Low-dose dobutamine stress echo to quantify the degree of remodelling after cardiac resynchronization therapy

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Aims
Presence of contractile reserve during low-dose dobutamine stress echo (DSE) appears predictive of cardiac resynchronization therapy (CRT) outcome. We hypothesize that changes in left bundle branch block (LBBB)-induced dysynchronous motion during low-dose DSE could be related to the extent of reverse remodelling.

Methods and results
Fifty-two patients (69 ± 2 years, EF: 24 ± 7%, QRS: 120 ms) were studied pre- and post-CRT (7 ± 1 months). Reduction in left ventricular end-systolic volume (LVESV) ≥10% defined response. A clinical improvement was sought additionally prior to implant and after CRT (NYHA class reduction >1), increase in 6 min walk test (>10%), and fall in BNP (≥30%). To identify the presence of septal scar and its impact on our assessment during low-dose DSE, a cardiac magnetic resonance was performed pre-CRT. Presence of an abnormal short-lived septal motion occurring during the isovolumic contraction time [septal flash (SF)] identified LBBB-induced dyssynchrony. Septal flash extent was quantified from M-mode and radial velocity traces. At baseline, 31/52 patients had an SF. In all patients, DSE increased SF. Twenty-nine out of thirty-one patients responded with reverse remodelling post-CRT. The degree of peak low-dose stress SF correlated with the extent of reverse remodelling (R = 0.6, P = 0.0001). Additionally, SF increase correlated with greater fall in BNP post-CRT (R = 0.4, P = 0.01). Among patients with no SF at rest (21/52 patients), low-dose DSE induced an SF and a fall in stroke volume (SV) in five patients who all showed reverse remodelling after CRT. With low-dose DSE, the remaining 16 patients all failed to demonstrate a SF, and all but one patient with additional atrioventricular dyssynchrony were non-responders.

Conclusion
Low-dose DSE increases and unmasks LBBB-induced dyssynchronous motion, easing its detection. The degree of clinical and echocardiographic response correlated with the extent of peak SF seen during low-dose DSE.

Keywords
Dobutamine stress echo • Cardiac resynchronization therapy • Heart failure

Introduction
A number of parameters have already been suggested which may modify response to cardiac resynchronization therapy (CRT), including viability, contractile reserve, and left ventricular (LV) lead position. Conflicting reports based on exercise stress echo have shown exercise to reduce or increase the magnitude of mechanical dysynchrony (as determined by the timing of long-axis systolic velocities and/or delayed longitudinal strain), and sub-clinical ischaemia was a suggested mechanism. However, technetium-99 m sestamibi showed that perfusion was unchanged in similar patients during exercise. In a small subgroup of narrow QRS patients, exercise appeared also to induce dyssynchrony in those with raised baseline LV filling pressures.

We hypothesized that low-dose dobutamine stress echo (DSE) could (i) reduce LV wall stress due to vasodilatation, and this may...
help unmask dysynchronous motion and (ii) increase contractility in viable myocardium, thereby also making dysynchronous motion more easily detectable.

Methods

Patient population
We assessed prospectively 52 consecutive patients (42 men and 10 women, aged 69 ± 2 years, 44% ischaemic cardiomyopathy) who were to undergo CRT as part of their clinical management in line with the current international guidelines (EF < 35%, QRS duration > 120 ms, NYHA class III–IV, and under optimal pharmacotherapy). Patients were not pre-selected for markers of dysynchrony, and those whose condition might improve from coronary revascularization or valve replacement were excluded. All patients were recruited during a hospital admission or following attendance to clinical appointments in cardiology outpatient clinics between November 2005 and September 2007. Among patients initially assessed, 20 were dropped due to exclusion criteria at the time of recruitment, 6 of which were excluded due to an improvement in LV function under medical therapy, 7 refused further follow-up after CRT, 5 patients refused a low-dose DSE as part of their work-up, and 2 patients died before having CRT. All of the remaining could be followed-up for at least the 6 months. The study was approved by the Local Ethics Committees and informed consent was obtained from each participant. Device optimization (iterative method) was performed at a mean of 1 (1–2) months. Clinical assessment [NYHA class, LV dysfunction questionnaire (LVD-36), and plasma NT-pro-BNP] and echocardiographic evaluations were performed at baseline prior to CRT and after a mean of 1 (1–2) months. Cardiac magnetic resonance (CMR) was also performed prior to CRT.

Definition of response
Response was defined as a reduction of LV end-systolic volume ≥ 10% as previously described. Clinical improvement was additionally sought and defined as a reduction in NYHA class ≥ 1, a reduction in LVD-36 ≥ 15%,14 increase in 6MWT > 10% or any distance walked zero at baseline, and a reduction in baseline plasma NT-pro-BNP ≥ 30%. These were assessed by a heart failure nurse blinded to echocardiographic results in all cases.

Echocardiographic acquisition
A standard transthoracic ultrasound examination was performed both at rest and during stress, by a single investigator. This included the acquisition of standard grey scale imaging data sets and spectral Doppler flows as well as myocardial velocity data, using a GE Vivid 7 scanner. For each acquisition, three heart cycles were stored for post-processing (EchoPac, GE).

The following parameters were measured at rest and at stress. Left ventricular internal dimensions in end diastole and end systole were measured from parasternal long-axis (PLAX) M-mode images. Left ventricular volumes and ejection fraction (LVEF) were measured using the 2D Simpson method. Trans-mitral flow velocities were obtained from the apical 4-chamber view (4-CH) using pulsed-wave Doppler positioned at the tip of the leaflets. Peak E wave, its deceleration time, and A wave velocities were measured. Mitral regurgitation (MR) was quantified as described previously. Stroke volume (SV) was obtained at rest and at stress by LV outflow (LVOT) Doppler method (outflow tract area × LVOT time – velocity integral). Cardiac output (CO) was calculated as the product of SV and heart rate.

Dobutamine stress echo protocol
Beta-blocker therapy was stopped 24 h prior to the test. A standard low-dose DSE17 was performed by a graded dobutamine infusion, starting at a dose of 5 μg/kg/min, increasing at 3 min intervals to 10, 15, maximum 20 μg/kg/min. Blood pressure (BP) and ECG recordings were obtained at rest and at the end of every stage of the protocol. The infusion was terminated, if any of the following events occurred: (i) severe haemodynamic decompensation; (ii) arrhythmias; (iii) angina associated with ECG changes; (iv) new wall-motion abnormalities in at least two segments; or (v) achievement of 85% of the maximum age-predicted heart rate or completion of the protocol.

Cardiac magnetic resonance data
All patients without contraindications (n = 42) also had a CMR (1.5 T GE scanner) to identify the extent and localization of scar before CRT. Late enhancement images (LGEs) were obtained 5–10 min after administration of gadolinium 0.1 mmol/kg i.v using a segmented inversion-recovery technique. Observers blinded to the stress echo data analysed the presence and localization of scar as well as its transmurality. Transmurality of scar was evaluated visually by two different observers, according to a standard 5 grades scoring system, where lack of enhancement was quoted 0%, presence of subendocardial late enhancement was defined as a percentage of the total wall thickness ranging from 1 to 25, 26 to 50, 51 to 75%, and >75% defining transmurally infarcted myocardium.

Left ventricular lead position
Left ventricular lead implant site was determined using angiographic and radiographic data and was aimed away from areas of CMR-identified LGEs.

Assessment of left ventricular mechanical dyssynchrony

Septal flash method
Although dyssynchrony can be identified with long-axis tissue Doppler velocity and strain/strain-rate imaging, this has proved challenging in pre-CRT patients owing to the presence of globular, thin-walled ventricles subject to excessive translational motion. Left bundle branch block and RV pacing have been associated with a characteristic abnormal septal motion identified during ICT on a standard M-mode. We hypothesized that this early and short-lived septal motion abnormalities in at least two segments; or (v) achievement of 85% of the maximum age-predicted heart rate or completion of the protocol.

Low-dose DSE to quantify degree of remodelling post-CRT

Dobutamine myocardial imaging velocity data were recorded using a narrow sector and optimal depth of imaging (frame rates of 200–300 Hz), using apical (long-axis motion) and short-axis (SAX) (radial) motion views as previously described. The velocity range setting was adjusted in order to avoid aliasing, still maximizing velocity resolution. Timing of diastole, systole, and isovolumic contraction (ICT) and relaxation times (IVRT) were determined using transmitral and aortic Doppler profiles.
To provide more accurate timing of the SF, early radial septal velocities were used. Timing from onset of QRS, peak early septal velocity, and the comparison of the velocity profiles of septal vs. inferolateral wall (normal LV = mirrored velocity profile, LV dyssynchrony = non-mirrored or parallel velocities, Figure 1) were performed.

The amplitude of the early forward septal motion was also measured as the maximal excursion on PLAX, SAX, or a transverse M-mode in an apical 4-CH. A SF could be identified with all of the above techniques and the maximal septal excursion was recorded. The timing was recorded using radial velocity profiles, providing an easily recognizable peak to measure.

Inter-ventricular delay was calculated at baseline as the difference between the LV and RV pre-ejection periods.

Following this assessment, patients were divided according to the presence of intra-ventricular dyssynchrony (SF patients) or not (non-SF patients).

**Statistics**

Statview 5.0 (SAS institute Inc.) was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± SD or median (interquartile range) when large deviations from the Gauss distribution were observed. Continuous variables within and between groups were compared using two-tailed paired and unpaired Student’s *t*-test. Categorical data were compared using a Fisher’s exact test. Continuous variables were correlated using a simple regression test. There was no inflation of Type I error as all values were tested within one subgroup, comparing baseline and follow-up values. We planned to test the following parameters a priori for significance: increase in SF excursion during low-dose DSE, correlation between peak SF and degree of reverse remodelling as a witness of recruitable myocardial function, fall or abnormal increase in SV associated with increasing degree of SF as a proof of mechanism, fall or abnormal increase in CO with increasing SF, lengthening of QRS duration with increasing SF, and fall in filling time during low-dose DSE in SF patients with a lengthening in ejection time as a result of LV inefficiency. A statistically significant value was defined as a *P*-value <0.05.
Results

Baseline clinical and echocardiographic indices

Baseline patients’ clinical characteristics are displayed in Table 1.

At baseline, 31 patients (60%) showed an abnormal SF (SF patients). Mean SF excursion was 4.3 ± 2 mm. Fusion of E and A waves with pre-systolic MR was seen in 35% (n = 11/31).

Significant inter-ventricular dyssynchrony was noticed in 60% (n = 31). This included SF and non-SF patients. Responders had a longer baseline inter-ventricular delay (P = 0.04).

Baseline cardiac magnetic resonance data

Areas of subendocardial LGEs identifying previous infarcts were seen in 40% of patients (n = 17) who had a CMR scan. The majority (53%, n = 9) had infarction in the left anterior descending artery territory. Among them, three patients had transmural infarction of basal to apical septum, and one of these displayed a SF. Four patients had a transmural infarction of mid to apical septum and one a subendocardial infarct of the mid anteroseptum. These patients displayed a SF in the viable regions of the septum. A transmural infarction of the basal inferolateral wall was seen in one patient and a subendocardial infarct of basal-mid inferolateral wall in another. Although clinical response to CRT was seen in one patient and a subendocardial infarct of basal-mid septum. A transmural infarction of the basal inferolateral wall (2 mm). Fusion of E and A waves with pre-systolic MR was seen in 35% (n = 11/31).

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Stress echocardiographic indices

Changes in baseline parameters compared with those at peak stress are shown in Tables 2 and 3.

During low-dose DSE, no patients experienced chest pain, induced ischaemia, severe hypo- or hypertension, or arrhythmias; however, one patient who had stopped all medications including diuretics for 24 h prior to the test developed acute pulmonary oedema, responding quickly to diuretics.

While systolic BP increased during low-dose DSE, dobutamine reduced diastolic BP (P = 0.04) and QRS duration shortened significantly in all patients. During dobutamine infusion, three different types of responses could be identified.

(i) All patients with SF at rest showed a significant increase in SF excursion (4.6 ± 2 vs. 8.6 ± 3.5 mm at peak stress, P < 0.0001). Small baseline SF patients (SF ≤ 4 mm) experienced the highest increase during DSE (2.5 ± 0.9 vs. 6.9 ± 8 mm at peak, P < 0.0001), making detection of SF much easier at peak stress (Figure 2).

(ii) In patients with no detectable SF at baseline, 5/21 patients (24%) developed a SF during stress (0 vs. 4.8 ± 1.3 mm) (Figure 2). In these two groups of patients, SF increase during low-dose stress was associated with unchanged SV at a group level (mean ΔSV: 2 ± 1 mL). At an individual level,

(P = 0.57), LV reverse remodelling was less in patients with previous myocardial infarction.

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<th>Table 1 Baseline patients’ characteristics</th>
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BP, blood pressure; LVD-36, LV dysfunction questionnaire; 6MWT, 6 min walk test; LVEF, LV ejection fraction; LVESD, LV end-diastolic dimension; LVESV, LV end-systolic volume; LVEDV, LV end-diastolic volume; IVD, inter-ventricular delay.
55% of them (n = 20) had a fall in SV during DSE (median ∆SV: 10 ± 5 mL, mean reduction of 15.7%, P < 0.0001). Cardiac output rose throughout the test in all patients, as a result of increasing heart rate. Peak SF excursion at stress correlated closely with changes in SV with DSE, with the greatest SF associated with the largest fall in SV with stress (R = 0.7, P < 0.0001). Moreover, there was a significant correlation between peak SF excursion and reduction in diastolic BP (R = 0.5, P = 0.01) with the largest peak SF excursion for lowest values of diastolic BP. Left ventricular filling time and ejection time adjusted to heart rate increased during DSE, whereas the ICT became markedly shorter. The IVRT was not significantly affected.

(iii) In the remaining patients (n = 16, 31%), DSE increased contractility in the viable segments but failed to induce a SF. All had a marked and significant increase in SV and CO compared with baseline. Filling time, ejection time, ICT, and IVRT were not significantly different during low-dose DSE.

There was a similar proportion of non-ischaemic and ischaemic cardiomyopathy in each subgroup, and there was no correlation between degree of baseline systolic MR and changes in SV.

Changes in SV during low-dose DSE was not correlated with the number of infarcted segments (P = 0.66).

**Response to cardiac resynchronization therapy**

All patients underwent successful LV lead implantation away from scarred area. Thirty-five patients (67%) showed LV reverse remodelling after CRT. All patients with significant reverse remodelling were also clinical responders.
Changes in septal flash excursion during low-dose dobutamine stress echo and response to cardiac resynchronization therapy

The presence or absence and the extent of SF could be assessed in all patients. The resolution of SF by pacing was associated with LV reverse remodelling in 100%. In two patients, SF was not abolished, and both failed to respond to CRT. One had a proven LV lead displacement during the follow-up, but improved after SF elimination by lead repositioning. The second patient had a good functioning device with an anterior LV lead.

Low-dose DSE induced an SF de novo in five patients and reverse remodelling was seen in all patients after CRT (median Δ LVESV: 14.5% (17.6–11.1), P = 0.007).

All SF patients except two (with persistent SF after CRT) improved clinically with marked LV remodelling (median Δ LVESV: 26.81% (33–11.2) following SF resolution by CRT.

Although the extent of SF at baseline correlated (R = 0.4, P = 0.02) to the degree of reverse remodelling after CRT, a strongest correlation was seen between peak stress SF and degree of LV reverse remodelling (R = 0.6, P = 0.0004) after CRT (Figure 3). Increase in SF during DSE also correlated with greater fall in plasma NT-pro-BNP values post-CRT (R = 0.4, P = 0.01).

Changes in QRS duration, systolic BP, LVEF, and CO during stress did not appear to be linked to an improvement after CRT.

Among patients with no baseline or stress-induced SF, all but one (96%, n = 15) failed to demonstrate LV reverse remodelling post-CRT. This patient did not display any significant interventricular dyssynchrony but had features of a foreshortened atrioventricular delay with a truncated A wave, the correction of which could potentially account for response to CRT.
Discussion
The results of this study suggest that a dobutamine challenge may be valuable as part of the assessment of pre-CRT candidates.

(i) First, LV intra-ventricular dyssynchrony, as identified by a SF, becomes more prominent during low-dose DSE, thus easing its detection.
(ii) In a proportion of patients, dobutamine unmasks significant dyssynchrony, which could not be identified at baseline.
(iii) The degree of LV dyssynchrony during DSE, as identified by the extent of peak SF, correlates with the degree of post-CRT remodelling and clinical response.
(iv) Despite increased myocardial contractility, a reduction in SV with low-dose DSE is paradoxically related to clinical and volume response after CRT.

Therefore, a low-dose DSE can be used as a simple method of estimating the degree of dyssynchrony amenable to correction, thus helping to guide physicians as to the extent of LV reverse remodelling that may be expected post-CRT.

Assessment of abnormal left ventricular activation induced by left bundle branch block
The presence of an abnormal, abrupt septal motion occurring during the pre-ejection period was first described in 1973 on M-mode traces of patients with LBBB. The mechanism was suggested as an early septal contraction following an abnormal activation of the ventricular septum from right to left, unopposed by forces generated by the late contracting free wall. This phenomenon appeared quite distinct to the left–right ventricular interaction seen with other pathologies (right ventricular overload, ischaemic cardiomyopathy). Several investigators suggested thereafter that in LBBB or single-chamber pacing, the early septal contraction, taking place during the ICT, occurred against a reduced load. This translates into a fast motion interrupted at the start of systole by the delayed onset of lateral wall contraction. This abnormal SF has also been described recently using CMR tagging. Although we could identify this same phenomenon using tissue Doppler-derived strain and strain rate in some patients, this was challenging and time-consuming, and image quality and low frame rate prevented assessment in 10% of patients.

A SF was not identified in any patient with a fully infarcted septum. Increased SF during low-dose DSE suggests that this short-lived early septal motion can be used as a marker of mechanical dyssynchrony and that the degree of SF reflects the degree of inefficient work performed by the dyssynchronous LV.

Changes in blood pressure, heart rate, and QRS duration during dobutamine stress echo
Interestingly, while systolic BP increased during low-dose DSE, there was a significant fall in diastolic BP in all patients. This can be explained by the direct physiological effects of dobutamine on the peripheral vascular resistance. Diastolic BP has been used in previous studies as a surrogate for calculating end-systolic wall stress, suggesting that a reduction in LV wall stress could be obtained with low-dose DSE, potentially unmasking a SF. In agreement with previous reports, all 52 patients showed a significant reduction in QRS duration during dobutamine infusion. While shortening of PR interval as a result of enhanced atrioventricular conduction by dobutamine has been well described, the mechanism behind QRS shortening appears unclear. However, shortening of QRS duration during DSE was not predictive of response.

Changes in septal flash with low-dose dobutamine stress echo
In our population, dobutamine appeared to exacerbate baseline SF in all patients with a viable septum, regardless of the aetiology of heart failure. This phenomenon can be explained by the direct physiological effects of dobutamine on the cardiovascular system. For a marginal increase in heart rate, there is an increase in contractility in viable myocardium with a reduction in preload and afterload. The pre-CRT failing heart usually faces high regional wall stress due to a combination of high LV end-diastolic pressure in the settings of a poor systolic function and a globular-shaped LV increasing the localized wall stress. In this particular setting, increased SF could be explained by a combination of dobutamine-induced increase in contractility and reduced LV wall stress. Similarly, in patients with no detectable SF at baseline, dobutamine unmasks the underlying SF, recruiting contractility and partly overcoming the high wall stress affecting the LV, enabling the identification of dyssynchrony. Supporting this hypothesis, changes in diastolic BP between rest and stress, as a surrogate for end-systolic wall stress, correlated with peak SF excursion, with the smallest SF excursion for the highest diastolic BP values.

Changes in stroke volume with low-dose dobutamine stress echo
In healthy volunteers, SV (as assessed by fractional shortening, LVEF, aortic flow velocity, and LVOT time–velocity integral) increases significantly during low-dose DSE, with maximal values at 20 μg/kg/min of dobutamine. However, all SF patients and dobutamine-induced SF patients failed to demonstrate this increase in SV, and in patients with the most pronounced peak SF, SV fell and changes in SV correlated with peak SF (R = 0.7, P < 0.0001). In contrast, patients without SF had the expected rise in SV (Figure 4).

As dobutamine has clearly been reported to reduce the degree of MR by altering loading conditions (reduction in pre-load and after-load), changes in SV during low-dose DSE could not be ascribed to an increase in regurgitant volume.

Response to cardiac resynchronization therapy
In our population, all patients with a baseline SF and all patients with induced SF during low-dose DSE were responders with reverse remodelling if the underlying SF could be corrected.

This highlights the major role of low-dose DSE in the work-up of pre-CRT patients as by searching for a SF at rest, a proportion of responders would not have been predicted.
In addition, peak SF with low-dose DSE correlated to the amount of reverse remodelling ($R = 0.6, P = 0.0004$), which would allow prediction by clinicians of the extent of response to be expected.

Although response to CRT remains a complex issue dependant upon several post-implant factors, the presence of viable myocardium, made inefficient by the underlying dyssynchrony appears as a major parameter in prediction of response and ability for future reverse remodelling. In this small cohort, response was not reliant on LV lead position (Table 1).

One patient, however, responded to CRT, despite lack of baseline and stress-inducible SF. This suggests that there may be other mechanisms involved in a CRT response.

**Limitations**

We present a relatively small sample in this report. Moreover, we assessed specifically the effect of low-dose DSE on the SF alone. In our series, none of the patients experienced unchanged SF excursion or a SF reduction during low-dose CRT, which might have different implications in post-CRT response. The follow-up was relatively short- and long-term predictive value of DSE in response after CRT is unknown. Moreover, the incremental value of SF over standard dyssynchrony indices and the presence of other parameters of response warrant specific investigations.

**Conclusions**

Low-dose DSE increased the degree of LBBB-induced dyssynchrony motion and helped to identify patients with reverse remodelling after CRT.

The degree of increase in SF with a lack of increase in SV predicted the degree of clinical and echocardiographic response to CRT. In some patients, DSE unmasked LBBB-induced dyssynchrony, thus revealing potential responders, who were missed at rest.

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**References**


