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Identification of responders to cardiac resynchronization therapy by contractile reserve during stress echocardiography

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Aims The identification of responders to cardiac resynchronization therapy (CRT) remains a challenge. We assessed the role of dyssynchrony (DYS) and contractile reserve (CR) in identifying CRT responders.

Methods and results Sixty-nine patients (55% with ischaemic aetiology) referred for CRT (ejection fraction $\leq$35%, New York Heart Association $\geq$III, and QRS duration $\geq$120 ms) underwent baseline evaluation of DYS and dobutamine stress-echo [up to 40 μg/kg/min: CR was defined as a wall motion score index (WMSI) variation $\geq$0.20]. CRT responders were identified by clinical and/or echocardiographic [end-systolic volume (ESV) decrease $\geq$15%] follow-up criteria. During a median follow-up of 11 months, 46 patients (66%) were classified as clinical responders. Reverse remodelling was found in 34 of the 59 patients (58%) with echocardiographic follow-up. CR was present in 78% of clinical responders ($P = 0.001$) and in 69% with reverse remodelling ($P = 0.005$). DYS was equally present in the two groups. Reverse remodelling was correlated with rest–stress changes in ESV ($r = 0.439$, $P = 0.003$) and in WMSI ($r = 0.450$, $P = 0.001$), but not with DYS. CR (OR = 6.2, 95% CI = 1.4–27.6, $P = 0.015$) was the best predictor of response to CRT.

Conclusion Patients with CR show a favourable clinical and reverse LV remodelling response to CRT. This finding shifts the focus from electrical (dyssynchrony) to the myocardial substrate of functional response.

Keywords Cardiac resynchronization therapy • Contractile reserve • Stress echocardiography • Heart failure

Introduction

Ventricular dyssynchrony appears to have a deleterious impact on the natural history of heart failure (HF), as a wide QRS complex has been associated with increased mortality in patients experiencing HF.[1,2] Despite major advances in medical therapy, morbidity and mortality in HF remain high.[3] Cardiac resynchronization therapy (CRT) was introduced in the mid-1990s, and has developed dramatically over time.[4] CRT was approved by the Food and Drug Administration in 2001 and was classified in the ESC guidelines for cardiac pacing and CRT with Level of Evidence IA.[5] CRT is increasingly used in patients with HF, but the identification of 'responders' remains challenging, since up to one in three patients do not show symptomatic improvement with this costly and demanding electrical therapy.[6] QRS width remains to be the single established criterion to assess intraventricular dyssynchrony according to guidelines; however, there is no accepted consensus on which imaging parameter is best to predict CRT response. Promising but somewhat inconsistent results have been obtained with several indices of left ventricular (LV) dyssynchrony,[7,8] and more recently with myocardial viability.[9,10] Functional dyssynchrony and anatomic scar assess conceptually different variables, and it is not clear at present whether they offer clinically redundant or additive information for predicting response to CRT. Echocardiography can offer insights into LV dyssynchrony, for instance with tissue Doppler imaging, and LV viability, which is mirrored

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by the presence of contractile reserve (CR) by dobutamine stress echo.[11]

The aim of this study was therefore to assess the value of intraventricular dyssynchrony at rest and stress echo myocardial CR, for identifying responders to CRT.

Methods

Study patients

This was a prospective, multicentre study, conducted in Italy between 2004 and 2007. Patients were enrolled at three centres; the Cardiology Division, Benevento ($n = 37$), the Institute of Clinical Physiology, National Council of Research ($n = 36$), and Cardiology Division, Vallo della Lucania ($n = 6$). The study population consisted of patients with HF referred for CRT, who met the following criteria: (i) severe HF with New York Heart Association (NYHA) functional class $\geq$III; (ii) global LV dysfunction (ejection fraction $\leq$35% by biplane area length method on resting echocardiogram); (iii) wide QRS complex with duration $>$120 ms.[5] All patients were required to have an adequate transthoracic echocardiogram from which resting regional wall function could be assessed (the echocardiogram was considered adequate if $>$13 of the maximum 17 segments were visualized in at least one projection). Exclusion criteria were: (i) technically poor acoustic window precluding satisfactory imaging of the LV (for two-dimensional echo); (ii) haemodynamic instability; (iii) documentation of life-threatening ventricular arrhythmias (sustained ventricular tachycardia or ventricular fibrillation); (iv) significant co-morbidity reducing life-expectancy to $<$1 year, and (v) unwillingness to give informed consent.

Of the 79 patients initially selected for the study, 10 patients were subsequently excluded owing to inadequate echocardiographic image quality during stress because of inadequate wall motion analysis. Thus, 69 patients were included in the final study group. The study was approved by the relevant Institutional Review Board. All patients gave their written informed consent prior to undergoing stress echocardiography. When patients signed the written informed consent they also authorized physicians to use their clinical data according to Italian Law.

Sixty-five patients were in normal sinus rhythm and four in atrial fibrillation. All patients were on optimal and maximally tolerated pharmacological therapy, according to current guidelines for treatment of HF.[12] Thirty-eight patients (55%) had ischaemic heart disease: previous inferior and infero-lateral myocardial infarction in 16 (42%) and previous anterior and apical myocardial infarction in 22 patients (58%). All patients with ischaemic cardiomyopathy had undergone a previous revascularization procedure, 18 by percutaneous coronary intervention and 20 by coronary artery bypass grafting. No patients with ischaemic cardiomyopathy had a positive test for myocardial ischaemia during dobutamine stress echocardiography, and no patients showed viability in the segments with akinesia during stress echocardiography. Coronary angiography was performed in all patients and none of the patients had a coronary anatomy suitable for further revascularization.

Clinical information was recorded on the case report form at study entry by the accredited cardiologist/echocardiographer at each centre. Resting and stress echocardiography was performed in each of the three recruiting centres by cardiologists-sonographers accredited by the European Association of Echocardiography, who had passed the training course and quality control reading test of the stress echocardiography multi-centre trial network.[13,14] Images were coded and read in the core laboratory by observers blinded to clinical conditions and follow-up data. All measurements were obtained following the recommendations of the American Society of Echocardiography[15] at baseline and during follow-up. In particular, LV volumes and ejection fraction were assessed from two-dimensional, two- and four-chamber views by biplane area.

Stress echocardiography protocol

All patients underwent high-dose dobutamine stress echocardiography. Dobutamine was infused in 3 min dose increments, starting at 5 μg/kg/min and increasing to 10, 20, 30, and 40 μg/kg/min. Wall Motion Score Index (WMSI, defined as 1 = normal to 4 = dyskinetic in a 17-segment model of the LV) was assessed following the recommendations of the American Society of Echocardiography and European Association of Echocardiography.[15,16] A stress test was considered maximal when the highest dose of dobutamine was reached. The infusion was discontinued before the maximal dose was reached if 85% of the maximal predicted heart rate for the age group was achieved, or symptomatic non-sustained or sustained ventricular tachycardia was observed.

Ongoing medical therapy (including β-blockers) was kept unchanged at the time of the stress test. CR was defined as a delta variation of (rest−stress) $\geq$0.20 in WMSI.[17,18] We also measured LV end-diastolic (EDV) and end-systolic volumes (ESV) at baseline and peak stress.

Intraventricular dyssynchrony

Tissue Doppler was performed in 55 of the 69 patients. Gain and filters were adjusted as needed to eliminate background noise and to allow for a clear tissue signal. The tissue Doppler signals were recorded at a sweep speed of 100 mm/s. From the apical four- and two-chamber view, a 5 mm sample volume was placed in the LV basal portions of the lateral and septal, inferior and anterior walls. Intraventricular dyssynchrony was calculated by off-line analysis of pulsed wave Doppler as the maximal difference in time intervals between the onset of the QRS complex and the peak mitral annulus systolic velocities of the four ventricular segments.[7,19] Measurements were made between three to five cardiac cycles and averaged.

Cardiac resynchronization therapy implantation

A coronary sinus venogram was obtained using a balloon catheter, followed by insertion of the LV pacing lead. The LV pacing lead was inserted transvenously via the subclavian route. An 8F guiding catheter was used to position the LV lead in the coronary sinus. The preferred position was a lateral or posterolateral vein. The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual-chamber biventricular pacemaker or an internal defibrillator. At implantation, both the sensing and pacing thresholds (at pulse duration of 0.5 ms) of the LV pacing lead were measured. The final position of the LV pacing lead was assessed with cine fluoroscopy. CRT devices were optimized for atrioventricular (AV) and interventricular (VV) delays after CRT.

Follow-up data

Follow-up data were obtained from at least one of the following four sources: review of the patient's hospital records, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient conducted by trained personnel, a staff physician seeing the patient at regular intervals in the outpatient clinic. Clinical follow-up data were obtained in all patients. Events were defined as all-cause death, cardiac death, and

development or progression of HF. For patients who died in-hospital or at home, the cause of death was elucidated from the medical record, the family, and the local physician who signed the death certificate. The definition of cardiac death required documentation of significant arrhythmias or cardiac arrest, or both; or death attributable to congestive HF or myocardial infarction in the absence of any other precipitating factors. In case of deaths out of hospital for which no autopsy was performed, sudden unexpected death was attributed to a cardiac cause. The development or progression of HF was defined as at least one of the following: worsening of functional class to NYHA class III and IV, new hospitalization for HF, or heart transplantation. Therefore, the outcome events were all-cause death (defined as cardiac and non-cardiac death) for survival, and spontaneous events (death and the development or progression of HF) for spontaneous event-free survival. When more than one of these events occurred, the patient was censored at the time of the most severe event. According to the study protocol follow-up information were obtained every 6 months.

Clinical responders were defined as survivors who had a $\geq$1 grade improvement in NYHA class, and no new hospital admission for acute HF. Echocardiographic responders were defined as patients who showed LV reverse remodelling, defined as a decrease in LV ESV of $\geq$15% at 6 months follow-up, compared with the baseline value before CRT.[7,20]

Statistics

Data are expressed as mean $\pm$ standard deviation for continuous variables and as numbers (%) for categorical variables. The individual effect of variables on event-free survival was evaluated with a Cox regression model. The analysis was performed according to an unmodified, forward-selection, stepwise procedure. In this analysis, variables were entered into the model on the basis of a computed significance probability; accordingly, the variable that seemed to have the most significant relationship with the dependent outcome was selected for inclusion in the model, and a solution to the functional form of equation was computed. The remaining variables were evaluated successively, and the most significant were included if they seemed to improve the outcome prediction (dependent variable). In this case the probability was dependent on the presence of the variables, which were already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model. The variables selected for examination were age, NYHA class, history of ischaemic cardiomyopathy, QRS duration, LV EDV and LV ESV diameters, LV EDV and LV ESV, ejection fraction at rest and at peak stress, WMSI at rest and peak of stress, high-dose rest–stress wall motion index variation (ΔWMSI). Continuous variables were compared by paired-samples *t*-test. Proportions were compared by χ^2 statistics. Fisher's exact test was used when appropriate. Clinical event curves were analysed using the Kaplan–Meier method. Bland–Altman analysis was performed to evaluate interobserver variability of LV ESVs in a subset of 10 randomly selected patients.

A probability value of $<$0.05 was considered statistically significant. All statistical calculations were performed using SPSS for Windows, release 12.0 (Chicago, IL, USA).

Results

Patient characteristics

Sixty-nine patients were enrolled (49 males, mean age 70 $\pm$ 8 years). The baseline clinical and echocardiographic characteristics of the patients are summarized in *Table 1*. All patients received optimized medical therapy for at least 8 weeks if tolerated. Device implantation was successful in all patients and no procedure-related complications were observed. One patient was admitted for LV lead repositioning during follow-up, because of LV dislocation resulting in non-capture.

Table 1 Clinical and baseline echocardiographic characteristics (n = 69)

Age (years)	70 $\pm$ 8
Males, *n* (%)	49 (71)
New York Heart Association functional class (III/IV)	57/12
Ischaemic heart disease, *n* (%)	38 (55)
QRS complex duration (ms)	150 $\pm$ 27
Left ventricular end-diastolic diameter (mm)	66 $\pm$ 6
Left ventricular end-systolic diameter (mm)	56 $\pm$ 7
Left ventricular end-diastolic volume (mL)	176 $\pm$ 64
Left ventricular end-systolic volume (mL)	129 $\pm$ 52
Left ventricular ejection fraction (%)	27 $\pm$ 6
Mitral regurgitation (moderate to severe), *n* (%)	26 (38)
Restrictive transmitral pattern, *n* (%)	12 (20)
Intraventricular dyssynchrony (ms)	81 $\pm$ 39
Dyssynchrony index (%)	42/55 (76%)
Medication, *n* (%)	
Diuretics	67 (97)
ACE-inhibitors	61 (88)
β-Blockers	62 (90)

Feasibility and tolerability of high-dose dobutamine stress echocardiography

All patients reached the maximal dose of dobutamine during stress echocardiography (up to 40 μg/kg/min). During dobutamine infusion, non-sustained ventricular tachycardia was observed in nine patients (13%) and hypotension in one patient (1%). These types of complications were always well-tolerated and did not cause premature interruption of the test. Technically adequate images were obtained for all patients at baseline and during the stress test. Haemodynamic and echocardiographic responses to dobutamine stress are described in *Table 2*. A CR (defined as WMSI variation $\geq$0.20 between rest and peak stress) was found in 45 patients (65%). Interobserver variability in the measurement of LV ESVs by the two independent sonographers showed excellent correlation (r = 0.89, $P < 0.01$) with no significant difference at rest (0.7 $\pm$ 22 mL, 95% confidence interval: $-$43.7 to 45.2 mL, P = 0.8) or peak stress (5.4 $\pm$ 12 mL, 95% confidence interval: $-$19.4 to 30.2 mL, P = 0.4).

Clinical follow-up

All patients completed the clinical follow-up with median duration of 11 months. Forty-six patients (66%) were classified as clinical responders to CRT and 23 patients (34%) as clinical non-responders: eight deaths (11%), 12 acute HF (17%), and three unchanged NYHA class (4%). The characteristics of the clinical

Table 2 Haemodynamic and echocardiographic responses to dobutamine stress

	Rest	Stress	Δ (%)	*P*-value
Heart rate (b.p.m.)	72 ± 15	104 ± 22	+57 ± 49	0.023
Systolic blood pressure (mmHg)	110 ± 23	125 ± 29	+14 ± 27	<0.001
Double product	7900 ± 1819	12 926 ± 3631	+66 ± 39	<0.001
End-diastolic volume (mL)	176 ± 64	155 ± 58	−9 ± 15	<0.001
End-systolic volume (mL)	129 ± 52	99 ± 53	−23 ± 21	<0.001
LV ejection fraction (%)	27 ± 6	38 ± 13%	+47 ± 46	<0.001
WMSI	2.33 ± 0.29	1.99 ± 0.43	−0.33 ± 0.28	<0.001

WMSI, wall motion score index.

Table 3 Characteristics of clinical responders and non-responders

	Clinical responders (*n* = 46)	Clinical non-responders (*n* = 23)	*P*-value
Age (years)	68 ± 9	70 ± 6	N.S.
Ischaemic heart disease, *n* (%)	21 (46)	17 (74)	N.S.
QRS complex duration (ms)	152 ± 22	148 ± 27	N.S.
Interventricular septum (mm)	10 ± 2	10 ± 2	N.S.
E-wave deceleration time (ms)	195 ± 84	185 ± 67	N.S.
LV ejection fraction at rest (%)	27 ± 6	25 ± 5	N.S.
Intraventricular dyssynchrony (ms)	76 ± 35	81 ± 52	N.S.
Dyssynchrony index (%)	29/38 (76%)	13/17 (76%)	N.S.
ΔWMSI during SE (%)	0.42 ± 0.28	0.17 ± 0.19	<0.001
Contractile reserve, *n* (%)	36 (78)	9 (39)	0.001

Δ, change between rest and stress echo (SE); WMSI, wall motion score index; LV, left ventricular.

responders and non-responders were comparable at rest, but there was a significant difference in myocardial CR, evaluated during stress echocardiography, in the two patient groups (*Table 3*).

By log-rank analysis, event-free survival was also significantly better in patients with CR than in the group without CR (log-rank = 4.26, $P = 0.039$; *Figure 1*).

Left ventricular reverse remodelling during follow-up

Fifty-nine patients (85%) completed the echocardiographic follow-up. LV reverse remodelling (LV ESV decrease ≥15% at follow-up) was found in 34 patients (58%). The characteristics of the patients with and without reverse remodelling are shown in *Table 4*. At rest, patients with LV reverse remodelling had a thicker interventricular septum, higher E-wave deceleration time, and a significantly higher myocardial CR compared with patients without LV reverse remodelling.

LV reverse remodelling was correlated with pre-CRT rest–stress changes in ESV ($r = 0.439$, $P = 0.003$) and in WMSI

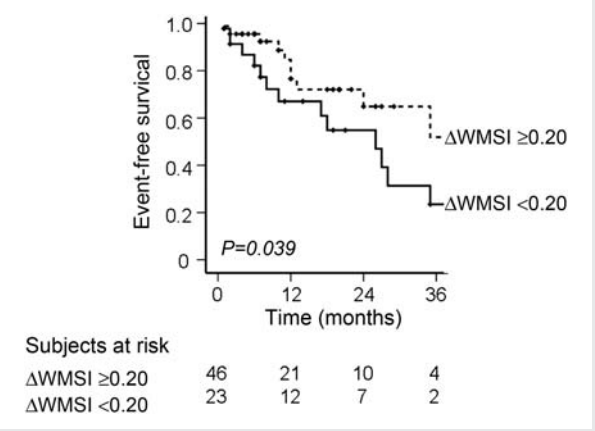

Figure 1 Kaplan–Meier survival curves in patients after cardiac resynchronization therapy, stratified according to the results of rest–stress wall motion score index (WMSI) variation during dobutamine stress echo. Event-free survival was better for patients with a larger variation of WMSI (≥0.20).

Table 4 Characteristics of echocardiographic responders and non-responders

	Reverse remodelling ($n = 34$)	No reverse remodelling ($n = 25$)	*P*-value
Age (years)	69 ± 8	69 ± 8	N.S.
Ischaemic heart disease, *n* (%)	14 (42)	16 (64)	N.S.
QRS complex duration (ms)	150 ± 27	150 ± 29	N.S.
Interventricular septum (mm)	11 ± 2	9 ± 2	<0.001
E-wave deceleration time (ms)	215 ± 83	161 ± 66	0.015
LV ejection fraction at rest (%)	27 ± 6	27 ± 6	N.S.
Intraventricular dyssynchrony (ms)	74 ± 34	91 ± 49	N.S.
Dyssynchrony index (%)	22/29 (76%)	14/20 (70%)	N.S.
ΔWMSI during SE (%)	0.43 ± 0.30	0.25 ± 0.23	0.015
Contractile reserve, *n* (%)	29 (85)	13 (52)	0.005

Δ, change between rest and stress echo (SE); WMSI, wall motion score index; LV, left ventricular.

($r = 0.450$, $P = 0.001$). CR was correlated with change in WMSI at follow-up ($r = -0.661$, $P < 0.001$).

Ischaemic vs. non-ischaemic cardiomyopathy

Thirty-eight HF patients (55%) showed an ischaemic aetiology. During dobutamine stress echocardiography none of the patients with ischaemic cardiomyopathy showed an ischaemic or biphasic response. In fact, coronary artery angiography excluded suitability for further revascularization. Moreover, patients with ischaemic cardiomyopathy had a similar ejection fraction at rest (26 ± 4% vs. 27 ± 7%, P = N.S.), ESV at rest (127 ± 43 mL vs. 133 ± 61 mL, P = N.S.), and WMSI at rest (2.09 ± 0.3 vs. 1.88 ± 0.5, P = N.S.) compared with patients without ischaemic cardiomyopathy. In addition, there was no difference during dobutamine stress echocardiography in: ejection fraction at peak (38 ± 10% vs. 38 ± 15%, P = N.S.), ESV at peak (94 ± 37 mL vs. 104 ± 67 mL, P = N.S.), difference in WMSI between rest and stress (0.27 ± 0.2 vs. 0.4 ± 0.3, P = N.S.), and presence of myocardial CR (63% vs. 71%, P = N.S.), between these two groups. There was a similar incidence of clinical responders (*Table 3*) and echocardiographic responders (*Table 4*), in patients with and those without ischaemic cardiomyopathy.

Intraventricular dyssynchrony and contractile reserve

Fifty-five HF patients underwent analysis of intraventricular dyssynchrony and echocardiographic follow-up. *Figure 2* shows the percentage of CRT responders for four different patient categories based on the presence or absence of myocardial CR in combination with the presence or absence of intraventricular tissue Doppler dyssynchrony (≥65 ms). On individual patient analysis, myocardial CR was more often associated with a favourable outcome, whereas dyssynchrony criteria were equally present in the two groups (*Figure 2*). On multivariate analysis, in the 55 HF patients with intraventricular dyssynchrony and echocardiographic follow-up, the presence of myocardial CR (OR = 6.2, 95% CI = 1.4–27.6, P = 0.015) was the best predictor of clinical and echocardiographic response to CRT, regardless of the presence of wide QRS and tissue Doppler intraventricular dyssynchrony.

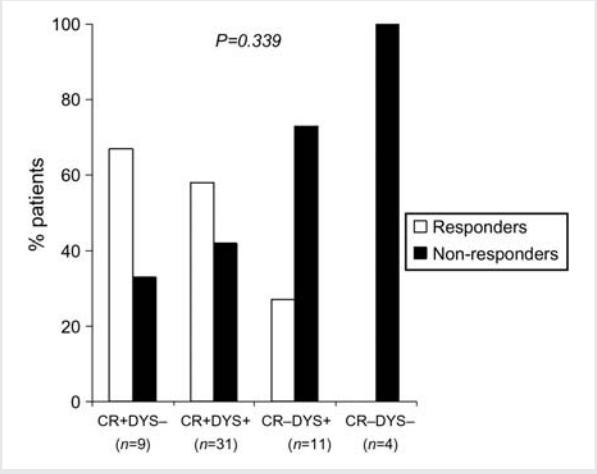

Figure 2 Percentages of responders to cardiac resynchronization therapy for four different patient categories based on the presence or absence of contractile reserve (CR+/CR−) in combination with the presence or absence of baseline tissue Doppler criteria of intraventricular dyssynchrony (DYS+/DYS−).

Discussion

In this study, we have demonstrated that patients with CR during stress echocardiography show a favourable clinical and echocardiographic response to CRT. In fact, the presence of CR was related to better event-free survival, with an inverse relationship between CR and reverse remodelling, while the ECG and echocardiographic dyssynchrony criteria were equally present in clinical and echocardiographic responders and non-responders.

Intraventricular dyssynchrony and the uncertain prediction of cardiac resynchronization therapy response

Several echocardiographic techniques have been used to assess intraventricular dyssynchrony; however, tissue Doppler is the most extensively tested technique.[5,6] Promising but somewhat inconsistent results have been obtained with several indices of LV dyssynchrony. The results of the PROSPECT study showed that no single echocardiographic measure of dyssynchrony was reliable and ready for widespread use in the selection of candidates for CRT.[21] Indeed, recent ESC guidelines for cardiac pacing and HF do not suggest specific echocardiographic dyssynchrony criteria, and at present, QRS width remains to be the ventricular dyssynchrony criterion to identify HF patients suitable for CRT.[5] In accordance with this evidence, in our multicentre study we found that tissue Doppler intraventricular dyssynchrony was equally present in clinical and echocardiographic responders and non-responders to CRT (*Tables 3* and *4*). In addition, on multivariate analysis, wide QRS and tissue Doppler intraventricular dyssynchrony did not predict the response to CRT.

Myocardial viability predicts response to cardiac resynchronization therapy

In patients with depressed ejection fraction ($<35\%$), the identification of CR during dobutamine stress echocardiography has been shown to provide important prognostic information[22] in revascularized ischaemic cardiomyopathy,[23] as well as in non-ischaemic cardiomyopathy patients on medical therapy,[18,24] and in low-flow, low-gradient severe aortic stenosis patients undergoing valve replacement.[25]

More specifically, in patients with dilated cardiomyopathy referred for CRT, Da Costa *et al.*[26] observed that the presence of myocardial CR was an independent predictor of event-free survival after CRT. CR is a specific marker of underlying myocardial viability, which can also be assessed with similar accuracy by nuclear medicine and cardiac magnetic resonance techniques.[27,28] These techniques also showed that the extent of viable myocardium and/or transmural scar tissue play an important role in identifying responders to CRT.[9,10,29–32]

Study limitations

We assessed wall motion score index in a standard, eyeballing, semi-quantitative manner,[15] as recommended by the most recent guidelines of the American Society of Echocardiography and European Association of Echocardiography.[16] Wall motion is subject to variability,[33] particularly in HF patients owing to pre-existing wall motion abnormalities and the substantial number of patients with left bundle branch block; for this reason images were coded and read in the core laboratory, as recommended by the American Society of Echocardiography for use of stress echocardiography in clinical trials.[34] The sonographers acquiring the stress echocardiography data in each of the three recruiting centres had all passed the accreditation process on stress echocardiography reading, as previously described,[13] to ensure consistency in acquisition, segmentation, and execution. The core laboratory reader was also accredited by the European Association of Echocardiography. The inherent variability and subjectivity of the stress echocardiography reading was therefore minimized in this study.[35]

In the present study we did not analyse either AV or VV dyssynchrony, in addition, VV dyssynchrony was only assessed in 55 patients. This is a potential limitation of the study and may have lowered the power of stratification in this set of patients. This reflects the wide deregulation and continuous update of proposed dyssynchrony criteria, with different waves and fashions in the echocardiography laboratory.[36] We shifted at a certain time from M-mode-based to tissue Doppler-based criteria, which held the promise of greater feasibility, reproducibility, and accuracy. Speckle tracking strain analysis is a novel method that permits the assessment of myocardial deformation in two dimensions; the role of a strain delay index by speckle tracking for the prediction of response to CRT in both ischaemic and non-ischaemic patients has been recently demonstrated.[37]

We used a high-dose protocol for dobutamine stress echocardiography, without atropine administration. The high-dose plus atropine protocol is currently recommended by the American Society of Echocardiography and European Association of Echocardiography for dobutamine stress testing for the diagnosis of coronary artery disease.[33] We decided to use the high dose of dobutamine, but to avoid the use of atropine. The high dobutamine dose is particularly advisable in our patients, who were mostly on β-blockers at the time of testing (which may determine a rightward shift in the dobutamine dose-contractile response curve). In addition, our patients have β-adrenoreceptor downregulation as a part of their adaptation to HF. Lower doses would have been inadequate to elicit a full contractile response, and higher doses with atropine co-administration might have been unsafe in patients with depressed resting function. Even without atropine co-administration, we observed significant arrhythmias in over 10% of our population.

Finally, we assessed volume changes of the LV in two dimensions, both at stress and during follow-up studies. Two-dimensional study recognizes limitations in distorted and dilated LVs, because of the need for geometric modelling and the errors caused by foreshortened views. A real-time three-dimensional technique would have been more accurate for volume calculations at baseline and during stress. However, the two-dimensional approach, which was the only one available to recruiting centres at the time of study design, provides consistent information especially when each patient acts as his/her own control, during stress and at serial follow-up examinations.[15]

Conclusion

Patients with CR during stress echocardiography show a favourable clinical and reverse LV remodelling response to CRT. This finding shifts the focus from electrical (dyssynchrony) to the myocardial substrate of functional response. The use of dobutamine stress echocardiography has obvious potential for a better selection of CRT candidates, although larger studies are clearly needed at this point.

Conflict of interest: none declared.

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