European Journal of Echocardiography (2009) **10**, 663–668
doi:10.1093/ejechocard/jep033

Myocardial contractile reserve during exercise predicts left ventricular reverse remodelling after cardiac resynchronization therapy

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Received 19 November 2008; accepted after revision 13 March 2009; online publish-ahead-of-print 7 April 2009

KEYWORDS
Cardiac resynchronization therapy;
Left ventricular dyssynchrony;
Viability;
Exercise;
Echocardiography

Aims Lack of response to cardiac resynchronization therapy (CRT) may be due to the presence of significant amount of scar or fibrotic tissue at myocardial level. This study sought to investigate the potential impact of myocardial contractile reserve as assessed during exercise echocardiography on left ventricular (LV) reverse remodelling (decrease in LV end-systolic volume $\geq$15% after 6 months of CRT).
Methods and results Fifty-one consecutive patients with heart failure underwent exercise Doppler echocardiography before CRT implantation to assess global contractile reserve and local contractile reserve (assessed by two-dimensional speckle tracking) in the region of the LV pacing lead. Responders (30 patients) showed a greater exercise-induced increase in left ventricular ejection fraction (LVEF) compared with non-responders ($P < 0.001$). Contractile reserve was directly related to the improvement in LVEF and to LV reverse remodelling after 6 months of CRT ($P < 0.001$). A 6.5% exercise-induced increase in LVEF yielded a sensitivity of 90% and a specificity of 85.7% to predict the response after 6 months of CRT. Baseline myocardial deformation as well as contractile reserve in the LV pacing lead region was greater in responders than in non-responders ($P < 0.0001$).
Conclusion Myocardial contractile reserve (global and regional) is a strong predictive factor of LV reverse remodelling after CRT.

Introduction

Cardiac resynchronization therapy (CRT) has significantly changed the treatment of patients with end-stage heart failure.[1] Currently, CRT is an adjunctive treatment indicated for treating patients with heart failure and significant ventricular conduction delay who remain symptomatic, despite optimal drug therapy.[2] CRT improves clinical status, quality of life and exercise capacity, prolongs survival, and promotes various haemodynamic and structural ventricular changes.[3,4] Reduction in left ventricular (LV) end-systolic volume—LV reverse remodelling—after 6 months under stimulation is a major determinant of long-term survival after CRT.[5] However, still 30% of patients do not present LV reverse remodelling, and thus do not respond to CRT. Response to CRT largely depends on the extent of LV dyssynchrony, the severity of LV remodelling, and the possibility offers to the LV to recruit function.[6,7] CRT response could thus correlate with myocardial viability and inversely be associated with the extent of myocardial fibrosis.[8,9] Furthermore, scar tissue or fibrosis—characterized by lack of contractile reserve—in the LV pacing lead region may prohibit response to CRT. Myocardial contractile reserve— important prognostic marker in heart failure—can be reliably assessed during exercise echocardiography.[10] This study sought to investigate the potential impact of myocardial contractile reserve—global and in the LV pacing lead—as assessed during exercise echocardiography on LV reverse remodelling.

Methods

Patient population

From March 2004 to January 2008, 133 patients were planned for a biventricular pacing implantation according to available recommendations. Fifty-five of them who met the following criteria were enrolled in the present study: (i) NYHA functional class III/IV heart

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failure, (ii) QRS duration $\geq$120 ms, (iii) chronic LV systolic dysfunction (ejection fraction $\leq$35%), (iv) optimal medical treatment for heart failure, (v) sinus rhythm, and (vi) capable of exercising. Exclusion criteria were: (i) recent myocardial infarction ($<$6 months), (ii) recent coronary revascularization ($<$6 months), (iii) poor echogenicity, (iv) haemodynamic instability, and (v) atrial fibrillation. Four patients were subsequently excluded for the failure of CRT implantation. The final population consisted of the 51 remaining patients. The aetiologies of heart failure were idiopathic dilated cardiomyopathy in 17 patients and ischaemic heart disease in 34 patients. All patients underwent exercise Doppler echocardiography before CRT implantation to assess global LV contractile reserve [(improvement in left ventricular ejection fraction (LVEF)] and local contractile reserve in the region of the LV pacing lead (assessed by longitudinal strain using speckle tracking analysis). No patients with ischaemic disease presented inducible ischaemia during the test. The protocol was approved by the Human Ethical Committee of our University Hospital and all patients gave informed consent.

Exercise echocardiography

A symptom-limited graded bicycle exercise test was performed in a semi-supine position on a tilting exercise table. After an initial workload of 25 W maintained for 2 min, the workload was increased every 2 min by 25 W. Blood pressure and a 12-lead electrocardiogram were recorded every 2 min. Two-dimensional echocardiographic recordings were made throughout the test.

Echocardiographic measurements

All echocardiographic parameters were obtained at rest and at peak exercise in the same cycling semi-supine position (Vivid 7 imaging device, GE Healthcare, UK) and were obtained in digital format and stored on optical disks for off-line analysis. Two-dimensional grayscale images (frame rates $\geq 70\ s^{-1}$) and colour-tissue Doppler imaging (frame rates $\geq 115\ s^{-1}$) were performed in the apical views using a narrow sector angle. Left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured by the biapical Simpson disk method. Wall motion score analysis was applied to a 16-segment model of the LV with a semi-quantitative scoring system (1 = normal, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia). To determine LV dyssynchrony with colour-tissue Doppler imaging, the sample volume (6 $\times$ 6 mm) was placed in the LV basal parts of the anterior, inferior, septal, and lateral walls (using the two- and four-chamber apical views), and the time interval between the onset of the QRS complex and the peak systolic velocity per region was derived (i.e. the electrosystolic delays). Intra-LV dyssynchrony was referred to LV dispersion and was calculated as the difference between the longest and the shortest times to peak systolic velocities of four opposing basal walls.[11] Global LV contractile reserve was expressed as the change in LVEF from rest to peak exercise. Regional contractile reserve in the pacing lead was assessed using speckle tracking analysis from LV long-axis images (mid-segments). After tracing the endocardial borders in the end-systolic frame, an automated tracking algorithm outlined the myocardial deformation in the dedicated LV segments.[12] Peak systolic longitudinal strain was only measured in the lateral, posterior, and anterior regions, where the LV lead was positioned. Aortic and pulmonary Doppler flows were recorded in the pulsed mode from the apical four-chamber view and parasternal short-axis view, respectively. The aortic and pulmonary ejection delays (interventricular dyssynchrony) were defined as the delay between the onset of the QRS complex or the surface ECG and the onset of the aortic and pulmonary waves. Quantitation of mitral regurgitation was performed by the proximal isovelocity surface area method.[4]

Cardiac resynchronization therapy implantation and setting

All patients received a biventricular pacing device for CRT with a right ventricular apical lead and LV pacing electrodes positioned through the coronary sinus in a LV epicardial vein. This coronary sinus lead was placed in a lateral position in 32 patients, in a posterolateral position in 16 and in anterior position in 3. After a successful implant, echocardiography was used to optimize the atrioventricular delay in order to maximize LV filling time. Interventricular pacing interval was set to a default value (V-V = 0 ms). One day after implantation, the LV lead position was assessed from a chest X-ray. Using the frontal and lateral views (scored anterior, lateral, or posterior), we determined the LV lead locations. To note six patients received a defibrillator.

Follow-up and cardiac resynchronization therapy response definition

Follow-up clinical and echocardiographic examinations were obtained at 6 months. Responders were defined by a $\geq$15% decrease in LV end-systolic volume.[5] During this period, no patient died nor was rehospitalized for either heart failure or significant arrhythmias.

Statistical analysis

Data are expressed as mean $\pm$ 1 SD (STATISTICA version 6). Student's paired two-tailed *t*-test was used to compare measurements obtained at rest and during exercise. Categorical variables were compared with Fisher's exact test. A value of $P < 0.05$ was considered significant. Categorical data are summarized as frequencies and percentages. Linear regression analysis was performed to evaluate the relation between the improvement in LVEF during exercise and changes in LV end-systolic volume after 6 months of CRT. The optimal improvement in LVEF and in myocardial strain during exercise to predict response to CRT was determined by receiver operating characteristic (ROC) curve analysis. To detect independent cofactors associated with response to CRT, a logistic multivariate analysis was performed. All significant variables were included in the multivariate model. Reproducibility of echocardiographic measurements has been previously published.[13]

Results

Table 1 summarizes the baseline characteristics in the studied population. Patients were predominantly of male sex and were in general optimally treated.

Response to cardiac resynchronization therapy

During follow-up, the NYHA class improved from 3.06 $\pm$ 0.24 to 2.3 $\pm$ 0.8 ($P < 0.0001$). The LVEF improved significantly from 27 $\pm$ 5 to 34 $\pm$ 7% ($P < 0.001$), and significant reductions in LV end-diastolic (184 $\pm$ 39 to 172 $\pm$ 38 mL; $P < 0.001$) and LV end-systolic volume (134 $\pm$ 31 to 114 $\pm$ 32 mL; $P < 0.001$) were observed. Thirty patients were classified as responders to CRT, according to the predefined criterion of a reduction in LV end-systolic volume.

Responders vs. non-responders

Baseline clinical and echocardiographic parameters between responders and non- responders were similar, except for higher degree of interventricular mechanical delay and mitral regurgitation and better myocardial deformation by two-dimensional speckle tracking in the LV lead region in responders (*Table 2*). During exercise, responders

Table 1 Responders vs. non-responders: baseline characteristics

Variables	All patients ($n = 51$)	Responders ($n = 30$, 59%)	Non-responders ($n = 21$, 41%)	*P*-value
Age (years)	70 ± 9	70 ± 8	69 ± 9	0.85
Male [*n* (%)]	32 (63)	20 (67)	12 (57)	0.56
Ischaemic cardiomyopathy [*n* (%)]	34 (67)	17 (57)	17 (85)	0.07
QRS duration (ms)	161 ± 25	154 ± 24	169 ± 25	0.03
Diuretic [*n* (%)]	42 (82)	23 (77)	19 (90)	0.28
β-Blockers [*n* (%)]	44 (86)	26 (87)	18 (86)	0.68
ACEi [*n* (%)]	41 (80)	24 (80)	17 (81)	0.61
AR blockers [*n* (%)]	5 (9.8)	3 (10)	2 (9.5)	0.68
Spironolactone [*n* (%)]	23 (45)	14 (47)	9 (43)	0.51
LV–RV dyssynchrony (ms)	52 ± 16	56 ± 16	46 ± 15	0.029
LV–RV ≥ 40 ms	36 (71)	24 (80)	12 (57)	0.039
LV dispersion (ms)	85 ± 47	111 ± 39	48 ± 29	<0.0001
LV dispersion ≥ 80 ms	28 (55)	24 (80)	4 (19)	<0.0001
Mitral effective regurgitant orifice (mm^2)	18 ± 11	23 ± 10	14 ± 9	0.011

Ischaemic cardiomyopathy: ACEi, angiotensin-converting enzyme inhibitors and AR, angiotensin receptors; LV, left ventricle; RV, right ventricle.

Table 2 Responders vs. non-responders: rest and exercise echocardiographic data

Variables	All patients ($n = 51$)	Responders ($n = 30$, 59%)	Non-responders ($n = 21$, 41%)	*P*-value
LV function				
LV end-diastolic volume at rest (mL)	184 ± 39	183 ± 41	186 ± 37	0.80
LV end-diastolic volume at exercise (mL)	180 ± 40	179 ± 43	182 ± 36	0.79
LV end-diastolic volume diff. (mL)	−3.9 ± 7.5	−3.9 ± 7.5	−3.7 ± 6.7	0.90
LV end-systolic volume at rest (mL)	134 ± 32	133 ± 34	134 ± 28	0.95
LV end-systolic volume at exercise (mL)	120 ± 30	118 ± 33	124 ± 27	0.45
LV end-systolic volume diff. (mL)	14 ± 7	16 ± 7	10 ± 5.3	0.001
LV ejection fraction at rest (%)	27.4 ± 5.1	27.1 ± 5.2	27.7 ± 5.0	0.68
LV ejection fraction at exercise (%)	34 ± 6	35 ± 5.7	31 ± 4.7	0.009
LV ejection fraction diff. (%)	6.2 ± 3.3	8.2 ± 2.3	3.5 ± 2.4	<0.0001
Number of akinetic segments				
Rest	6.5 ± 4	6.9 ± 3.3	5.9 ± 3.4	0.26
Exercise	5.1 ± 3.1	4.8 ± 2.9	5.5 ± 3.3	0.47
Wall motion score index				
Rest	2.24 ± 0.3	2.25 ± 0.29	2.23 ± 0.32	0.91
Exercise	2.1 ± 0.36	1.9 ± 0.35	2.2 ± 0.33	0.008
Diff.	−0.21 ± 0.25	−0.3 ± 0.27	−0.08 ± 0.13	0.0009
Strain target LV lead wall (%)				
Rest	12.7 ± 5.4	14.1 ± 3.8	10.6 ± 6.7	0.023
Exercise	14.9 ± 7.5	18.0 ± 3.4	10.4 ± 9.3	0.00017
Diff.	2.1 ± 3.2	3.8 ± 1.8	−0.26 ± 3.3	<0.0001

LV, left ventricle; Diff, difference between exercise and rest.

showed a greater increase in LVEF. Improvement in LVEF at peak test was correlated to the improvement in LV end-systolic volume after CRT ($r = 0.61$) (*Figure 1*). An increase in LVEF during exercise by ≥6.5% (ROC curve) yielded a good sensitivity (90%) and specificity (85.7) for predicting LV reverse remodelling after CRT (*Figure 2*). Responders presented more LV dyssynchrony at baseline than non-responders. The area under the curve for LV dispersion was 0.88, and the optimal cut-off value to predict response to CRT was 80 ms, yielding a sensitivity and specificity of 73.3 and 95.2%, respectively. By multivariate logistic regression analysis, LV dyssynchrony (OR = 0.92, 95% CI: 0.87–0.98; $P = 0.012$) and the presence of contractile reserve at exercise (OR = 0.24, 95% CI: 0.08–0.75; $P = 0.017$) emerged as independent predictors of response to CRT. Among responders, 25 patients had both LV dyssynchrony and global contractile reserve at exercise (*Figure 3*). Non-responders were characterized by no significant LV dyssynchrony and no contractile reserve.

Regional contractile reserve and response to cardiac resynchronization therapy

During exercise, the extent of improvement in regional strain (3.6 ± 1.8 vs. −0.26 ± 3.3; $P < 0.0001$) was greater in patients who presented reverse LV remodelling at

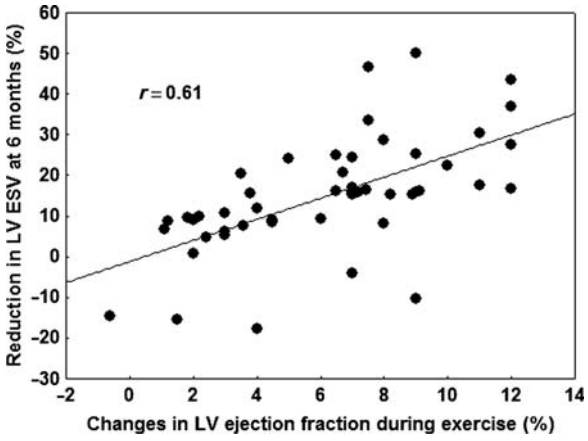

Figure 1 Relationship between contractile reserve (improvement in left ventricular ejection fraction during exercise) at inclusion and left ventricular reverse remodelling (improvement in left ventricular end-systolic volume) after 6 months of cardiac resynchronization therapy.

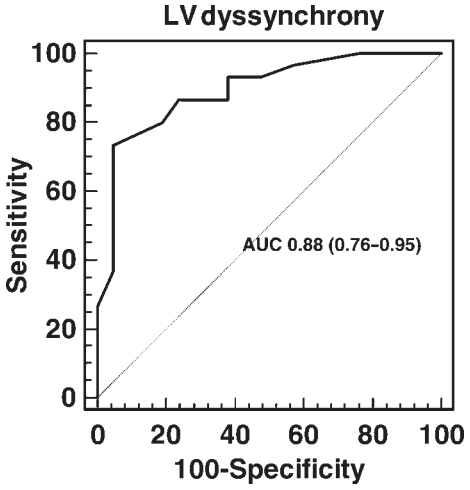

Figure 2 Receiver operating characteristic curve analysis on left ventricular dyssynchrony to predict the response after cardiac resynchronization therapy.

follow-up. An exercise increase in strain values of the target LV lead wall by >2% (ROC curve) yielded a good sensitivity (86.7%) and specificity (81%) for predicting LV reverse remodelling after CRT (*Figure 4*). Among responders, 22 patients had both LV dyssynchrony and regional contractile reserve at exercise (*Figure 5*). *Figure 6* showed a patient without posterolateral contractile reserve during exercise. By multivariate logistic regression analysis, LV dyssynchrony (OR = 0.96, 95% CI: 0.93–0.98; $P = 0.0007$) and the presence of contractile reserve in the LV lead region at exercise (OR = 0.39, 95% CI: 0.19–0.81; $P = 0.013$) emerged as independent predictors of response to CRT.

Discussion

Response to CRT is modulated by several factors. In the present study, we confirm that the chronic benefit to CRT depends in part on the presence of residual myocardial viability and the degree of LV dyssynchrony. A direct relationship existed between the extent of myocardial contractile

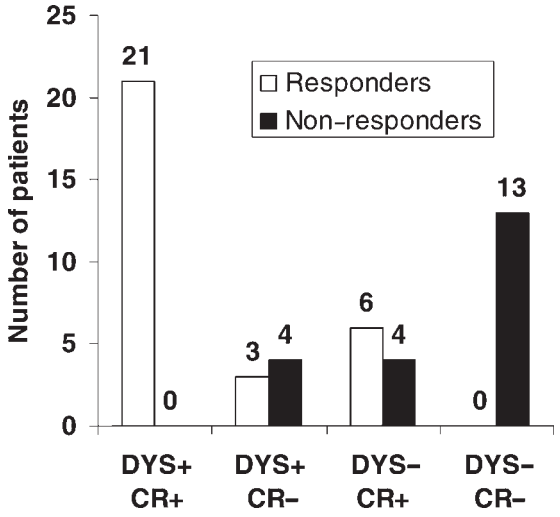

Figure 3 Number of responders to cardiac resynchronization therapy for four different patient categories based on the presence or absence of left ventricular dyssynchrony (DYS+/DYS−) in combination with the presence or absence of global contractile reserve (CR+/CR−).

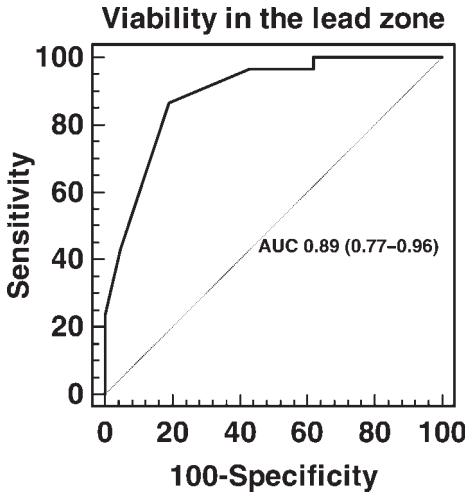

Figure 4 Receiver operating characteristic curve analysis on contractile reserve in the region of the lead pacing (improvement in regional strain during exercise) to predict the response after cardiac resynchronization therapy.

recruitment during exercise echocardiography and the extent of LV reverse remodelling. Conversely, the absence of contractile reserve, particularly in the region of the LV pacing lead, is likely associated with no or less reduction in LV end-systolic volume after CRT.

Role of left ventricular dyssynchrony

Several studies have demonstrated that the major predictor of responsiveness to CRT is mechanical rather than electrical dyssynchrony.[7,11,14] Among available techniques, tissue Doppler imaging has emerged as the most practical method for assessing LV dyssynchrony. As reported previously, we found that a significant mechanical delay between the basal segments of the LV, mainly the septum and the lateral wall, on tissue Doppler was highly predictive for response to CRT.[7,15] Patients with a delay ≥80 ms showed

a significant improvement in LV function and a considerable LV reverse remodelling after 6 months of CRT. However, although this beneficial effect was rarely observed in patients with a delay <80 ms, 20% of the patients with severe LV dyssynchrony did not respond to CRT. This emphasizes that other factors play a role; LV dyssynchrony is necessary but not sufficient for CRT response. Indeed, delayed wall motion is mainly a marker of myocardial dysfunction and could be exhibited in viable and scar tissue according to loading conditions.[16,17]

Global myocardial reserve and response to cardiac resynchronization therapy

In patients with depressed LV function, the identification of contractile reserve during dobutamine stress echocardiography has been shown to provide important prognostic information in both ischaemic and non-ischaemic cardiomyopathy.[18,19] More specifically, in patients with heart failure referred to CRT, few authors have reported that the presence of residual myocardial viability might modulate the response to CRT.[9,12,20–24] Contractile reserve is a specific marker of underlying myocardial viability, which can be reliably assessed during semi-supine exercise echocardiography.[10] To the best of our knowledge, this study was the first to examine the value of exercise echocardiography for predicting response to CRT. Global contractile reserve was characterized by the increase in LV ejection during exercise. An increase in LVEF by $\geq 6.5\%$ was found to be predictive for significant LV reverse remodelling under stimulation. Moreover, the extent of LV global contractile reserve was related to the degree of improvement in LV function. These data confirm and extend previous studies by demonstrating that a substantial amount of recruitable myocardium is needed to obtain improvement in LV function after CRT. It could be thus argued that in case of advanced myocardial remodelling process, fibrosis and loss of contractile material may severely altered myocardial conduction and contractile properties, which might in turn impede efficient biventricular pacing.[25]

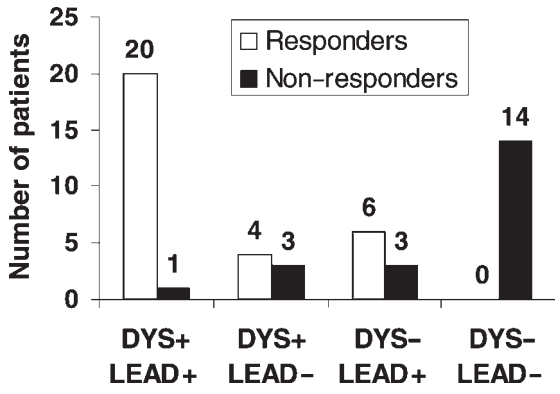

Figure 5 Number of responders to cardiac resynchronization therapy for four different patient categories based on the presence or absence of left ventricular dyssynchrony (DYS+/DYS−) in combination with the presence or absence of contractile reserve in the region of the pacing lead (LEAD+/LEAD−).

Role of the viability in the region of the pacing lead

Assessment of regional viability in patients referred to CRT is not of routine practice. However, few authors have recently emphasized that viability of the stimulated LV area seems to be required to obtain successful CRT response.[20–24] Indeed, patients with transmural scar in the posterolateral region as assessed by contrast-enhanced magnetic resonance imaging did not improve under stimulation.[8,23] Similarly, the absence of contractile reserve in the region of the LV pacing as manifested by no significant changes in wall motion score[9] or in two-dimensional strain[12] during dobutamine infusion precludes LV reverse remodelling in the majority of patients. In line with these data, we found that responders to CRT showed a greater increase in strain in the region of the LV pacing lead during exercise when compared with non-responders. An increase in local strain by $\geq 2\%$ was found to be predictive for significant LV reverse remodelling under stimulation.

Study limitations

Some limitations should be acknowledged. Our data pertain only to patients with current criteria for CRT implantation and who were able to exercise. As a result, our population represents a small subset of heart failure patients submitted to CRT. The high sensitivity and specificity to predict response to CRT reported in our study might reflect this bias of patient selection. These data should, furthermore, be confirmed in larger series of patients. The population studied was not completely homogenous since it was composed of patients with myocardial dysfunction of ischaemic and non-ischaemic origin. However, this represents our daily patients referred for CRT. Moreover, biventricular pacing is still a challenging therapy in both settings. Although, the accuracy of X-ray for assessing the lead position is imperfect, there was a good correlation between

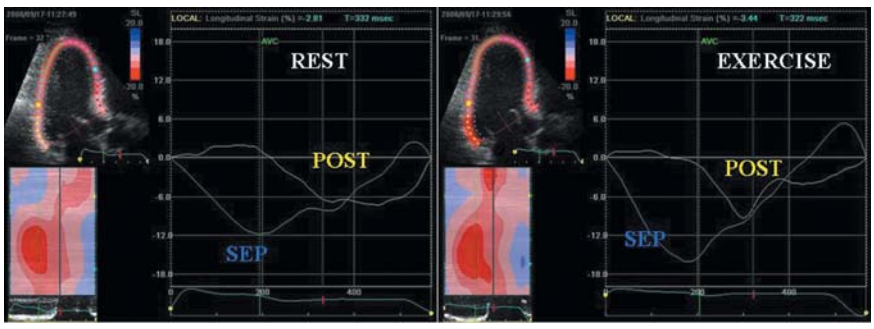

Figure 6 Example of a patient without contractile reserve in the region of the lead pacing. There is no increase in two-dimensional speckle tracking strain at exercise in the posterolateral wall (POST). SEP, septum.

viability in the lead region and response to CRT. Since only one patient had a right bundle branch block, the influence of this pattern on CRT response could not be analysed.

Conclusions

In heart failure patients with LV systolic dysfunction, response to CRT required both the presence of LV dyssynchrony and preserved contractile reserve in the region of the LV pacing. It might thus be proposed that the detection of myocardial viability as well as the assessment of LV dyssynchrony should be routinely performed before CRT to guide LV-pacing lead implantation.

Conflict of interest: none declared.

Funding

Marie Moonen is a fellow of the Belgian FRS-FNRS.

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