be due to effects of postoperative edema.[30] Di Donato et al. recently demonstrated that EDP was unchanged (from 20±12 to 17±8 mmHg) 10 days after SVR. These findings are in line with ours as EDP was unchanged (from 20±9 to 18±8 mmHg) after SVR at six months follow-up. In addition, diastolic chamber stiffness was unchanged after six months follow-up, indicating that volume reduction and insertion of patch

plasty does not increase diastolic chamber stiffness. These data imply that SVR does not alter diastolic function six months after surgery.

In conclusion, surgical ventricular restoration leads to clinical improvement with sustained LV reverse remodeling, improved global and intrinsic systolic function and unchanged diastolic function. The improved clinical status after six months may be related to improved mechanical efficiency, intrinsic systolic function and reduced mechanical dyssynchrony.

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CHAPTER 12

Summary and conclusions

SHORT INTRODUCTION

The number of patients with chronic heart failure is rapidly increasing as a result of an aging population and advanced medical therapy leading to a substantial number of patients who survive a myocardial infarction. Despite improvement of pharmacological treatment, drug-refractory end-stage heart failure is a challenging problem. Although successful, cardiac transplantation is limited and consequently alternative invasive therapies have been developed. Currently, most widely applied are cardiac resynchronization therapy (CRT), surgical ventricular restoration (SVR) and restrictive mitral annuloplasty (RMA). Despite promising clinical results of these therapies, the working mechanisms are still partly unknown. In this thesis, we investigated the acute and chronic hemodynamic effects of these therapies in patients with end-stage heart failure. Quantification of these effects may provide further insight in the working mechanisms of these therapies and may help to explain clinical improvement in heart failure patients treated with these therapies.

Chapter 2. In this chapter we evaluated the application of the conductance catheter technique in the operating room. Peri-operative quantification of systolic and diastolic load independent left ventricular (LV) function by pressure-volume relations is advantageous since loading conditions are varying during cardiac surgery induced by anesthesia, cardiopulmonary bypass (CPB) and the surgical procedure itself. In 8 patients undergoing elective CABG, complete hemodynamic data was derived within 15 minutes before and after CPB without any complications. Load-dependent and load-independent indices of systolic function were unchanged after CPB. However, diastolic function changed significantly after CPB with a significant increase of end-diastolic pressure and the diastolic chamber stiffness constant. Active relaxation, quantified by the active relaxation time constant (tau), decreased significantly. We conclude that the conductance catheter method provides detailed data on peri-operative LV function. Therefore, this method may be used to evaluate the acute effects of new surgical procedures and the data acquired in the group of elective CABG-patients may serve as reference data.

Chapter 3. In this chapter new parameters of LV mechanical dyssynchrony in patients with chronic heart failure were introduced, which were derived from online segmental conductance catheter signals obtained during diagnostic cardiac catheterization. We

determined cardiac function and LV mechanical dyssynchrony in heart failure patients with intraventricular conduction delay and a group of patients with coronary artery disease and relatively preserved LV function. The heart failure patients showed depressed systolic and diastolic function. However, the most marked hemodynamic differences between the groups were found for mechanical dyssynchrony indicating a high sensitivity and specificity of the new indices. Comparison of conductance catheter derived indices of mechanical dyssynchrony with septal-to-lateral dyssynchrony derived by tissue-Doppler velocity imaging showed highly significant correlations. We concluded that the proposed indices provide additional, new and quantitative information on temporal and spatial aspects of mechanical dyssynchrony in patients with heart failure. They may refine diagnosis of cardiac dysfunction and evaluation of interventions.

Chapter 4. In this chapter, the baseline and chronotropic effects of normothermic CABG with intermittent antegrade warm blood cardioplegia on LV function were quantified. This on-pump approach has been applied in all heart failure patients who underwent SVR and/or RMA in this thesis and thus quantification of these effects in a control group was warranted. Our findings indicate that on-pump normothermic CABG with intermittent antegrade warm blood cardioplegia preserves systolic function, increases diastolic stiffness, and improves systolic and diastolic chronotropic responses. Normalization of the chronotropic responses after CPB is likely due to the effects of successful revascularization and subsequent relief of ischemia. The baseline effects on LV function reported in this chapter are used as reference data to interpret baseline effects on LV function after SVR and RMA in patients with heart failure.

Chapter 5. In this study we quantified the acute effects of RMA on LV systolic and diastolic function by pressure-volume analysis using the conductance catheter. In 10 patients with end-stage heart failure and concomitant severe mitral regurgitation, stringent RMA (two sizes under) effectively restored mitral valve competence (leaflet coaptation 8.0±0.2mm) without inducing significant acute changes in LV systolic or diastolic function. This study shows that undersizing the mitral annulus has no adverse effects on intrinsic systolic and diastolic LV function, and this procedure can be safely applied in patients with severe heart failure.

Chapter 6. In this chapter, we described the acute effects of SVR on LV systolic and diastolic function in patients with ischemic dilated cardiomyopathy. The results show that SVR achieves normalization of LV volumes, improves systolic function and decreases LV wall stress and mechanical dyssynchrony. 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 while the pressure-volume area was significantly reduced after SVR. Therefore, 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.

Chapter 7. This chapter gives an overview of the potential applications of pressure-volume measurements by the conductance catheter during cardiac catheterization. This review showed that, in the context of CRT, pressure-volume measurements by conductance catheter have been mainly applied to study the basic mechanisms of dyssynchronous and resynchronized cardiac contraction. In this field important new insights were obtained from pressure-volume measurements. There are certainly possibilities and distinct advantages in the field of patient selection but this application will remain limited by the invasive character of the conductance method. Currently, ongoing studies apply pressure-volume measurements to optimize CRT in individual patients and evaluate the chronic hemodynamic effects of CRT. The possibility to assess cardiac function and mechanical dyssynchrony during implantation and the possibility to study the immediate effects of changes in lead position, AV and VV-delay, in an on-line and quantitative fashion makes this a promising tool to optimize CRT. Load-independent quantitative parameters of systolic and diastolic function derived from pressure-volume relations should provide more insight in the working mechanisms of chronic CRT.

Chapter 8. In this chapter the chronic effects of CRT on LV hemodynamics were reported. Acute hemodynamic improvements of CRT have been studied previously, but detailed invasive studies showing hemodynamic consequences of chronic CRT are not available. We demonstrated that hemodynamic improvements previously shown in acute studies are maintained mid-term. In addition, ventricular-arterial coupling,

mechanical efficiency, and chronotropic responses are improved after 6 months CRT. These findings may help to explain the improved functional status and exercise tolerance in heart failure patients treated with cardiac resynchronization.

Chapter 9. In this chapter clinical efficacy was evaluated 6 months after surgery in a cohort of patients with end-stage heart failure who underwent combined SVR and RMA, isolated SVR or isolated RMA. Clinical parameters, including NYHA classification, Minnesota Quality of Life questionnaire, and 6-minute walking distance, were assessed at baseline and 6 months after surgery. Mortality at 6 months was 12% and was associated with highly significant improvements in clinical parameters. We concluded that surgical treatment of end-stage heart failure by SVR and RMA seems relatively safe with a clear clinical benefit at 6-months follow-up.

Chapter 10. In this chapter, a comprehensive analysis of SVR and if indicated mitral and/or tricuspid annuloplasty on mid-term hemodynamic and clinical status was performed. In a selected group of 21 patients who had complete echocardiographic follow-up including tissue Doppler imaging at 6 months, clinical and echocardiographic parameters were assessed. In particular, the effects of this surgical approach on LV volumes, LV dyssynchrony, right ventricular (RV) reverse remodeling and RV functional parameters (severity of tricuspid regurgitation and pulmonary artery pressure) were studied. It was demonstrated that this approach resulted in significant improvements of clinical status and heart failure symptoms, combined with a reduction in LV volume and LV dyssynchrony with minimal residual mitral regurgitation. In addition, a decrease in pulmonary artery pressure, RV reverse remodeling and reduced tricuspid regurgitation was observed. Therefore, this approach proved to have beneficial mid-term effects in terms of clinical and hemodynamic status.

Chapter 11. In this chapter, chronic effects of SVR on pressure-volume relations were evaluated. Hemodynamic data showed significantly improved LVEF, sustained LV volume reduction and significantly improved intrinsic systolic function. In addition, mechanical efficiency significantly improved with significant reduction of mechanical dyssynchrony. Interestingly, parameters of diastolic function remain unchanged 6 months after surgery. From these results, we conclude that SVR leads to improved LV systolic function with unchanged diastolic function at 6 months follow-up. The

improved LV systolic function after 6 months may be related to reduced LV mechanical dyssynchrony and improved LV efficiency.

CONCLUSIONS

This thesis demonstrates the feasibility and value of LV pressure-volume measurements by conductance catheter during cardiac surgery. Besides assessment of load-dependent and load-independent parameters of systolic and diastolic LV function, the conductance catheter can quantify LV mechanical dyssynchrony, which is an important determinant of cardiac (dys)function and a new sensitive parameter in patients with chronic heart failure.

Prior to our studies in heart failure patients, we evaluated our methodology in patients with relatively normal LV function who underwent elective normothermic CABG. Like the heart failure patients, these patients were operated during intermittent antegrade warm blood cardioplegia. Our peri-operative measurements showed no significant changes in LV systolic function. However, diastolic chamber stiffness significantly increased, while active relaxation (tau) improved. These effects are probably related to effects of cardiopulmonary bypass, cardioplegic arrest, and the revascularization. In general, such effects should be taken into consideration when evaluating peri-operative hemodynamic measurements in patients with heart failure who undergo surgery with the same on-pump approach.

With regard to surgical therapies, we focused on SVR and RMA in patients with end-stage heart failure. Earlier studies have suggested that correction of mitral regurgitation may decrease LV systolic function in the acute phase. In addition, with regard to diastolic function, mitral valve repair by RMA might potentially impair filling. These concerns have caused hesitation to apply these procedures in patients with advanced heart failure. However, we have demonstrated by pressure-volume analysis that RMA did not affect systolic and diastolic function in the acute phase. Interestingly, our results show a clear tendency for a reduced mechanical dyssynchrony after RMA. These findings support the use of this approach even in patients with severely depressed LV function in view of beneficial long-term results.

SVR is increasingly applied in patients with ischemic dilated cardiomyopathy and anteroseptal dyskinesia or akinesia. However, limited data are currently available about the acute and chronic effects of this therapy on LV function. The present thesis provides

measurements of LV systolic and diastolic function and dyssynchrony by use of pressure-volume relationships. In addition, mid-term (6 months) effects of SVR on clinical status and biventricular function were provided by clinical parameters (6-min walk test, Minnesota Living with Heart Failure questionnaire, NYHA classification) and echocardiography including tissue Doppler imaging. SVR resulted in significant acute improvement of systolic function, significant acute reduction of LV mechanical dyssynchrony, and significant reduction of LV wall stress. 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 while the pressure-volume area was significantly reduced after SVR. Therefore, mechanical efficiency was significantly improved, presumably resulting from reduced LV wall stress and reduced mechanical dyssynchrony. The changes in diastolic stiffness were relatively limited and were comparable with the changes in patients with preserved LV function who underwent elective CABG suggesting that this effect was importantly related to procedure-induced myocardial edema and may be partially transient.

These acute beneficial effects on systolic function are largely maintained chronically with no significant effects on diastolic function at mid-term follow-up. The pressure-volume data at 6 months follow-up showed significantly improved LVEF, sustained LV volume reduction and significantly improved intrinsic systolic function. In addition, mechanical efficiency was improved with a reduction of mechanical dyssynchrony. Clinical and echocardiographic data at 6 months follow-up showed improvement of clinical status and a significant LV volume reduction and reduced LV dyssynchrony. In addition, RV reverse remodeling after SVR and, if indicated, mitral or tricuspid annuloplasty was noted with reduction in tricuspid regurgitation and pulmonary artery pressure. These data indicate that SVR improves LV global and intrinsic systolic function by reducing mechanical dyssynchrony and LV wall stress without inducing diastolic dysfunction. In addition, SVR leads to additional beneficial effects at mid-term follow-up such as reduced pulmonary artery pressure and RV reverse remodeling. The beneficial hemodynamic effects described in this thesis can explain the improved clinical status and survival of patients after SVR at long-term follow-up.

A third important new technique to treat patients with end-stage heart failure is CRT, which is highly effective in patients with left bundle-branch block and severe heart failure. Previous studies showed long-term clinical benefit, improved LV function and reverse LV remodeling. Acute hemodynamic effects, previously described, consist of increased LV ejection fraction and stroke volume, accompanied by increased systolic

pressure, dP/dt_{MAX}, and stroke work, reduced mechanical dyssynchrony and reduced diastolic pressure. In the present thesis, we obtained invasive hemodynamics by pressure-volume loops at baseline and after 6 months of CRT and showed that these improvements are still present at 6 months follow-up. Moreover, our results show improved ventricular-arterial coupling and improved mechanical efficiency, which constitute a more optimal energetic condition. In addition, we demonstrated improved responses to increased heart rate, which may partly explain the enhanced exercise capacity of patients treated with CRT. However, despite conversion to a more physiological chronotropic response, the capacity to increase cardiac output remains limited. The latter presumably is partly due to an abnormal relaxation reflected by a relatively long isovolumic relaxation time (tau), which did not improve after CRT. These effects of CRT help to explain the improved functional status and exercise tolerance in heart failure patients treated with CRT.

In summary, recently several new therapies were introduced to treat patients with end-stage heart failure. These therapies, SVR, RMA and CRT have all demonstrated to have clinical benefit. In this thesis, we documented the acute and chronic effects of these therapies on LV function by pressure-volume analysis. Our findings provide insight in the underlying mechanisms and help to explain improved functional status achieved with these therapies.

Samenvatting en conclusies

KORTE INLEIDING

Het aantal patiënten met chronisch eindstadium hartfalen neemt snel toe als gevolg van de vergrijzing en de verbeterde medische behandeling van het acute myocardinfarct. Ondanks verbeterde medicamenteuze therapie blijft een substantieel deel van deze groep patiënten symptomatisch. Harttransplantatie, hoewel succesvol, blijft beperkt tot een kleine groep patiënten. Hierdoor zijn de afgelopen jaren een aantal alternatieve behandelingen ontwikkeld en toegepast, waaronder cardiale resynchronisatie therapie (CRT), aneurysmectomie volgens Dor (Dor procedure) en chirurgische mitralisklep-reparatie door middel van een restrictieve mitralisklep annuloplastiek (RMA). Ondanks de veelbelovende klinische resultaten van deze behandelingen zijn de werkingsmechanismen nog grotendeels onbekend. In dit proefschrift worden de acute en chronische hemodynamische en cardiovasculaire effecten van deze behandelingen gekwantificeerd o.a. door middel van ventriculaire drukvolume analyse met behulp van de conductantiecatheter. Het kwantificeren van deze effecten kan meer inzicht verschaffen in de werkingsmechanismen van deze interventies en daarmee de klinische verbetering, die doorgaans optreedt na de behandeling in patiënten met chronisch eindstadium hartfalen, wellicht verklaren. Bovendien geeft het mogelijk aangrijpingspunten voor het verder verbeteren van deze therapieën.

Hoofdstuk 2. In dit hoofdstuk beschrijven we de toepassing van de conductantiecatheter in de operatiekamer. Met deze techniek kunnen acute effecten van hartchirurgische behandelingen worden gekwantificeerd. Met name het meten van parameters van intrinsieke systolische en diastolische linker kamerfunctie tijdens hartoperaties is belangrijk, omdat tijdens deze operaties belastingscondities van het hart sterk kunnen variëren als gevolg van de anesthesie, cardiopulmonale bypass (CPB) en de chirurgische interventie zelf. Om de toepassing van deze meettechniek te testen en acute effecten van een controlegroep patiënten met normale hartfunctie te verkrijgen, zijn metingen verricht in 8 patiënten die een electieve CABG ondergingen. Complete hemodynamische gegevens zijn verkregen binnen 15 minuten voor en na CPB. Hierbij traden geen complicaties op. Uit de resultaten blijkt dat zowel de belastingsonafhankelijke als de belastingsafhankelijke parameters van systolische

functie onveranderd bleven na CPB. De parameters van diastolische functie waren echter wel veranderd na CPB, waarbij de einddiastolische druk en de diastolische kamerstijfheidsconstante significant waren toegenomen. Actieve relaxatie, gekwantificeerd door de relaxatie constante tau, verbeterde significant na CPB.
De resultaten in dit hoofdstuk laten zien dat de conductantiecatheter waardevolle informatie kan verschaffen over peri-operatieve linker kamerfunctie en dat deze methode kan worden toegepast om de acute effecten van nieuwe chirurgische procedures te kwantificeren. De gegevens in dit hoofdstuk zullen verderop in dit proefschrift worden gebruikt ter vergelijking met de acute hemodynamische effecten van chirurgische behandelingen in patiënten met ernstig hartfalen.

Hoofdstuk 3. In dit hoofdstuk worden nieuwe parameters van mechanische dissynchronie van de linker hartkamer bij patiënten met chronisch hartfalen geïntroduceerd, die gemeten kunnen worden met behulp van segmentale volumesignalen van de conductantiecatheter. Tijdens diagnostische hartcatheterisaties werden conductantiemetingen verricht waarbij de hartfunctie en mechanische dissynchronie werd gemeten in een groep patiënten met chronisch hartfalen. Deze metingen werden vergeleken met metingen in een groep patiënten met coronairlijden en een relatief normale linker kamerfunctie. De patiënten met hartfalen hadden een sterk verminderde systolische en diastolische linker kamerfunctie. De duidelijkste verschillen tussen de beide groepen werden echter gevonden in de parameters van mechanische dissynchronie. Vergelijking van deze nieuwe parameters met echografische parameters van mechanische dissynchronie waaronder *septal-to-lateral delay* liet een sterke significante correlatie zien. Hieruit werd geconcludeerd dat deze nieuwe parameters verkregen met de conductantiecatheter nieuwe additionele en kwantitatieve informatie kunnen geven over temporele en ruimtelijke aspecten van mechanische dissynchronie bij patiënten met hartfalen. Deze parameters geven meer inzicht in linker kamerdysfunctie bij patiënten met hartfalen. Ook kan het effect van interventies op deze parameters inzicht verschaffen in de werkingsmechanismen van nieuwe behandelingen voor hartfalen.

Hoofdstuk 4. In dit hoofdstuk worden de acute effecten besproken van normotherme CABG met intermitterend antegrade warm bloed cardioplegie op de linker kamerfunctie. Naast de effecten op de hartfunctie bij een frequentie van 80 slagen per minuut, worden ook de effecten op de hartfunctie tijdens hogere hartfrequenties

(chronotrope respons) besproken. Aangezien dezelfde *on-pump* benadering wordt toegepast bij patiënten met hartfalen die een Dor procedure en/of een RMA ondergaan in de volgende hoofdstukken van dit proefschrift, is kwantificatie van de effecten van deze benadering allereerst zinvol in een controle groep. De bevindingen in deze controle groep laten zien dat *on-pump* normotherme CABG met intermitterend antegrade warm bloed cardioplegie geen systematisch effect heeft op de systolische linker kamerfunctie maar wel op de diastolische linker kamerfunctie. De diastolische linker kamerstijfheid neemt toe en de actieve relaxatie verbeterd. Bovendien verbetert zowel de systolische als diastolische chronotrope respons na CPB. De verbetering van actieve relaxatie en de normalisatie van de chronotrope respons is waarschijnlijk het gevolg van de succesvolle revascularisatie.

Hoofdstuk 5. In dit hoofdstuk beschrijven we de acute effecten van chirurgische mitralisklep reparatie door middel van RMA op de systolische en diastolische linker kamerfunctie door middel van drukvolume relaties verkregen met de conductantiecatheter. De resultaten verkregen bij 10 patiënten met eindstadium hartfalen laten zien dat RMA door middel van het inbrengen van een *undersized* ring, d.w.z. twee maten kleinere ring dan de maat die werd gemeten, de coaptatie van de mitralisklep kan herstellen (8.0±0.2 mm). Hierbij werd de ernstige mitralis-insufficiëntie opgeheven en de metingen met de conductantiecatheter lieten geen veranderingen zien in de systolische en diastolische linker kamerfunctie na CPB. Dit toont aan dat RMA in patiënten met een verminderde linker kamerfunctie geen nadelige effecten heeft op de intrinsieke diastolische en systolische linker kamerfunctie en dat deze chirurgische techniek veilig kan worden toegepast bij deze groep ernstig zieke patiënten

Hoofdstuk 6. In dit hoofdstuk worden de acute effecten op de systolische en diastolische linker kamerfunctie beschreven van de Dor procedure, uitgevoerd bij patiënten met ischemische, gedilateerde cardiomyopathie met een anteroseptaal aneurysma. De gegevens laten zien dat de Dor procedure resulteert in normalisatie van de linker kamervolumina met een verbetering in systolische functie, een afname van de linker kamerwandspanning en mechanische dissynchronie. Ten koste van een hogere einddiastolische druk als gevolg van veranderende diastolische eigenschappen na de operatie blijft de cardiale pompfunctie weergegeven door de slagarbeid (oppervlakte van de drukvolume lus) en de cardiale output vrijwel onveranderd. Daarnaast neemt de

mechanische efficiëntie significant toe na de Dor procedure, waarschijnlijk als gevolg van een vermindering van de wandspanning en mechanische dissynchronie van de linker kamer. De diastolische kamerstijfheidsconstante neemt echter toe alhoewel deze toename vergelijkbaar is met die in de controlegroep (zie hoofdstuk 4,5).

Hoofdstuk 7. Dit hoofdstuk geeft een overzicht van de mogelijke toepassingen van de conductantiecatheter tijdens hartcatheterisaties. Het laat zien dat drukvolume relaties kunnen worden toegepast in de context van CRT om de basale mechanismen van dissynchrone en geresynchroniseerde cardiale contractie te bestuderen. Op dit gebied zijn dan ook belangrijke nieuwe inzichten verkregen met drukvolume metingen. Deze meettechniek biedt o.a. voordelen op het gebied van patiëntselectie, al blijft de toepassing van de techniek relatief beperkt vanwege het invasieve karakter van de conductantiecatheter. Er zijn diverse studies uitgevoerd die drukvolume analyse toepassen om CRT te optimaliseren in individuele patiënten en de hemodynamische effecten van CRT te evalueren. De mogelijkheid om de hartfunctie en mechanische dissynchronie te kwantificeren gedurende implantatie van een biventriculaire pacemaker en de mogelijkheid om direct de effecten van de positie van de pacemakerdraad, de AV en VV *timing* te kunnen meten, maakt deze techniek aantrekkelijk om CRT te optimaliseren. Belastingsonafhankelijke kwantitatieve parameters van systolische en diastolische functie verkregen door middel van drukvolume relaties kan meer inzicht verschaffen in de werkingsmechanismen van CRT op de intrinsieke hartfunctie.

Hoofdstuk 8. In dit hoofdstuk worden de chronische effecten van CRT op de linker kamerfunctie beschreven. Acute hemodynamische verbeteringen van CRT zijn reeds bekend, maar gedetailleerde invasieve metingen van hemodynamische effecten op lange termijn zijn nog niet beschikbaar. De resultaten in dit hoofdstuk laten zien dat de acute gunstige effecten van CRT op de linker kamerfunctie ook op lange termijn aanwezig blijven. Daarnaast verbetert de ventriculaire-arteriële koppeling, vermindert de mechanische dissynchronie en is er sprake van een verbetering in de chronotrope respons na 6 maanden CRT. Deze bevindingen verklaren mede de verbetering van klinische parameters en de toename van de inspanningstolerantie in patiënten met hartfalen die worden behandeld met CRT.

Hoofdstuk 9. In dit hoofdstuk worden klinische parameters gebruikt om het effect van de gecombineerde Dor/RMA procedure, de geïsoleerde Dor procedure en de geïsoleerde

RMA te evalueren in een cohort patiënten met hartfalen. Klinische parameters, inclusief NYHA classificatie, de kwaliteit-van-leven-test en de 6 minuten looptest zijn bepaald vóór en 6 maanden na de operatie. De mortaliteit na 6 maanden was in deze selecte groep patiënten 12% en de klinische parameters verbeterde significant na 6 maanden. Hieruit werd geconcludeerd dat de chirurgische behandeling van eindstadium hartfalen door middel van de Dor procedure en/of de RMA relatief veilig is met een duidelijk klinische verbetering na 6 maanden.

Hoofdstuk 10. In dit hoofdstuk wordt een uitvoerige analyse verricht van de effecten van de Dor procedure en, indien geïndiceerd, RMA en/of tricuspidalisklepplastiek op de hemodynamische en klinische status van patiënten met eindstadium hartfalen. In een selecte groep patiënten met een complete echocardiografische follow-up, inclusief *tissue-Doppler imaging*, werden vóór en na 6 maanden klinische en echocardiografische parameters bepaald. Echocardiografische parameters die werden bepaald waren: het linker kamervolume, linker kamerdissynchronie, rechter kamerdimensies, de ernst van de tricuspidalis insufficiëntie en de pulmonale arteriële druk. Na 6 maanden werd een significante verbetering in klinische conditie van de patiënt gevonden, gecombineerd met een reductie in linker kamervolume en dissynchronie met een minimale residuele mitralis/tricuspidalis insufficiëntie. Bovendien werd een significante reductie in het volume van de rechter kamer gezien met een afname van de pulmonale arteriële druk. Deze gegevens tonen aan dat deze chirurgische benadering positieve klinische en hemodynamische effecten heeft op de middellange termijn.

Hoofdstuk 11. In dit hoofdstuk worden de chronische hemodynamische effecten van de Dor procedure geëvalueerd. De drukvolume relaties, gemeten tijdens hartcatheterisaties, tonen een verbetering in linker kamerejectiefractie, een reductie van linker kamervolume en een significante verbetering van de intrinsieke systolische linker kamerfunctie. Daarnaast neemt de mechanische efficiëntie significant toe na 6 maanden met een reductie van de linker kamerdissynchronie. Een belangrijk gegeven uit dit hoofdstuk vormen de onveranderende parameters van de diastolische functie na 6 maanden vergeleken met de parameters voor de operatie. Hieruit kunnen we concluderen dat de Dor procedure leidt tot een verbetering in globale en intrinsieke systolische linker kamerfunctie waarbij de diastolische functie na 6 maanden onveranderd blijft. De verbetering in systolische functie na 6 maanden is mogelijk

gerelateerd aan de reductie van linker kamerdissynchronie en de verbetering in linker kamerefficiëntie.

CONCLUSIES

In dit proefschrift wordt de haalbaarheid en het belang van drukvolume metingen tijdens hartchirurgische en cardiologische interventies aangetoond. Naast het verkrijgen van belastingsafhankelijke en belastingsonafhankelijke parameters van systolische en diastolische linker kamerfunctie, kan de conductantiecatheter parameters van mechanische dissynchronie bepalen. Deze parameters zijn sensitief en bepalen mede de mate van cardiale dysfunctie bij patiënten met chronisch hartfalen.

Voorafgaand aan onze studies in hartfalen patiënten, hebben we de conductantiecatheter methode geëvalueerd in patiënten met een relatief normale linker kamerfunctie die een electieve normotherme CABG ondergingen. Evenals bij de hartfalen patiënten, werden deze patiënten geopereerd met intermitterend antegrade warm bloed cardioplegie. Onze peri-operatieve metingen toonden geen significante veranderingen in systolische linker kamerfunctie. De diastolische linker kamerstijfheid in deze patiënten nam echter significant toe, terwijl de actieve relaxatie constante (tau) significant verbeterde. Deze effecten zijn hoogst waarschijnlijk het gevolg van de cardiopulmonale bypass, de cardioplegie en de revascularisatie. In het algemeen, moeten deze effecten in beschouwing worden genomen wanneer peri-operatieve metingen worden geïnterpreteerd van patiënten met hartfalen die worden geopereerd onder dezelfde omstandigheden.

In dit proefschrift hebben we onder andere de effecten chirurgische behandelingen zoals de Dor procedure en de RMA onderzocht. Op basis van vroegere studies bestaan aanwijzingen dat RMA in de acute fase na de operatie de linker kamerfunctie in patiënten met hartfalen verder kan verslechteren. Daarnaast zou RMA mogelijk een nadelig effect hebben op de diastolische vullingsfase. Deze vermoedens hebben geleid tot twijfel of deze operatie wel moet worden toegepast bij patiënten met hartfalen. In dit proefschrift wordt met drukvolume relaties echter aangetoond dat chirurgische mitralisklep-reparatie door middel van RMA (met een twee maten kleinere ring dan de ringmaat die werd gemeten) geen nadelig effect heeft op de intrinsieke systolische en diastolische linker kamerfunctie in patiënten met hartfalen. Daarnaast was er een trend

tot reductie van de linker kamerdissynchronie. Deze bevindingen ondersteunen het gebruik van RMA zelfs in patiënten met een sterk verminderde linker kamerfunctie.

Naast de RMA wordt ook de Dor procedure in toenemende mate toegepast bij patiënten met eindstadium hartfalen. Deze techniek wordt toegepast in patiënten met ischemisch gedilateerde cardiomyopathie met anteroseptale dyskinesie of akinesie. Er zijn momenteel nog weinig gegevens beschikbaar over de acute en chronische effecten van deze techniek op de linker kamerfunctie bij patiënten met hartfalen. In dit proefschrift worden met behulp van drukvolume relaties de acute en chronische effecten op de systolische en diastolische linker kamerfunctie en op de mechanische dissynchronie beschreven. Daarnaast worden de effecten van de Dor procedure na 6 maanden op de klinische status van de patiënt (6 minuten looptest, kwaliteit van leven test en NYHA classificatie), de biventriculaire functie en linker kamerdissynchronie, met behulp van echocardiografie en *tissue Doppler imaging* bestudeerd. De acute effecten van de Dor procedure, zoals beschreven in dit proefschrift, bestaan uit een verbetering in globale en intrinsieke systolische functie, een reductie van linker kamerdissynchronie en een significante afname van de linker kamerwandspanning. Ondanks veranderende diastolische eigenschappen (verhoogde einddiastolische druk en een toegenomen linker kamerstijfheidsconstante) na de operatie blijft de pompfunctie (cardiale output en slagarbeid) onveranderd. De *pressure-volume area* was significant verminderd na de Dor procedure hetgeen uiteindelijk leidt tot een verbetering in mechanische efficiëntie van de linker kamer. Dit effect is waarschijnlijk het gevolg van een reductie van linker kamerwandspanning en een reductie van mechanische dissynchronie. De toename in diastolische linker kamerstijfheid neemt toe na de Dor procedure, deze toename is echter vergelijkbaar met de toename in de controle CABG patiënten en waarschijnlijk het gevolg van tijdelijk oedeem dat ontstaat na de operatie. De positieve effecten op de systolische linker kamerfunctie, gemeten met drukvolume relaties, zijn na 6 maanden nog steeds aanwezig. Opmerkelijk is dat de diastolische functie na 6 maanden onveranderd is ten opzichte van voor de operatie. Kennelijk is de toename in linker kamerstijfheid, die direct na de operatie aanwezig is, tijdelijk van aard. De drukvolume gegevens na 6 maanden laten een significante verbetering zien in linker kamerejectiefractie, een significante reductie van het linker kamervolume en een significante verbetering in intrinsieke systolische functie. Daarnaast neemt de linker kamerefficiëntie toe met een reductie in mechanische dissynchronie. Ook de klinische parameters verbeterden 6 maanden na de Dor procedure. Daarnaast treedt *reverse remodeling* op van de rechter kamer en vindt een significante reductie plaats van de

pulmonale arteriële druk na de operatie. Deze resultaten tonen aan dat de Dor procedure, indien noodzakelijk met een tricuspidalisklepplastiek of een mitralisklepplastiek, de globale en intrinsieke systolische linker kamerfunctie verbetert door een reductie in mechanische dissynchronie en linker kamerwandspanning, zonder verandering in diastolische linker kamerfunctie. Bovendien treedt *reverse remodeling* op van de rechter kamer met een afname van de pulmonale arteriële druk. Al deze verbeteringen in functie verklaren mede de gunstige klinische lange termijn resultaten na de Dor procedure.

Een derde belangrijke behandelingstechniek voor patiënten met eindstadium hartfalen is CRT dat effectief is gebleken bij patiënten met een ernstig hartfalen en een linker bundeltak blok. Eerdere studies laten gunstige lange termijn effecten zien met een verbetering in overleving en symptomen en een verbetering in linker kamerfunctie met *reverse remodeling* van de linker kamer. De reeds bekende acute effecten na CRT zoals toename in ejectiefractie, slagvolume, systolische druk, dP/dt_{max} en slagarbeid, en reductie in mechanische dissynchronie en diastolische druk zijn volgens de resultaten van dit proefschrift nog steeds aanwezig na 6 maanden behandeling met CRT. Bovendien laten deze resultaten een verbetering in ventriculaire-arteriële koppeling en een verbetering in mechanische efficiëntie zien. Verder laten deze resultaten een verbetering in chronotrope response zien, dat mogelijk de verbetering in inspanningstolerantie na CRT in deze patiënten mede verklaart. Ondanks conversie naar een meer fysiologische chronotrope response werd echter een beperkte toename gezien van de cardiale output na toename van de hartfrequentie. Dit is mogelijk het gevolg van een abnormale relaxatie door de vertraagde isovolumetrische relaxatie die niet verbeterde na CRT. Deze hemodynamische verbeteringen na CRT verklaren voor een deel de toename van de inspanningstolerantie in hartfalen patiënten die worden behandeld met CRT.

In dit proefschrift zijn de acute en chronische hemodynamische effecten van de Dor procedure, RMA en CRT onderzocht met behulp van ventriculaire drukvolume analyse met de conductantiecatheter. De klinische effecten van deze behandelingen bij patiënten met hartfalen zijn over het algemeen gunstig. De bevindingen in dit proefschrift geven inzicht in de onderliggende werkingsmechanismen en kunnen de klinische verbeteringen in deze patiënten mede verklaren.

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 19 februari 1973 te Gouda. In 1991 behaalde hij zijn Gymnasium diploma aan Het Nieuwe Lyceum te Hilversum, waarna hij een algemeen oriënterend jaar volgde op de Vrije Hogeschool te Driebergen.
Na een jaar studie Economie (in verband met uitloting), begon hij in 1993 met de studie Geneeskunde aan de Rijksuniversiteit Groningen. Tijdens de doctoraalfase was hij student-assistent bij de vakgroep Anatomie en Embryologie (dr. P. Room, Prof. dr. G. Holstege) en volgde hij diverse stages in buitenlandse ziekenhuizen (Freeman Hospital, New Castle upon Tyne, Engeland en Hospital de São Paulo, Brazilië). In 1998 behaalde hij zijn doctoraal diploma aan de Rijksuniversiteit Groningen.
Tussen 1998 en 2000 deed hij zijn co-assistentschappen in het Academisch Medisch Centrum te Amsterdam. Eind september 2000 behaalde hij het artsexamen aan de Universiteit van Amsterdam, waarna hij een jaar als arts-assistent Heelkunde heeft gewerkt in het St. Lucas Andreas ziekenhuis te Amsterdam (Dr. E.Ph. Steller). Tijdens dit jaar deed hij onderzoek bij de afdeling Orthopedie (dr. G.R. Schaap, Prof. dr. R.K. Marti) van het Academisch Medisch Centrum te Amsterdam naar de behandeling van posttraumatische osteomyelitis van de tibia.
In januari 2002 startte hij met promotieonderzoek onder leiding van dr. P. Steendijk op de afdeling Cardiologie (Prof. dr. E.E. van der Wall, Prof. dr. M.J. Schalij) en Thoraxchirurgie (Prof. dr. R.A.E. Dion) van het Leids Universitair Medisch Centrum te Leiden. Het promotieonderzoek werd gesubsidieerd door de Nederlandse Hartstichting (NHS 2002B133). Tijdens dit onderzoek werkte hij bij Bio Implant Service (onderdeel van de Nederlandse Transplantatie Stichting) als zelfstandig hartexplanteur. Eind december 2005 heeft hij het promotieonderzoek afgerond.. Per 1 januari 2006 is hij gestart met de vooropleiding heelkunde in het VU Medisch Centrum te Amsterdam (Prof. dr. J.A. Rauwerda) in het kader van de opleiding tot orthopedisch chirurg.