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# Improvement in diastolic function and left ventricular filling pressure induced by cardiac resynchronization therapy

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**Background** Variable results of cardiac resynchronization therapy (CRT) on diastolic function have been described. We investigated 3 and 12 months' effect of CRT on diastolic function and left ventricular (LV) filling pressures and their relation to LV reverse remodeling.

**Methods** Fifty-two patients' (36 male,  $69 \pm 8$  years, QRS duration  $170 \pm 29$  milliseconds) echo-Doppler was performed before and 3 and 12 months after CRT. Tissue Doppler early diastolic annular (Em) and color M-mode-derived flow propagation (Vp) velocities were used to estimate LV filling pressures by E/Em and E/Vp ratios.

**Results** After 12 months, LV reverse remodeling (end-systolic volume decrease  $>15\%$ ) was observed in 58%. Despite a significantly more compromised baseline diastolic function of patients without LV reverse remodeling, multivariate analysis revealed that only LV dyssynchrony could predict LV reverse remodeling. Grades 2 and 3 diastolic function improved only in LV reverse remodeling patients (from 34% to 13% to 10%), whereas a nonsignificant increase from 59% to 67% to 72% was observed in patients without reverse remodeling. Irrespective of LV volume response, short-term symptomatic benefit was related to decreased filling pressure. However, after 12 months, E/Em and E/Vp only significantly decreased in patients with LV reverse remodeling (from  $16.0 \pm 6$  to  $10.4 \pm 4$  and  $2.2 \pm 0.6$  to  $1.5 \pm 0.4$ , respectively).

**Conclusions** Left ventricular reverse remodeling induced by CRT is accompanied by improvement in diastolic function and estimated LV filling pressure. Short-term symptomatic benefit was related to decreased filling pressure. However, for longer-term symptomatic improvement and decreased filling pressures, LV reverse remodeling appeared mandatory. (Am Heart J 2007;153:843-9.)

Cardiac resynchronization therapy (CRT) improves functional capacity, left ventricular (LV) function, and survival in patients with congestive heart failure and left bundle branch block.<sup>1-4</sup> Approximately 70% of patients respond symptomatically, whereas LV reverse remodeling occurs in an even smaller subset of patients. Previous reports on diastolic function after CRT are equivocal and often only assessed by preload-dependent Doppler transmitral flow.<sup>2-4</sup> Less load-dependent techniques

such as tissue Doppler early diastolic annular (Em) and color M-mode-derived flow propagation (Vp) velocities may be used to assess diastolic function more accurately. Moreover, these newer techniques allow assessment of LV relaxation and derived LV filling pressure.<sup>5-9</sup>

Therefore, we investigated diastolic function with these latter techniques and its relation to symptoms and improved systolic LV function after up to 12 months of CRT.

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## Methods

### Patients

Sixty-nine patients with heart failure New York Heart Association (NYHA) class III or IV, despite optimal medication, LV ejection fraction below 35%, sinus rhythm, and left bundle branch block, received CRT. Patients with mitral valve replacement or severe valvular disease other than secondary mitral regurgitation (MR) were excluded. In 17 patients, diastolic function could not be assessed because of technically suboptimal Doppler recordings or fusion of the mitral E and A waves; therefore, 52 patients entered the study. According to coronary

angiography, etiology of heart failure was ischemic in 25 and idiopathic dilated in 27 patients. Baseline QRS duration was  $170 \pm 29$  milliseconds with a PR interval of  $186 \pm 31$  milliseconds.

Diuretics were prescribed in 94% of patients, angiotensin-converting enzyme inhibitors in 79%,  $\beta$ -blocker in 64%, spironolactone in 52%, and digoxin in 21%. Changes in medication were avoided unless clinical mandatory. The local ethics committee approved the study protocol, and informed consent was obtained from all patients.

### Biventricular pacemaker implant

The coronary sinus lead (Medtronic 4193, Minneapolis, MN) was positioned in a posterior or posterolateral branch of the coronary sinus; the right ventricular lead was positioned in the apical or mid septal region and the right atrial lead in the atrial appendage. All leads were connected to a Medtronic InSync 8042 pulse generator. The atrioventricular delay and interventricular pacing interval were optimized within 1 day after implant using invasive  $LV_{dp/dt}$  measurements with a sensor-tipped pressure guide wire<sup>10</sup> (PW-4; RADI Medical Systems, Uppsala, Sweden). In 4 patients in whom invasive measurements could not be performed, intervals were optimized by echo-Doppler using the maximal mitral stroke volume as previously described.<sup>11</sup>

### Echocardiography

Echocardiography was performed with a Sonos 7500 and S3 transducer (Philips Medical Systems, Andover, MA) less than 1 week before and 3 and 12 months after biventricular pacemaker implant. Nomenclature of LV segments and measurements of LV dimensions were according to the recommendations of the American Society of Echocardiography.<sup>12</sup> Left ventricular volumes and ejection fraction were obtained in the apical 4- and 2-chamber views (biplane method). The degree of MR (grade I-IV) was assessed both by color jet area and as midsystolic percentage jet area relative to the left atrial size in the apical 4-chamber view. Left ventricular ejection time and cardiac index were obtained by pulsed wave Doppler of the LV outflow tract. Left ventricular filling time (FT) was measured from transmitral flow recorded from the apical 4-chamber view at end expiration at the mitral leaflets tips, from the onset of the E wave to the end of the A wave. Isovolumic time was obtained by subtracting LV ejection time and FT from the R-R interval. The duration of each phase of the cardiac cycle was then expressed as a percentage of the R-R interval.

Doppler recordings were made at a sweep speed of 100 mm/s with an electrocardiogram superimposed. Measurements were made in 3 digitally stored cardiac cycles, and the results were averaged.

To determine intraventricular dyssynchrony, pulsed wave tissue Doppler was used to calculate the SD of the time to onset of systolic velocity of 6 basal LV segments (SD-TsO-6). We previously reported that an SD-TsO-6 of more than 20 milliseconds had a sensitivity of 97% and a specificity of 74% in relation to LV reverse remodeling.<sup>13</sup>

### Assessment of diastolic function

**Standard diastolic parameters.** The peak rapid filling velocity (E wave), peak atrial filling velocity (A wave), E wave deceleration time (DT), and diastolic FT were measured, and

**Table I.** Baseline clinical characteristics

Baseline variable	All	LV reverse remodeling	
		Yes (n = 30)	No (n = 22)
Age (y)	69 $\pm$ 8	68 $\pm$ 9	71 $\pm$ 7, ns
Male/female	36/16	19/11	17/5, ns
ICM/DCM	25/27	9/21	16/6, ns
QRS (ms)	170 $\pm$ 29	172 $\pm$ 29	168 $\pm$ 30, ns
LV dyssynchrony SD-TsO-6 (ms)	28.8 $\pm$ 15	36.4 $\pm$ 13	18.4 $\pm$ 12*

ICM, Ischemic cardiomyopathy; DCM, dilated cardiomyopathy; ns, not significant. \* $P < .0001$ .

the E/A ratio was calculated. Pulmonary venous flow velocities were recorded with the sample volume approximately 1 cm in the right upper pulmonary vein. Pulmonary venous systolic (Pvs), diastolic (Pvd), and atrial reversal (Pvar) velocities were measured.<sup>9,14</sup>

**Load-independent diastolic parameters.** Color M-mode and pulsed tissue Doppler were recorded in the apical 4-chamber view. To obtain flow propagation velocity (Vp), we aligned the color M-mode cursor with the direction of mitral inflow. The baseline of the color Doppler spectrum was shifted to obtain aliasing. The slope (cm/s) of the onset of early diastolic flow from the mitral leaflets to a distance of 4 cm into the LV was measured.

Tissue Doppler was performed by placing a 3-mm sample volume at the septal and lateral mitral annulus to obtain early diastolic annular velocity (Em). The average of the septal and lateral Em was calculated and used for the ratio E/Em. The average Em of the septal and lateral wall was used, while this has been found to be more reliable in patients with adjacent wall motion abnormalities, and half of our population had ischemic cardiomyopathy.<sup>7</sup> The normal values for septal Em is  $>6$  and  $>7$  cm/s for lateral Em.<sup>8,9</sup>

Left ventricular filling pressure was estimated by E/Em and E/Vp. An E/Em  $>15$  and E/Vp  $>2.0$  were considered to represent elevated filling pressure.<sup>5,9,14</sup>

An overall assessment of diastolic function was obtained by consideration of all measured parameters. Diastolic function was categorized as normal (grade 0), impaired relaxation (grade I), pseudonormal filling (grade 2), or restrictive filling (grade 3).<sup>8,14</sup> The E/A ratio was used for initial categorization: grade 1, E/A ratio  $<1$  with a DT of  $>240$  milliseconds; grade 3, E/A ratio  $>2$  with a DT  $<160$  milliseconds. If E/A was between 1 and 2 and DT between 160 and 240 milliseconds, diastolic function was either "normal" (grade 0) or "pseudonormal" (grade 2) when 2 or more Doppler indices suggested elevated filling pressures (Pvs  $<$  Pvd; Pvar duration  $>+30$  milliseconds than mitral A duration; E/Vp  $>2$  or E/Em  $>15$ ).

To assess the effect of CRT on systolic LV function, we divided patients according to presence or absence of LV reverse remodeling, which was defined as a reduction of LV systolic volume by more than 15% after 12 months of CRT as compared with baseline.

**Six-minute walking test.** Six-minute walking test (MWT) was performed under standardized circumstances observed by the same person before and 3 and 12 months after CRT.<sup>15</sup>

**Table II.** Baseline and follow-up characteristics

Variable	All (n = 52)	LV reverse remodeling					
		Yes (n = 30)			No (n = 22)		
		Pre	3 m	12 m	Pre	3 m	12 m
NYHA class (0/1/2/3/4)	0/0/0/49/3	0/0/0/29/1	0/1/26/3/0*	0/5/24/1/0*	0/0/0/20/2	0/0/9/13/0*	0/0/3/14/5
MWT (mt)	378 ± 136, n = 40	390 ± 151, n = 26	475 ± 118,* n = 26	485 ± 122,* n = 26	361 ± 93, n = 14	415 ± 112,* n = 14	378 ± 119, ns, n = 14
LVEF (%)	21 ± 7	22 ± 7	32 ± 10*	38 ± 11*	20 ± 8	22 ± 8	21 ± 9
LVEDV (mL)	235 ± 83	229 ± 83	189 ± 72*	159 ± 63*	243 ± 84	243 ± 87	257 ± 91
MR	2.2 ± 1.2	2.1 ± 1.2	1.7 ± 1.0*	1.3 ± 0.9*	2.2 ± 1.1	2.1 ± 1.2	2.1 ± 1.3
MR/LA (area)	0.31 ± 0.2	0.29 ± 0.2	0.18 ± 0.2*	0.10 ± 0.1*	0.33 ± 0.2	0.28 ± 0.2	0.31 ± 0.2
CI (L/[min m <sup>2</sup> ])	1.8 ± 0.5	1.8 ± 0.5	2.1 ± 0.5*	2.3 ± 0.4*	1.7 ± 0.5	1.8 ± 0.4	1.6 ± 0.4
Isovolumic time (%)	28.8 ± 202	29.3 ± 4	22.0 ± 3*	20.7 ± 4*	26.6 ± 5	23.6 ± 4*	22.6 ± 4*
FT (%)	43.0 ± 6	41.7 ± 6	47.7 ± 4*	48.7 ± 6*	44.8 ± 6	47.5 ± 6*	47.6 ± 5*
RR (ms)	905 ± 218	855 ± 202	906 ± 111	890 ± 138	974 ± 225†	952 ± 193	960 ± 113

LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume; LA, left atrium; CI, cardiac index; RR, duration of cardiac cycle; ns, not significant versus baseline values.

\*Significant difference of  $P < .05$  versus baseline values.

†Baseline significant difference of  $P < .05$  between patients with and without LV reverse remodeling.

### Statistics

The paired  $t$  test was used to compare parametric variables before and after CRT. For examining differences between patients with and without reverse remodeling with regard to clinical and demographic factors, independent sample  $t$  tests (continuous variables) and  $\chi^2$  tests (nominal variables) were used. Multivariate logistic regression analysis (enter method) was used to examine prediction of LV reverse remodeling. Only parameters that previously showed to be related to reverse remodeling were included in the regression analysis.

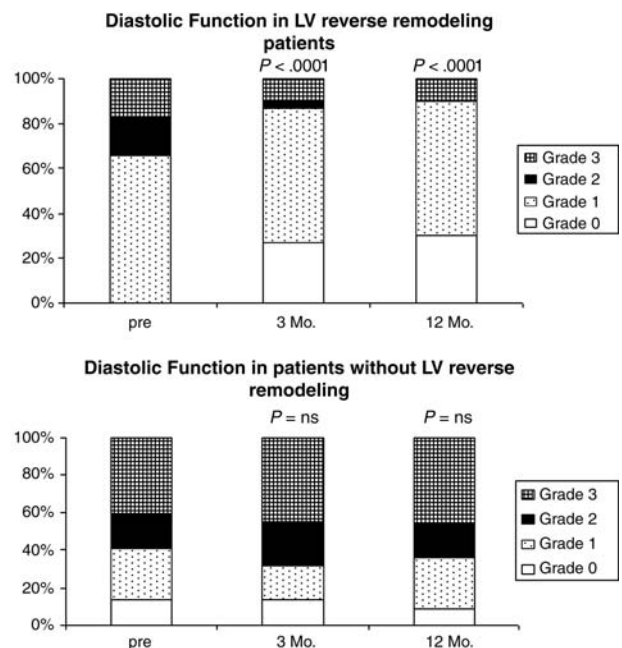
### Results

All patients survived during follow-up. Clinical and echocardiography variables are summarized in Tables I and II. After 12 months of CRT, 30 patients (58%) had LV reverse remodeling, whereas LV volumes and ejection fraction remained unchanged in the remaining 22. Both groups had similar baseline characteristics except for significantly more LV dyssynchrony measured by SD-TsO-6 and a higher heart rate in patients with LV reverse remodeling (Tables I and II).

After 3 months of CRT functional status, both by NYHA class and MWT significantly improved in both groups. From 3 to 12 months of follow-up, the initial functional improvement in patients without reverse remodeling disappeared, whereas a sustained and statistically significant improvement of functional status was evident in patients with LV reverse remodeling (Table II). Reverse remodeling was accompanied by a decrease in MR severity and an increased cardiac index, whereas such beneficial changes were absent in patients in whom CRT did not regress LV volume.

Irrespective of LV volume reduction, an increase in FT and decrease in isovolumic time was observed in both groups after 3 and 12 months of CRT.

**Figure 1**



Diastolic function at baseline and 3 and 12 months of CRT in patients with and without LV reverse remodeling. Significance of change in grade of diastolic function between baseline and follow-up.

Baseline diastolic function was significantly more compromised in the patients without subsequent LV reverse remodeling ( $P < .009$ ) (Figure 1). Baseline grade 2 or 3 diastolic function was present in 59% of patients without reverse remodeling compared with 34% of patients with LV reverse remodeling ( $P = .01$ ). After

**Table III.** Diastolic filling parameters in patients with and without LV reverse remodeling before and 3 and 12 months after CRT

Variable	LV reverse remodeling					
	Yes (n = 30)			No (n = 22)		
	Pre	3 m	12 m	Pre	3 m	12 m
E (cm/s)	62 ± 23	52 ± 20*	50 ± 21*	79 ± 35†	75 ± 32, ns	72 ± 31, ns
E/A	1.12 ± 0.9	0.88 ± 0.6*	0.90 ± 0.7*	1.74 ± 1.1†	1.93 ± 1.3, ns	2.3 ± 2.0, ns
DT (ms)	205 ± 67	249 ± 70*	282 ± 93*	191 ± 102, ns	193 ± 69, ns	204 ± 102, ns
Em (cm/s)	4.1 ± 1.3	5.2 ± 1.9*	5.0 ± 1.8*	4.8 ± 1.4, ns	4.7 ± 1.8, ns	4.4 ± 1.9, ns
Vp (cm/s)	30 ± 8, n = 26	37 ± 9*	36 ± 10*	33 ± 10, n = 18 ns	35 ± 11, ns	30 ± 9, ns
E/Em	16.0 ± 6	10.8 ± 4*	10.4 ± 4*	18.5 ± 10, ns	19.1 ± 11, ns	18.5 ± 9, ns
E/Vp	2.2 ± 0.6	1.6 ± 0.5*	1.5 ± 0.4*	2.5 ± 0.9, ns	2.1 ± 0.6, ns	2.3 ± 0.8, ns

E, Early transmitral flow; E/A, ratio of early to atrial transmitral flow; E/Em, ratio of transmitral early flow to mean velocity of early mitral annular ascent of the septal and lateral corners; E/Vp, ratio of E to the color M mode-derived flow propagation (Vp); ns, not significant versus baseline values.

\*Significant difference of  $P < .05$  versus baseline values.

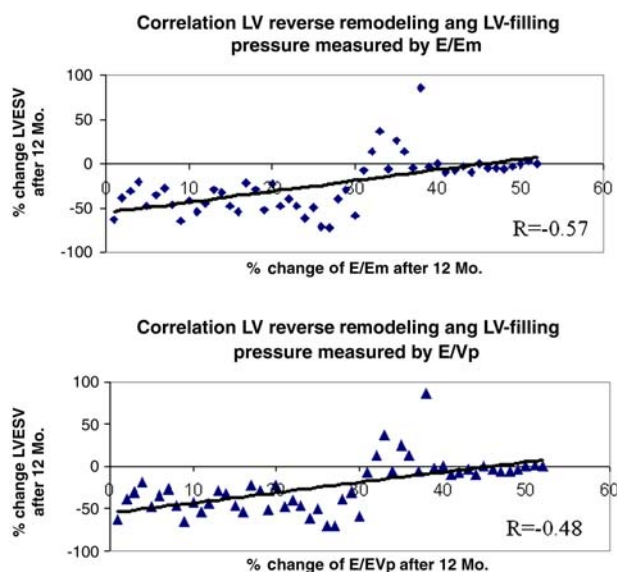
†Baseline significant difference of  $P < .05$  between patients with and without LV reverse remodeling.

3 months of CRT, diastolic function improved significantly only in patients with reverse remodeling ( $P < .0001$ ) (Figure 1). Prevalence of grade 2 or 3 diastolic dysfunction decreased from 34% to 13% ( $P = .0003$ ) in reverse remodeling patients, whereas a nonsignificant increase from 59% to 67% was observed in the patients without reverse remodeling.

Standard load-dependent diastolic parameters (provided in Table III) also showed E and E/A to be considerably lower at baseline in patients with reverse remodeling compared with patients without (E,  $62 \pm 23$  vs  $79 \pm 35$  cm/s,  $P = .04$ , and E/A,  $1.12 \pm 0.9$  vs  $1.74 \pm 1.1$ ,  $P = .03$ ). After 3 months of CRT, a significant decrease in E and E/A and increase in DT were seen only in patients with LV reverse remodeling (Table III).

Baseline load-independent parameters of LV relaxation Em and Vp were low in both groups (Table III), indicating disturbed LV relaxation. During CRT, both Em and Vp improved significantly only in the LV reverse remodeling group.

Estimated filling pressure significantly decreased in patients with reverse remodeling: E/Em from  $16.0 \pm 6$  to  $10.8 \pm 4$  ( $P = .0001$ ) and E/Vp  $2.2 \pm 0.6$  to  $1.6 \pm 0.5$  ( $P = .0006$ ) in contrast to patients with no volume reduction in whom filling pressure remained stable. Thus, a strong relation between LV reverse remodeling and normalization of diastolic function and filling pressures was observed. A correlation of  $r = -0.57$  and  $r = -0.48$  was observed between the change in LV end systolic volume after 12 months of CRT, and the estimated filling pressures were measured respectively by the change in E/Em and E/Vp (Figure 2). Interestingly, 9 patients who symptomatically improved despite no volume reduction showed a decrease in estimated filling pressure in contrast to patients with no symptomatic benefit in whom estimated filling pressures remained elevated (Table IV, Figure 3). Patients without

**Figure 2**

Correlation between percent of changes in LV end systolic volume after 12 months of CRT and estimated LV filling pressures measured by E/Em and E/Vp.

LV reverse remodeling but symptomatic improvement also had significantly more increase in MWT after 3 months of CRT ( $+35.0 \pm 33\%$  vs  $6.0 \pm 11\%$ ;  $P = .03$ ) compared with patients without symptomatic benefit.

Extended follow-up at 12 months revealed loss of functional improvement and elevated filling pressures in all patients without LV reverse remodeling (Tables III and IV). Changes in diastolic function were similar to those at 3 months, with improvement of diastolic function only in patients with reverse remodeling.

**Table IV.** Estimated filling pressure by E/Em and E/Vp in patients without LV reverse remodeling who are divided by their symptomatic benefit at 3 months of CRT

Patients without LV reverse remodeling	Symptomatic benefit at 3 m CRT						
	Pre	Yes (n = 9)			No (n = 13)		
		3 m	12 m	Pre	3 m	12 m	
E/Em	19.6 ± 17	12.1 ± 3, ns	17.4 ± 4, ns	17.6 ± 7	22.1 ± 12, ns	20.1 ± 11, ns	
E/Vp	2.5 ± 1, n = 7	1.7 ± 0.7, ns	2.6 ± 0.7, ns	2.4 ± 0.8, n = 11	2.2 ± 0.5, ns	2.2 ± 0.9, ns	
LV end-systolic volume (mL)	211 ± 107	206 ± 96, ns	222 ± 92, ns	193 ± 72	188 ± 82, ns	199 ± 89, ns	
MR severity	2.2 ± 1	2.2 ± 1, ns	2.2 ± 1, ns	2.0 ± 1	1.8 ± 1, ns	2.0 ± 1, ns	

P = significance versus baseline value.  
ns, Not significant versus baseline values.

Estimated filling pressures decreased significantly only in the LV reverse remodeling group: E/Em changed from 16.0 ± 6 to 10.4 ± 4 (P = .0001) and E/Vp from 2.2 ± 0.6 to 1.5 ± 0.5 (P < .0001) (Table III).

Baseline LV dyssynchrony, diastolic function, and load-dependent parameters like E and E/A were significantly different between patients with or without LV reverse remodeling. However, multivariate analysis revealed that only LV dyssynchrony measured by SD-TsO-6 could predict LV reverse remodeling after 12 months of CRT (OR 1.187, 95% CI 1.036-1.360; P = .013).

## Discussions

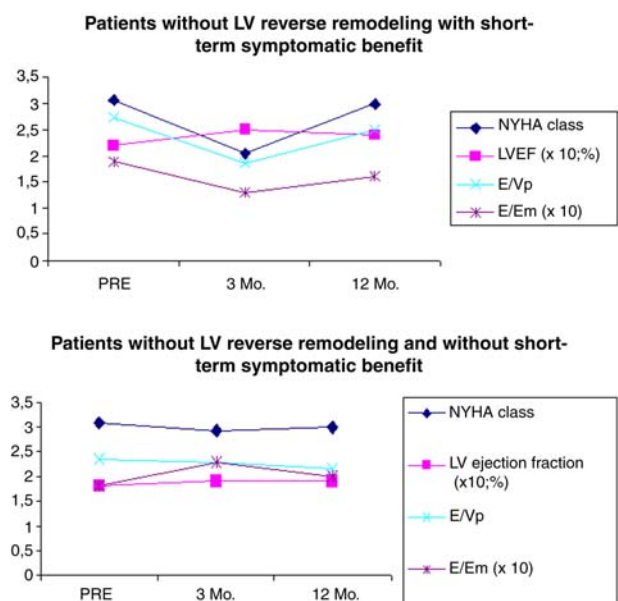
In the present study, the effect of CRT on diastolic function was assessed including the use of newer less load-dependent echo-Doppler parameters of LV filling. Among the determinants of LV filling are elastic recoil, active myocardial relaxation, and passive compliance. Furthermore, left atrial compliance, contractility, and pressure are important. Diastolic filling is the result of the transmural pressure gradient produced by these factors.<sup>8,9,14,16</sup>

In this study, patients were divided according to the presence of LV reverse remodeling defined by an LV end systolic reduction of more than 15% after 12 months of CRT, which occurred in 58% of patients. Left ventricular reverse remodeling was used as a surrogate end point of CRT because it has been shown to be related to improved survival.<sup>17</sup>

Diastolic function was graded on a scale from 0 to 3 based on the E/A ratio and DT together with Doppler indices of LV filling. Only patients with LV reverse remodeling after 12 months showed a significant sustained improvement in diastolic filling pattern (Figure 1). A good correlation was also observed between reverse remodeling and estimated LV filling pressure (Figure 2).

Patients without subsequent LV reverse remodeling had significantly more compromised baseline diastolic

**Figure 3**



Time course changes and relation of NYHA class, LV ejection fraction, and E/Em and E/Vp after 3 months of CRT in patients without LV reverse remodeling with (n = 9) and without (n = 13) symptomatic benefit.

function, whereas baseline LV dyssynchrony was significantly less.

The poorer start of the subsequent systolic nonresponders, earlier also described by Penicka et al,<sup>3</sup> may suggest more advanced and severe heart failure with less potential for improvement. However, multivariate analysis revealed that only LV dyssynchrony could significantly predict LV reverse remodeling after 12 months of CRT. Apparently, baseline LV dyssynchrony plays an important role in CRT. If CRT can correct LV dyssynchrony, LV reverse remodeling can be induced, and as a

consequence, diastolic properties may improve, which may also result in improved LV filling pressure.

Left ventricular dyssynchrony has an effect on early diastolic filling through asynchronous relaxation and is often the cause of prolonged isovolumic relaxation time.<sup>9,16</sup> Part of the hemodynamic benefit induced by CRT may be obtained by optimization of cardiac time intervals. It has been shown that diastolic FT increases after CRT.<sup>2-4,18</sup> However, in this study, an increase in FT irrespective of volume reduction was observed. Thus, cardiac time interval optimization alone by CRT appears insufficient to improve diastolic function (Table III).

We observed a significant decrease of MR severity after CRT in reverse remodeling patients, whereas regurgitation remained unchanged in patients without volume reduction. The decrease in MR could have a direct effect on the E and E/A ratio by reducing the preload. However, reduced MR in patients with reverse remodeling was accompanied by improved early LV relaxation, as determined by preload-independent parameters as both tissue Doppler Em and color M-mode Vp. Because these parameters are considered independent of LV loading,<sup>8,9</sup> they are unrelated to MR severity. Therefore, although reduction of MR severity is one of the beneficial effects of CRT, improvement of inherent LV diastolic function appears as an equally important explanation of its effect.

Recently, Waggoner et al<sup>18</sup> also showed that mitral E-wave velocity, E/A ratio, and estimated filling pressure improved after 4 months of CRT only in patients with increased systolic LV performance. However, in contrast to the present study, they found no change of Em or Vp after short-term CRT and concluded that benefits in diastolic function were related to LV-volume reduction and not to changes in LV relaxation. However, the baseline values of Em and Vp in the study of Waggoner et al (mean 8 cm/s, respectively 38 cm/s) were considerably higher than in the present study (mean 4.4 cm/s, resp. 31 cm/s), suggesting that their population had less diastolic abnormalities at baseline.

Estimated LV filling pressure has been shown to be related to symptoms in patients with congestive heart failure.<sup>19,20</sup> In our study, patients with reverse remodeling and symptomatically improved patients without reverse remodeling showed decreased filling pressures after CRT as estimated by E/Em and E/Vp ratios. In contrast, in patients without reverse remodeling and also no clinical response, LV filling pressures remained elevated (Table IV, Figure 2). After 12 months of follow-up, clinical benefit of CRT together with lowered estimated LV filling pressures was only sustained in the LV reverse remodeling group. Apparently, short-term symptomatic benefit related to decreased filling pressure may occur irrespective of LV reverse remodeling. However, for longer-term symptomatic improvement

and decreased filling pressures, reverse remodeling appears mandatory.

### Limitations

Left ventricular diastolic function and filling pressure are determined most directly and reliably by invasive pressure and volume measurements, which were not performed in this study. However, echo-Doppler is well established as a noninvasive tool to investigate diastolic function and filling pressure.<sup>8,14</sup> Also, the relatively small number of patients limits the study.

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