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

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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.

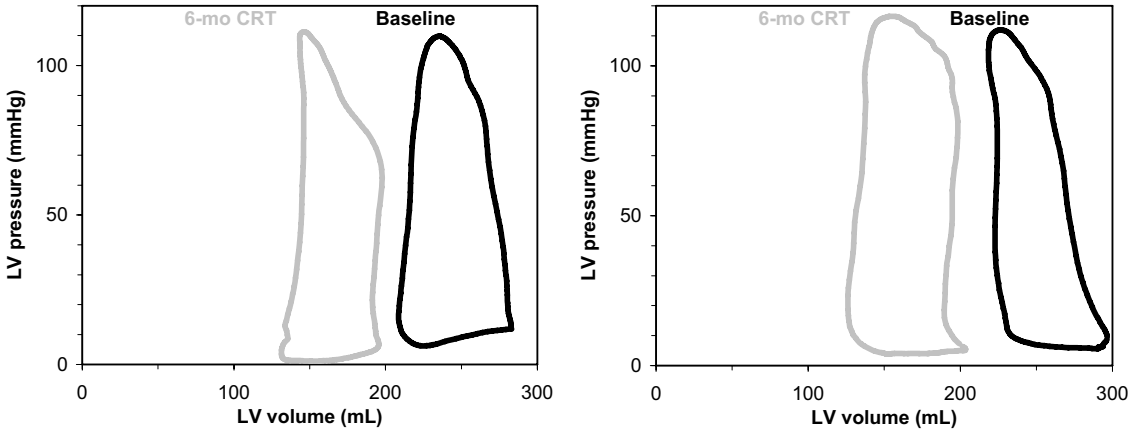

Figure 1. Effects of chronic CRT in two patients. Typical pressure-volume loops at baseline (grey) and after 6 months of chronic CRT (black) are shown (in all cases at a heart rate of 80 beats/min). Note the left ward shift of the pressure-volume loops indicating substantial reversed remodeling

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).

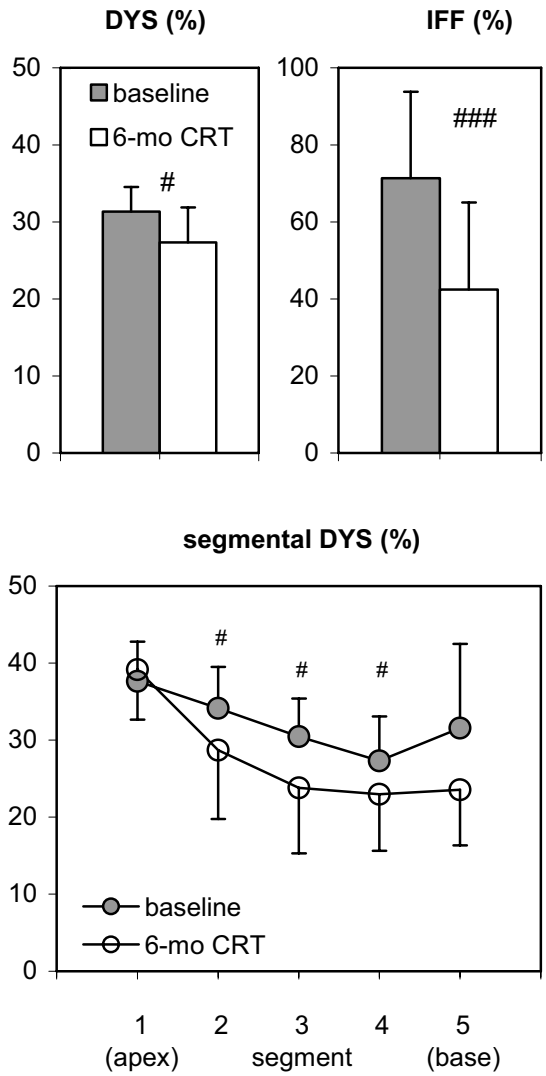

Figure 2. Mechanical dyssynchrony (DYS) and internal flow fraction (IFF) at baseline and after 6 months of CRT (at 80 beats/min). DYS is also shown per segment. Significances vs. baseline: # p<0.05, ## p<0.01, ### p<0.005, #### p<0.001

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.

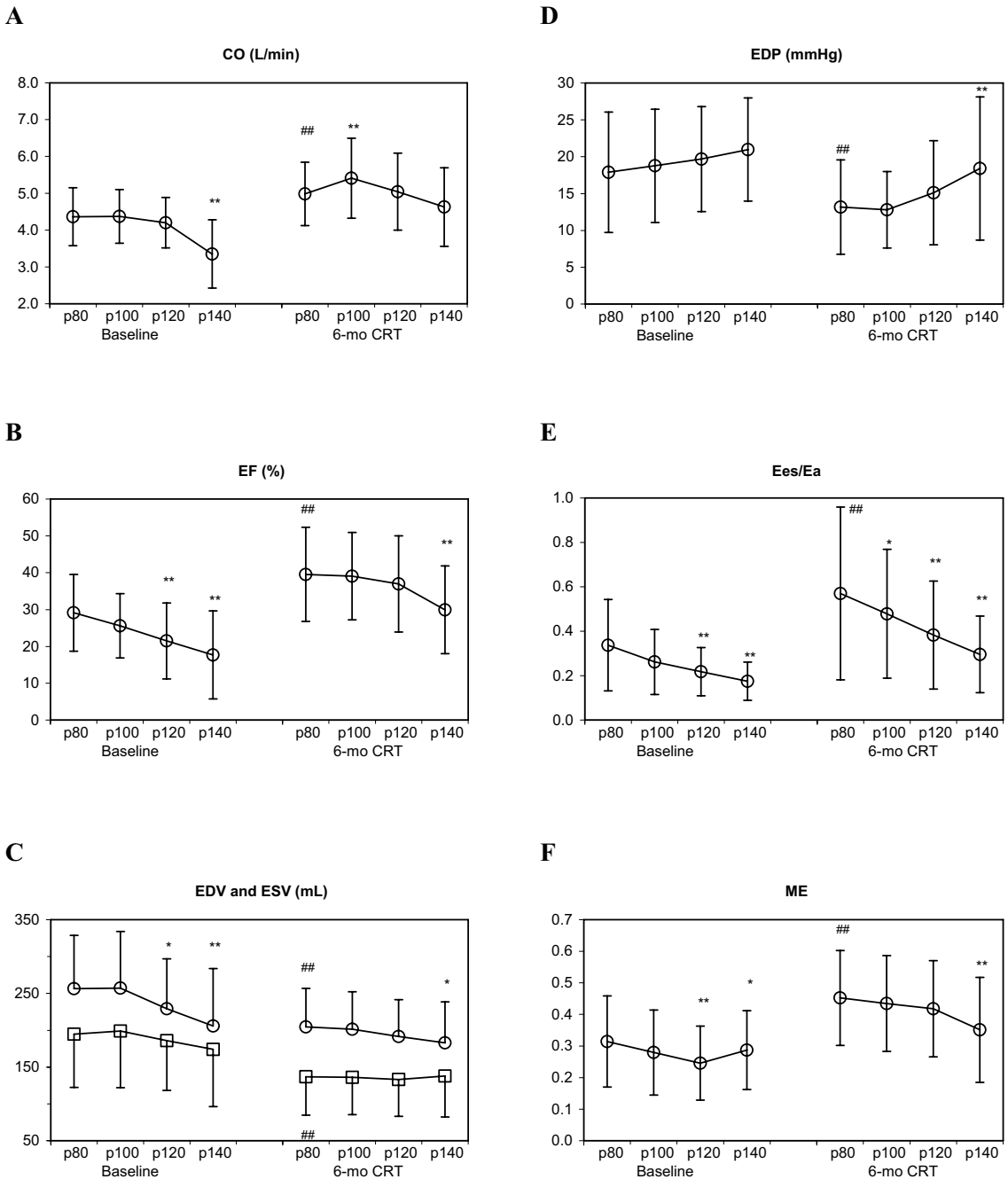

*Figure 3. Main hemodynamic indexes at baseline and after 6 months of CRT. CO indicates cardiac output; EDP, end-diastolic pressure; EF, LV ejection fraction; E_{ES}, end-systolic elastance; E_A, arterial elastance; EDV, end-diastolic volume; ESV, end-systolic volume; ME, mechanical efficiency. The Figures 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).

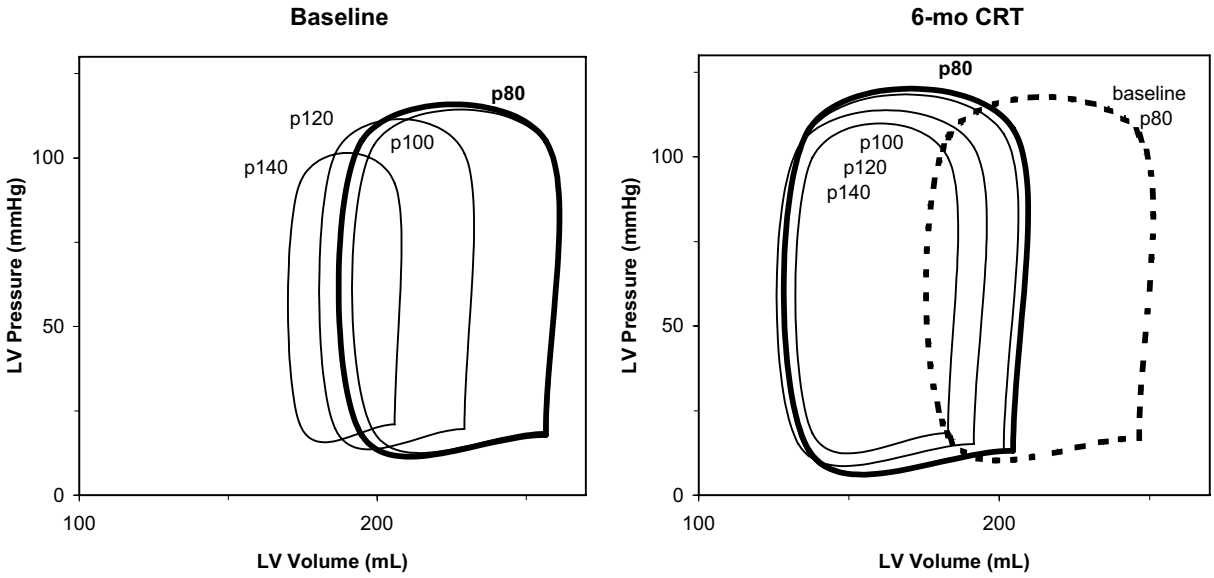

Figure 4. Mean pressure-volume loops at baseline and after 6 months of CRT. Mean pressure-volume loops are based on mean end-systolic and end-diastolic pressures and volumes and are shown at heart rates 80, 100, 120 and 140 beats/min. At baseline we used right atrial pacing via a temporary pacing lead;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

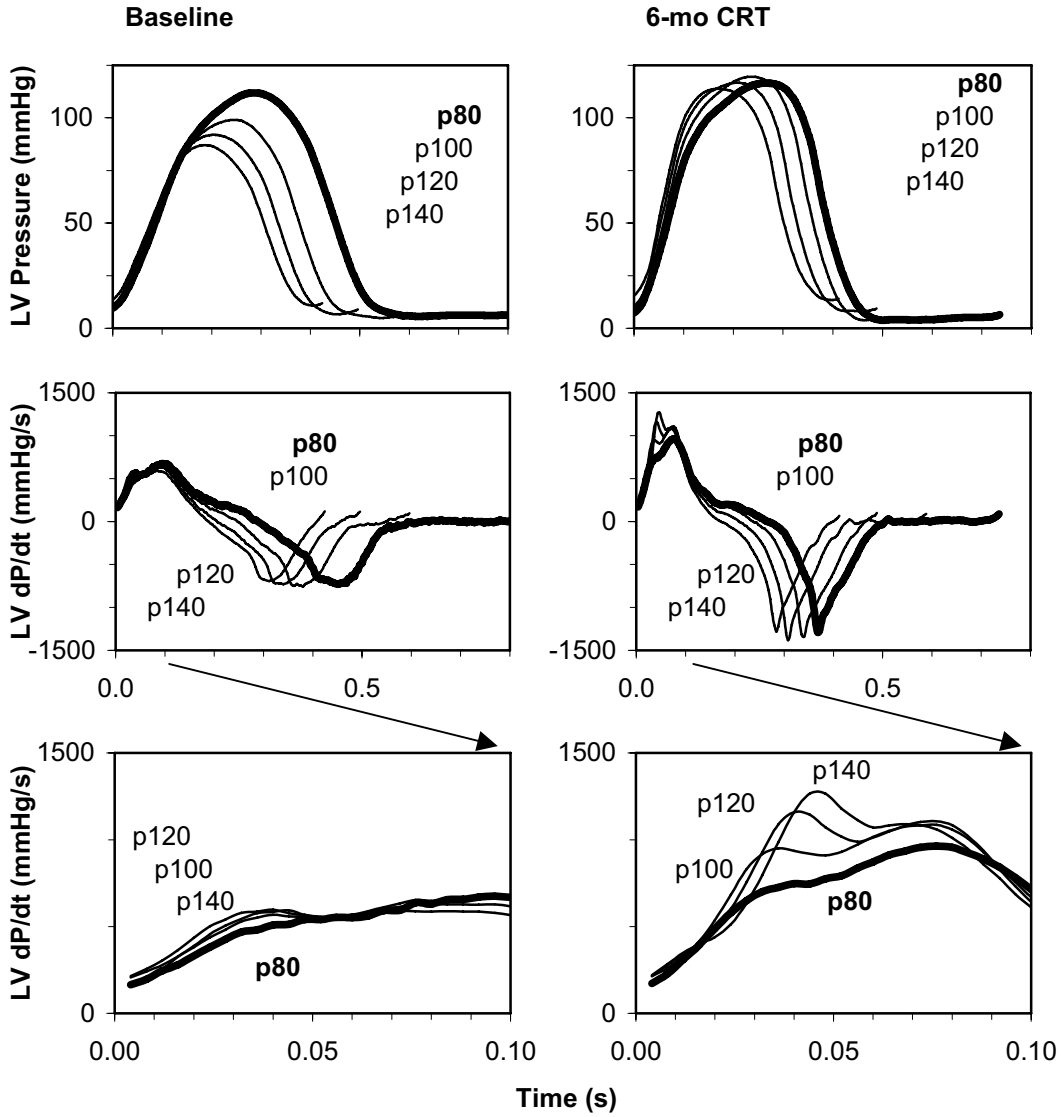

Figure 5. Typical examples of LV pressure and LV dP/dt during incremental pacing rate at baseline and after 6 months of CRT. Note that dP/dt_{MAX} was unchanged with increasing heart rate at baseline, whereas dP/dt_{MAX} substantially increased after CRT (See the bottom panels which extent the first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

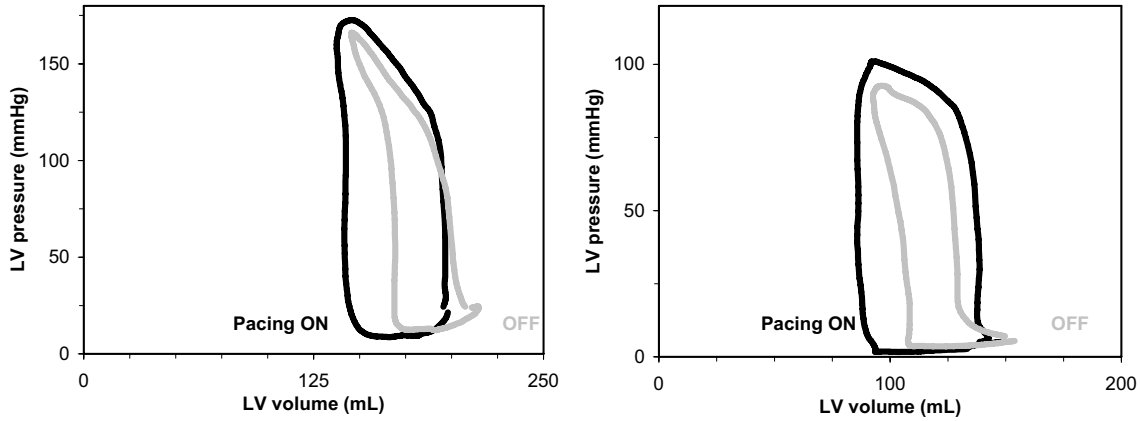

Figure 6. Immediate effects of cessation of biventricular pacing after 6-months CRT in two patients. Typical pressure-volume loops during pacing ON (black) and OFF (grey). Note the immediate reduction in stroke volume

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.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-1549.
3. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, Huth C, Schondube F, Wolfhard U, Bocker D, Krahnefeld O, Kirkels H. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:2026-2033.
4. Molhoek SG, Bax JJ, Bleeker GB, Boersma E, van Erven L, Steendijk P, van der Wall EE, Schalij MJ. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. *Am J Cardiol*. 2004;94:1506-1509.
5. Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BO, Mortensen PT. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol*. 2002;723-730.
6. Leclercq C, Kass DA. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol*. 2002;39:194-201.

7. Breithardt OA, Stellbrink C, Kramer AP, Sinha AM, Franke A, Salo R, Schiffgens B, Huvelle E, Auricchio A. Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. *J Am Coll Cardiol*. 2002;40:536-545.
8. Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS, Mortensen PT. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. *Circulation*. 2002;106:2078-2084.
9. Leclercq C, Faris O, Tunin R, Johnson J, Kato R, Evans F, Spinelli J, Halperin H, McVeigh E, Kass DA. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle- branch block. *Circulation*. 2002;106:1760-1763.
10. Kawaguchi M, Murabayashi T, Fetics BJ, Nelson GS, Samejima H, Nevo E, Kass DA. Quantitation of basal dyssynchrony and acute resynchronization from left or biventricular pacing by novel echo-contrast variability imaging. *J Am Coll Cardiol*. 2002;39:2052-2058.
11. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R, Tockman B, Pochet T, Spinelli J. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation*. 1999;99:2993-3001.
12. Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM, Kass DA. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. 2000;102:3053-3059.
13. St John Sutton MG, Plappert T, Abraham WT, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation*. 2003;107:1985-1990.
14. Sundell J, Engblom E, Koistinen J, Ylitalo A, Naum A, Stolen KQ, Kalliokoski R, Nekolla SG, Airaksinen KE, Bax JJ, Knuuti J. The effects of cardiac resynchronization therapy on left ventricular function, myocardial energetics, and metabolic reserve in patients with dilated cardiomyopathy and heart failure. *J Am Coll Cardiol*. 2004;43:1027-1033.
15. Baan J, Van Der Velde ET, De Bruin H, Smeenk G, Koops J, Van Dijk AD, Temmerman D, Senden J, Buis B. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation*. 1984;70:812-823.
16. Steendijk P, Staal E, Jukema JW, Baan J. Hypertonic saline method accurately determines parallel conductance for dual-field conductance catheter. *Am J Physiol Heart Circ Physiol*. 2001;281:H755-H763.
17. Steendijk P, Tulner SA, Schreuder JJ, Bax JJ, van Erven L, van der Wall EE, Dion RA, Schalij MJ, Baan J. Quantification of left ventricular mechanical dyssynchrony by conductance catheter in heart failure patients. *Am J Physiol Heart Circ Physiol*. 2004;286:H723-H730.
18. Langer SF. Differential laws of left ventricular isovolumic pressure fall. *Physiol Res*. 2002;51:1-15.
19. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, Kass DA. Effective arterial elastance as index of arterial vascular load in humans. *Circulation*. 1992;86:513-521.
20. Tachibana H, Cheng HJ, Ukai T, Igawa A, Zhang ZS, Little WC, Cheng CP. Levosimendan Improves Left Ventricular Systolic and Diastolic Performance at Rest and During Exercise after Heart Failure. *Am J Physiol Heart Circ Physiol*. 2004.
21. Nozawa T, Yasumura Y, Futaki S, Tanaka N, Uenishi M, Suga H. Efficiency of energy transfer from pressure-volume area to external mechanical work increases with contractile state and decreases with afterload in the left ventricle of the anesthetized open-chest dog. *Circulation*. 1988;77:1116-1124.
22. Arts T, Bovendeerd PH, Prinzen FW, Reneman RS. Relation between left ventricular cavity pressure and volume and systolic fiber stress and strain in the wall. *Biophys J*. 1991;59:93-102.
23. Deague JA, Wilson CM, Grigg LE, Harrap SB. Discrepancies between echocardiographic measurements of left ventricular mass in a healthy adult population. *Clin Sci (Lond)*. 1999;97:377-383.
24. Auricchio A, Ding J, Spinelli JC, Kramer AP, Salo RW, Hoersch W, KenKnight BH, Klein HU. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. *J Am Coll Cardiol*. 2002;39:1163-1169.
25. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38:963-974.
26. Kindermann M, Frohlig G, Doerr T, Schieffer H. Optimizing the AV delay in DDD pacemaker patients with high degree AV block: mitral valve Doppler versus impedance cardiography. *Pacing Clin Electrophysiol*. 1997;20:2453-2462.
27. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved

synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation*. 2002;105:438-445.
28. Hay I, Melenovsky V, Fetics BJ, Judge DP, Kramer A, Spinelli J, Reister C, Kass DA, Berger RD. Short-term effects of right-left heart sequential cardiac resynchronization in patients with heart failure, chronic atrial fibrillation, and atrioventricular nodal block. *Circulation*. 2004;110:3404-3410.
29. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, Nevo E. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation*. 1999;99:1567-73.
30. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol*. 2002;39:489-499.
31. Hay I, Rich J, Ferber P, Burkhoff D, Maurer MS. Role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure. *Am J Physiol Heart Circ Physiol*. 2005;288:H1203-H1208.
32. Sasayama S, Asanoi H. Coupling between the heart and arterial system in heart failure. *Am J Med.* 1991;90:14S-18S.
33. Starling MR. Left ventricular-arterial coupling relations in the normal human heart. *Am Heart J*. 1993;125:1659-1666.
34. Ohte N, Cheng CP, Little WC. Tachycardia exacerbates abnormal left ventricular-arterial coupling in heart failure. *Heart Vessels*. 2003;18:136-141.
35. Kim IS, Izawa H, Sobue T, Ishihara H, Somura F, Nishizawa T, Nagata K, Iwase M, Yokota M. Prognostic value of mechanical efficiency in ambulatory patients with idiopathic dilated cardiomyopathy in sinus rhythm. *J Am Coll Cardiol*. 2002;39:1264-1268.
36. Asanoi H, Kameyama T, Ishizaka S, Nozawa T, Inoue H. Energetically optimal left ventricular pressure for the failing human heart. *Circulation*. 1996;93:67-73.
37. Bordachar P, Lafitte S, Reuter S, Sanders P, Jais P, Haissaguerre M, Roudaut R, Garrigue S, Clementy J. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. *J Am Coll Cardiol*. 2004;44:2157-2165.
38. Stellbrink C, Breithardt OA, Franke A, Sack S, Bakker P, Auricchio A, Pochet T, Salo R, Kramer A, Spinelli J. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances(1). *J Am Coll Cardiol*. 2001;38:1957-1965.
39. Ukkonen H, Beanlands RS, Burwash IG, de Kemp RA, Nahmias C, Fallen E, Hill MR, Tang AS. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. *Circulation*. 2003;107:28-31.