

Dynamic relationship of left-ventricular dyssynchrony and contractile reserve in patients undergoing cardiac resynchronization therapy

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Received 21 January 2013; revised 18 June 2013; accepted 11 July 2013; online publish-ahead-of-print 4 August 2013

See page 13 for the editorial comment on this article (doi:10.1093/eurheartj/ehz364)

Aims

Contradicting reports have been published regarding the relation between a dobutamine-induced increase in either cardiac dyssynchrony or left-ventricular ejection fraction (LVEF) and the response to cardiac resynchronization therapy (CRT). Using apical rocking (ApRock) as surrogate dyssynchrony parameter, we investigated the dobutamine stress echocardiography (DSE)-induced changes in left-ventricular (LV) dyssynchrony and LVEF and their potential pathophysiological interdependence.

Methods and results

Fifty-eight guideline-selected CRT candidates were prospectively enrolled for low-dose DSE. Dyssynchrony was quantified by the amplitude of ApRock. An LVEF increase during stress of >5% was regarded significant. Scar burden was assessed by magnetic resonance imaging. Mean follow-up after CRT implantation was 41 ± 13 months for the occurrence of cardiac death. ApRock during DSE predicted CRT response (AUC 0.88, 95% CI 0.77–0.99, $P < 0.001$) and correlated inversely with changes in EF ($r = -0.6$, $P < 0.001$). Left-ventricular ejection fraction changes during DSE were not associated with CRT response ($P = 0.082$). Linear regression analysis revealed an inverse association of LVEF changes during DSE with both, total scar burden ($B = -2.67$, 95% CI -3.77 to -1.56 , $P < 0.001$) and the DSE-induced change in ApRock amplitude ($B = -1.23$, 95% CI -1.53 to -0.94 , $P < 0.001$). Kaplan–Meier analysis revealed that DSE-induced increase in ApRock, but not LVEF, was associated with improved long-term survival.

Conclusion

During low-dose DSE in CRT candidates with baseline dyssynchrony, myocardial contractile reserve predominantly results in more dyssynchrony, but less in an increase in LVEF. Dyssynchrony at baseline and its dobutamine-induced changes are predictive of both response and long-term survival following CRT.

Keywords

Dobutamine stress echocardiography • Heart failure • Contractile reserve • Dyssynchrony

Introduction

The implantation of a cardiac resynchronization therapy (CRT) device in a potential non-responder causes considerable costs and bears the risk of further worsening of cardiac function by inducing dyssynchrony where it did not exist before.¹ Therefore, several attempts have been made to predict non-response, with variable results.^{2–4} Previous studies used frequently echocardiographic parameters to evaluate cardiac dyssynchrony, and/or low-dose

dobutamine stress echocardiography (DSE) or contrast-enhanced magnetic resonance imaging (MRI) to assess myocardial viability.^{5,6}

As the success of CRT relies on the recruitment of contractile reserve, dedicated testing for this may be indeed advantageous.^{7,8} An increase in left-ventricular ejection fraction (LVEF) or stroke volume during a dobutamine challenge has been commonly considered a global marker of myocardial contractile reserve. Several studies have proved its clinical value and predictive power in the pre-operative testing of patients with aortic stenosis, coronary artery

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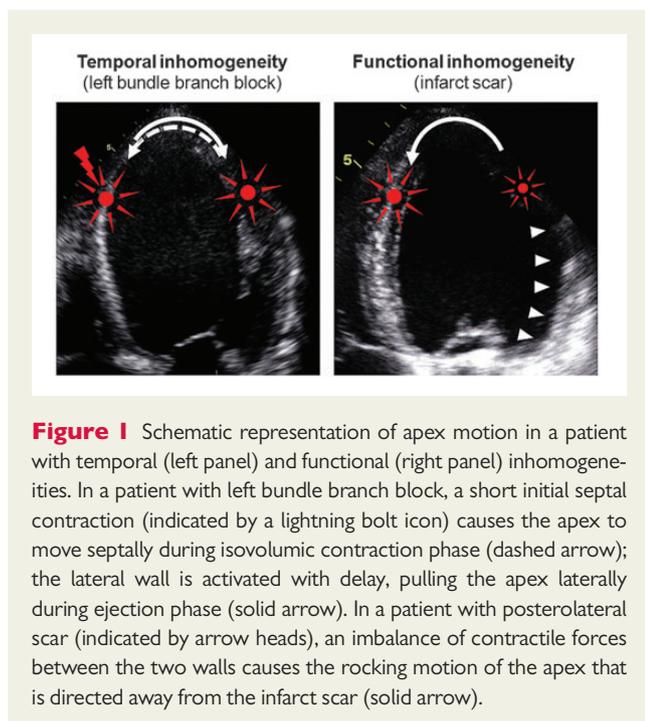


Figure 1 Schematic representation of apex motion in a patient with temporal (left panel) and functional (right panel) inhomogeneities. In a patient with left bundle branch block, a short initial septal contraction (indicated by a lightning bolt icon) causes the apex to move septally during isovolumic contraction phase (dashed arrow); the lateral wall is activated with delay, pulling the apex laterally during ejection phase (solid arrow). In a patient with posterolateral scar (indicated by arrow heads), an imbalance of contractile forces between the two walls causes the rocking motion of the apex that is directed away from the infarct scar (solid arrow).

disease, and other conditions.⁹ Reports on the role of contractile reserve in patients with conduction delays using LVEF or stroke volume as surrogates, however, have not been consistent.^{7,8,10,11} We hypothesize that in such patients the increased myocardial contractility may not necessarily result in a higher EF, but may instead be dissipated by intraventricular dyssynchrony. In the following, we will therefore strictly distinguish between the term ‘contractile reserve’ as a myocardial fibre property, and ‘LVEF’ as a parameter of global LV function.

Apical rocking is a new approach for assessing left-ventricular (LV) mechanical dyssynchrony. Apical rocking integrates both, regional myocardial function inhomogeneities (due to scar tissue) and temporal inhomogeneities (due to activation delays) in a single parameter¹² (Figure 1). Its ability to reflect LV mechanical dyssynchrony has already been demonstrated by its superior predictive power for CRT response.¹³

We use therefore in the following apical rocking, low-dose DSE and contrast-enhanced MRI to investigate the dynamic relationship between contractile reserve, LV dyssynchrony, and LVEF during a low-dose dobutamine challenge and relate them to CRT outcome.

Methods

Study population

We prospectively enrolled 58 consecutive heart failure patients (aged 63 ± 10 years, 22% women, 47% ischaemic cardiomyopathy) referred for CRT according to current guidelines criteria (LV ejection fraction $\leq 35\%$, QRS duration > 120 ms, NYHA functional class III or IV, and on optimized pharmacological therapy at least 3 months before CRT).¹⁴ All patients underwent clinical examination at baseline and 12 ± 2 months following CRT implantation by personnel blinded to the patients’ clinical characteristics. All patients had a coronary angiogram < 3 months

before baseline assessments and only those optimally revascularized entered the study. Data on mortality and causes for death were collected by interview with the patients’ general practitioner or relatives, national death registry, and/or information from local hospitals. The study protocol was approved by the local Ethics Committees and written informed consent was obtained from all patients.

Echocardiographic data acquisition and analysis

Patients underwent a standard two-dimensional and Doppler echocardiography before CRT and at follow-up as well as a low-dose dobutamine stress echocardiography before CRT. Data were acquired using a Vivid 7 scanner (GE Vingmed Ultrasound, Horten, Norway). During all examinations, additional high frame rate tissue Doppler data (> 110 fps) were acquired from apical 2-, 3-, and 4-chamber views (A2C, A3C, A4C, respectively). For all acquisitions, image loops of three consecutive heart cycles (five in patients with atrial fibrillation) were digitally stored for further off-line analysis by an EchoPac workstation (GE Vingmed). Left-ventricular volumes and ejection fraction (LVEF) were calculated using the modified Simpson biplane method (for patients with atrial fibrillation, the mean value of three consecutive cardiac cycles was reported). Spectral Doppler traces of the mitral inflow and the aortic outflow signals were used for defining cardiac time intervals.

Dobutamine stress echocardiography

All patients underwent a low-dose dobutamine stress echocardiography before device implantation. Beta-blocker therapy was withdrawn 48 h before the test. Infusion was started at $5 \mu\text{g}/\text{kg}/\text{min}$ and increased up to $20 \mu\text{g}/\text{kg}/\text{min}$ in 5 min steps in all patients. Tissue Doppler data were acquired at baseline and at each stage of the examination. An LVEF increase with low-dose DSE of $> 5\%$ was regarded significant, as this cut-off was used in previous studies.⁸ The results of the test did not influence any treatment decisions.

Apical rocking calculation

Apical rocking can be quantified by measuring the apical transverse motion (ATM), i.e. the motion of the LV apex perpendicular to the LV long axis. Assuming that the apex is a ‘cap’ which is pulled by opposing walls, ATM can be calculated from the longitudinal up-and-down motion of the apical myocardium close to the apex [Figure 2].

This method for measuring ATM has been previously described.¹² Briefly, the longitudinal (up-and-down) motion of the apical segment is calculated from tissue Doppler data and—since the apex is considered a homogeneous ‘cap’—ATM is supposed to be an average of the two motion curves. Calculations are done with dedicated MATLAB-based (The MathWorks, Inc., Natick, MA, USA) research software (TVA version 16–82, JU Voigt, Leuven) in a way that ATM towards the right side of the image (e.g. towards lateral in a 4CV) is described by positive values (Figure 2). Based on previous experience, ATM in the 4-chamber view during ejection time ($\text{ATM}_{4\text{CV_ET}}$) was used as the only quantitative measure of apical rocking, and with this LV dyssynchrony, in the present study with a cut-off value of 1.5 mm.¹³ $\text{ATM}_{4\text{CV_ET}}$ was measured at baseline, during low-dose DSE, and at the 12-month follow-up visit. Interobserver reproducibility of apical rocking in our lab has been published earlier and is 0.2 ± 0.6 mm.¹³

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) was performed as part of the baseline assessments in all patients without contraindications ($n = 49$), using a 1.5 T scanner (Magnetom Vision Plus; Siemens, Erlangen, Germany). Late-enhancement images were obtained 10–20 min after

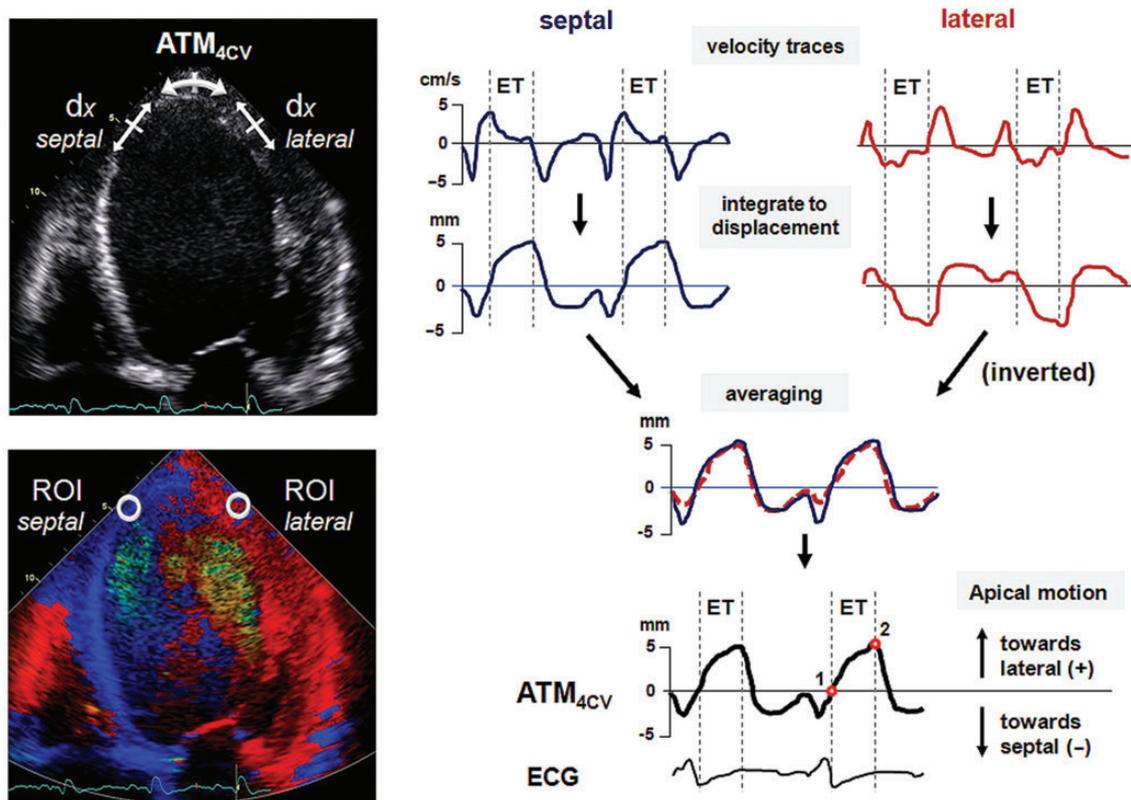


Figure 2 Calculation of the apical transverse motion in the apical 4-chamber view (ATM_{4CV}). The method assumes that ATM_{4CV} , the motion of the apex perpendicular to the LV long axis, can be approximated as the average of the longitudinal apical septal (dx_{septal}) and the inverted longitudinal apical lateral motion ($dx_{lateral}$). In the first step, after careful positioning of the regions of interest (ROI), longitudinal tissue Doppler velocity traces are obtained from both apical segments by tissue Doppler, and then integrated to motion (displacement) traces (two upper right panels). In the second step, longitudinal apical septal and inverted apical lateral displacement curves are averaged and the amplitude of ATM_{4CV} can be measured. In this study, we used amplitude and direction of ATM during ejection time (ET) obtained as difference between point 2 and point 1 in the ATM_{4CV} curve (lower right panel). ECG, electrocardiogram.

intravenous contrast injection (0.2 mmol/kg Magnevist, Schering, Berlin, Germany), late-enhancement images were obtained using an electrocardiogram-triggered segmented gradient echo technique. The acquired data were evaluated for the extent and localization of scar by an experienced observer blinded to all other data. Patients' segmental scar score was calculated using a 17-segment model of the left ventricle and a 5-point scale, as follows: 0 = absence of hyperenhancement, 1 = hyperenhancement of 1–25% of LV wall thickness, 2 = hyperenhancement extending to 26–50%, 3 = hyperenhancement extending to 51–75%, and 4 = hyperenhancement extending to 76–100% of the LV wall thickness. Scores of 3 and 4 were considered to reflect transmurally infarcted myocardium.¹⁵ Total scar burden score was calculated as average of the patients' segmental scores.¹⁶

Cardiac resynchronization therapy

All patients received a biventricular pacemaker. Transvenous LV pacing leads were used in 54 patients. In four patients, an epicardial lead was placed on the mid-lateral wall of the left ventricle. The leads were placed in a region of viable myocardium, as indicated by good capture and a pacing threshold of < 1.5 V/0.5 ms. Device settings were optimized the day after implantation by Doppler echocardiography using an iterative method.¹⁷

Response to CRT was defined as LV end-systolic volume reduction $> 10\%$ between the baseline examination and the 12-month follow-up. Patients were followed for an average period of 41 ± 13 months for the occurrence of cardiac death.

Statistical analysis

Continuous data are expressed as mean \pm standard deviation (SD). Normally distributed data were compared between groups using paired and unpaired *t*-test for continuous variables and Fisher's exact test for categorical variables. If the assumption of normality did not hold, the respective non-parametric tests were used. Correlation between the amplitude of apical rocking, changes in ejection fraction, total scar burden score, and the extent of reverse remodelling were described by Spearman or Pearson correlation coefficients, depending on the distribution of the data. Linear regression analysis was used to evaluate relations between apical rocking, ejection fraction changes, and scar burden. Receiver operating characteristics were analysed for apical rocking, EF increase, and total scar burden score. Survival rates were assessed with Kaplan–Meier analysis, while differences in survival were compared between-groups by a log-rank test. All statistical tests were two-tailed, and a *P*-value < 0.05 was considered significant. Statistical analysis was

performed using commercially available software (PASW Statistics 18, version 18, SPSS, Inc., Chicago, IL, USA).

Results

Baseline patients' characteristics

Characteristics of the study population are summarized in Table 1. Patients who responded to CRT (67%) were more frequently women, had more often non-ischaemic cardiomyopathy and wider QRS complexes.

Low-dose dobutamine stress echocardiography data

The low-dose dobutamine test was feasible in all patients. Two patients had self-terminating episodes of atrial fibrillation at peak stress, while other adverse events requiring the test interruption or medical intervention did not occur. Changes in heart rate, LVEF and volumes, and ApRock with low-dose DSE are shown in Table 2.

Left-ventricular ejection fraction changes during low-dose dobutamine stress echocardiography

During low-dose DSE, an increase in LVEF was observed in both responders and non-responders ($+4.4 \pm 3.1$ vs. $+5.9 \pm 2.7\%$, respectively; $P < 0.001$ vs. rest, for both) (Figure 3). In the non-responder group, LVEF increased in all patients, but only in 10 of 19 patients (53%), the increase exceeded the pre-defined significance level ($\Delta\text{EF} > 5\%$).

In patients who responded to CRT, a significant increase in LVEF ($>5\%$) was observed in 15 patients (38%, $P = 0.306$ vs. non-responders). The remaining patients ($n = 24$; 62%) showed a lower rise ($\leq 5\%$) in LVEF at peak stress (20 patients), no change (two patients), or decreased LVEF (two patients).

The change in LVEF was not associated with CRT response [area under the curve (AUC) 0.36, 95% CI 0.21–0.50, $P = 0.082$].

Apical rocking under low-dose dobutamine stress echocardiography

Calculation of apical rocking both at rest and during stress was possible in 55 patients (95% feasibility). At rest, apical rocking of more than 1.5 mm was present in 34 patients (62%), 31 of which were responders and three non-responders [sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV): 86, 84, 91, and 76%, respectively, AUC 0.84, 95% CI 0.70–0.98, $P < 0.001$].

During low-dose DSE, the amplitude of apical rocking significantly increased in responders ($+1.9 \pm 1.9$ mm, $P < 0.001$) but not in non-responders (-0.48 ± 1.1 , $P = 0.074$) (Figure 3). Two CRT responders with apical rocking < 1.5 mm at rest reached the cut-off during peak stress, which resulted in sensitivity, specificity, PPV, and NPV of 92, 84, 92, and 84%, respectively (AUC 0.88, 95% CI 0.77–0.99, $P < 0.001$). Changes in the amplitude of apical rocking during low-dose DSE were also associated with CRT response (AUC 0.89, 95% CI 0.80–0.97, $P < 0.001$).

Cardiac magnetic resonance data

Of 49 patients who underwent MRI, 17 (35%) had hyperenhancement in at least one segment. Scar burden was significantly higher in non-responders than responders, as indicated by the total scar burden score (0.83 ± 0.73 vs. 0.09 ± 0.22 , $P = 0.001$, Figure 4) and by the number of transmurally infarcted segments (2.1 ± 2.3 vs. 0.1 ± 0.4 , $P < 0.001$). All patients with total scar burden score of > 1.2 ($n = 7$) failed to respond to CRT. Applying this value as cut-off, the total scar burden score would have been associated with non-response to CRT with a sensitivity, specificity, PPV, and NPV of 47, 100, 81, and 100%, respectively (AUC 0.82, 95% CI 0.56–0.91, $P = 0.01$). Of note, the cut-off of 0.5 for total scar

Table 1 Baseline patients' characteristics

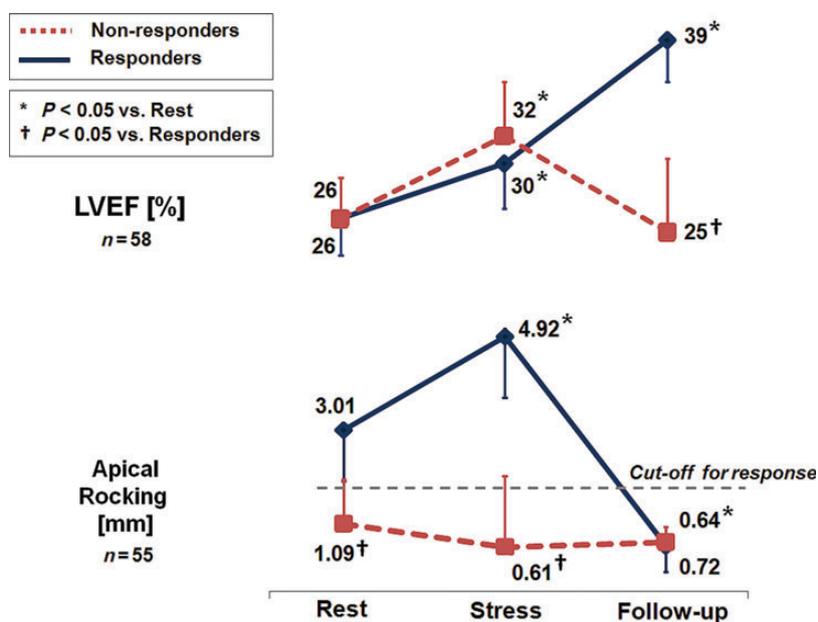
	All patients (n = 58)	Responders (n = 39)	Non-responders (n = 19)	P-value
Age, years	63 ± 10	64 ± 11	63 ± 8	0.63
Male/female, n	45/13	27/12	18/1	0.04
Ischaemic aetiology, n (%)	27 (47)	13 (42)	14 (58)	0.005
NYHA class	3.1 ± 0.3	3.1 ± 0.3	3.2 ± 0.4	0.30
QRS, ms	175 ± 25	181 ± 24	161 ± 22	0.005
Atrial fibrillation, n (%)	10 (17)	5 (13)	5 (26)	0.27
LVEF, %	26 ± 6	26 ± 6	26 ± 5	0.67
LVEDD, mm	71 ± 11	70 ± 11	73 ± 10	0.29
LVEDV, mL	228 ± 98	225 ± 104	234 ± 85	0.73
LVESV, mL	172 ± 82	170 ± 88	176 ± 71	0.82
ACE-inhibitors, %	100	100	100	n/a
Beta-blockers, %	93	92	95	0.98
Spironolactone, %	59	54	68	0.39

ACE, angiotensin-converting enzyme; LVEF, left-ventricular ejection fraction; LVEDD, left-ventricular end-diastolic diameters; LVEDV, left-ventricular end-diastolic volume; LVESV, left-ventricular end-systolic volume; NYHA, New York Heart Association.

Table 2 Changes in left-ventricular ejection fraction and apical rocking during low-dose dobutamine stress echocardiography

	Responders (n = 39)			Non-responders (n = 19)		
	Rest	Stress	P-value	Rest	Stress	P-value
Heart rate, beats/min	72 ± 39	97 ± 39	<0.001	71 ± 15	95 ± 17	<0.001
LVEF, %	26 ± 6	30 ± 8	<0.001	26 ± 6	32 ± 5	<0.001
LVEDV, mL	225 ± 104	182 ± 95	<0.001	234 ± 85	225 ± 87	0.304
LVESV, mL	170 ± 88	131 ± 79	<0.001	176 ± 71	154 ± 67	0.004
Apical rocking, mm	3.0 ± 1.8	4.9 ± 2.9	<0.001	1.1 ± 2.1	0.6 ± 2.5	0.074
Apical rocking ^a , mm	3.0 ± 1.8	4.9 ± 2.9	<0.001	0.7 ± 1.6 ^a	0.1 ± 2.1 ^a	0.029 ^a

LVEF, left ventricular ejection fraction.

^aThis excludes two non-responders in whom apical rocking was not corrected by CRT.**Figure 3** Average changes in LVEF and apical rocking amplitude before (at rest and at peak stress) and after cardiac resynchronization therapy implantation. Note the different patterns of changes in LVEF and apical rocking in responders and non-responders. The non-responders' group includes two patients in whom apical rocking was not corrected by cardiac resynchronization therapy. Error bars indicate one standard deviation. LVEF, left-ventricular ejection fraction.

burden score would result in sensitivity, specificity, PPV, and NPV of 97, 60, 82, and 90%, respectively ($P < 0.001$).

Relation between apical rocking, ejection fraction changes, and scar burden

Linear regression analysis revealed that the change in apical rocking amplitude from rest to peak stress ($B = -1.23$, 95% CI -1.53 to -0.94 , $P < 0.001$) was independently and negatively associated with the change in LVEF during low-dose DSE with a correlation of $r = -0.6$ ($P < 0.001$) (Figure 5). Likewise, total scar burden

showed an independent and negative association with the EF changes ($B = -2.67$, 95% CI -3.77 to -1.56 , $P < 0.001$).

In patients without apical rocking, scar burden and changes in LVEF during low-dose DSE were inversely correlated ($r = -0.9$, $P < 0.001$). In patients with apical rocking, no such correlation was found ($r = -0.2$, $P = 0.39$).

The amplitude of apical rocking both at rest and at peak stress, as well as its change, were negatively correlated with total scar burden score ($-0.5 < r < -0.4$, $P < 0.05$, for all). The strongest negative correlation was seen for the amplitude of apical rocking at stress ($r = -0.5$, $P = 0.001$) (Figure 6). At both, rest and stress, patients

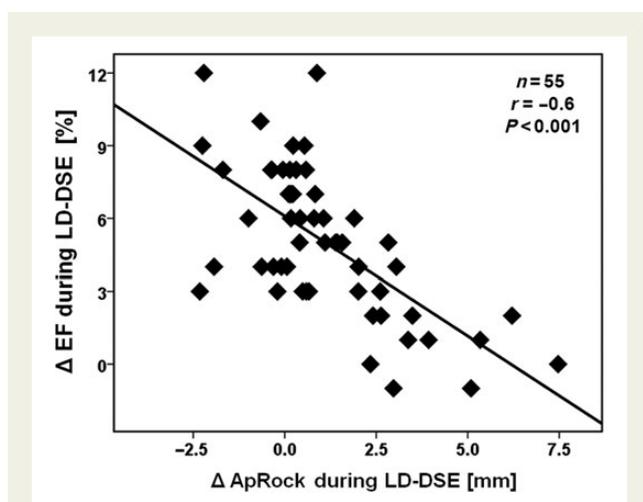
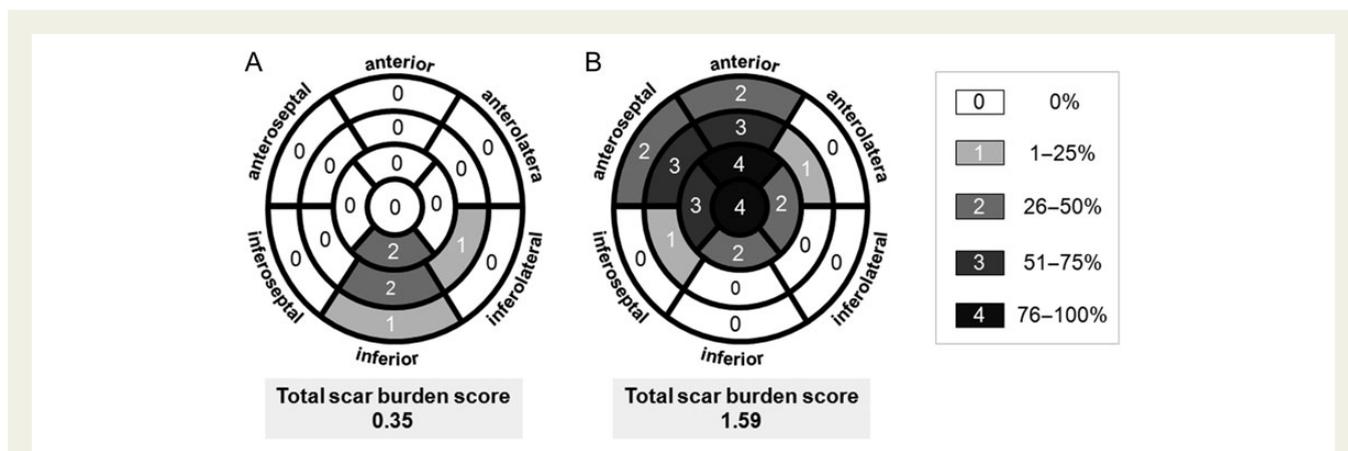


Figure 5 Changes in LVEF and apical rocking (ApRock) during low-dose dobutamine stress echo (LD-DSE). Correlation line indicates a strong negative correlation between LVEF and ApRock changes.

with the highest scar burden scores had the lowest values of apical rocking.

The extent of left-ventricular remodelling and long-term survival following cardiac resynchronization therapy

During follow-up, ESV decreased in responders by $36 \pm 18\%$ ($P < 0.001$ vs. non-responders). Patients who responded to CRT (ESV reduction $> 10\%$) had better survival than non-responders (log-rank test $P < 0.001$).

The extent of reverse remodelling following CRT correlated moderately with the amplitude of apical rocking at rest ($r = 0.5$,

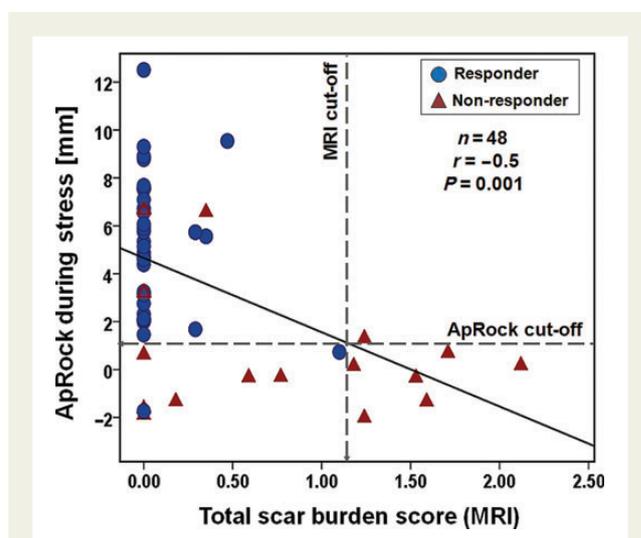


Figure 6 Relation between total scar burden score and apical rocking (ApRock) amplitude during low-dose dobutamine stress echo. Total scar burden score has a high negative predictive value, but fails to sensitively predict cardiac resynchronization therapy response. The latter can be achieved by assessing apical rocking. Dashed lines indicate cut-offs for response to cardiac resynchronization therapy for both parameters. Open triangles indicate two patients retaining apical rocking after cardiac resynchronization therapy.

$P < 0.001$), but strongly with changes in apical rocking during low-dose DSE ($r = 0.7$, $P < 0.001$) (Figure 7) and inversely with total scar burden score ($r = -0.5$, $P < 0.001$).

Kaplan–Meier analysis showed that the amplitude of apical rocking at peak stress (log rank test $P = 0.008$, Figure 8A), but not a significant increase in LVEF (log rank test $P = 0.605$, Figure 8B), was associated with improved long-term survival.

Of note, both the presence of apical rocking at rest (log rank test $P = 0.008$) and dobutamine-induced increase in the amplitude of apical rocking (with a cut-off of 0.3 mm, log rank test $P = 0.014$) were associated with improved survival following CRT.

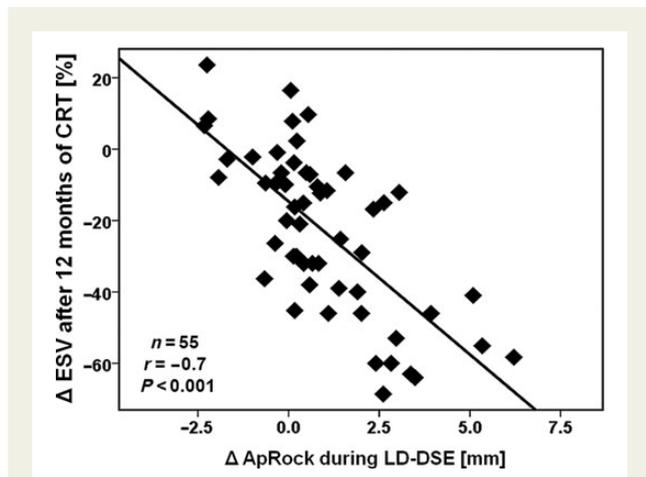


Figure 7 Correlation between changes in the amplitude of apical rocking (ApRock) during low-dose dobutamine challenge and the extent of reverse remodelling after 12 months of cardiac resynchronization therapy implantation. Patients with highest increase in ApRock during the test also had the highest decrease in left-ventricular end-systolic volume (LVESV) during follow-up.

Discussion

In this study, we could demonstrate a negative relation between cardiac dyssynchrony and changes in LVEF during low-dose DSE. Our findings indicate, that in CRT candidates, dobutamine-provoked contractile reserve of the myocardium predominantly increases dyssynchrony rather than LVEF, particularly in potential responders.

Further, we could show that both mechanical cardiac dyssynchrony and myocardial scar burden are important determinants of response to CRT. Both dyssynchrony and its increase during a low-dose dobutamine challenge predicted response to CRT with high accuracy. Magnetic resonance imaging had a low specificity for predicting CRT response, but showed an excellent negative predictive value when scar burden was high.

The role of contractile reserve in patients undergoing cardiac resynchronization therapy

In patients with resting LV dyssynchrony, failure to increase in LVEF during low-dose DSE was not associated with non-response to CRT. On the contrary, some responders showed a decreasing LVEF. A strong negative correlation between changes in LVEF and apical rocking during low-dose DSE suggests that stress-induced increase in dyssynchrony, and not the absence of recruitable myocardium, may prohibit significant rise in LVEF.

Our findings are in line with a previously reported observation that, irrespective of baseline QRS duration, stress-induced increase in dyssynchrony is associated with impaired cardiac performance, as indicated by haemodynamically significant decrease in stroke

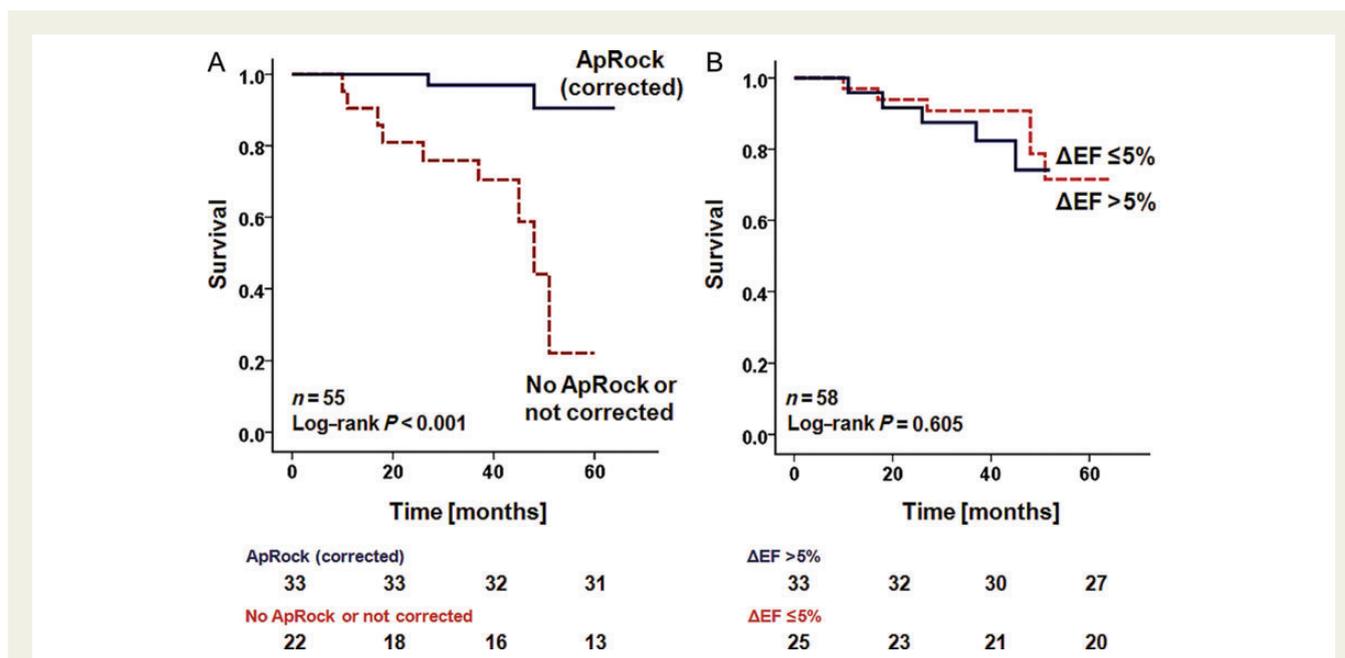


Figure 8 Long-term survival following cardiac resynchronization therapy. (A) Kaplan–Meier curves depicting long-term survival of patients with apical rocking at peak stress, corrected by cardiac resynchronization therapy (solid line) vs. patients with no apical rocking or uncorrected rocking despite cardiac resynchronization therapy (dashed line). (B) Comparison of long-term survival in patients with (solid line) and without (dashed line) significant increase in left-ventricular ejection fraction (LVEF) during low-dose dobutamine challenge.

volume and cardiac output.^{7,18,19} In addition, Rocchi *et al.*²⁰ suggested that exercise-induced exacerbation of dyssynchrony was the only parameter independently associated with LV reverse remodelling, whereas Parsai *et al.*⁷ reported that more than a half of patients with an abnormal septal motion as a marker of LV dyssynchrony failed to increase stroke volume during low-dose DSE which was associated with CRT response. Nevertheless, other publications have reported a CRT response in patients with resting LV dyssynchrony and a significant stress-induced increase in LVEF.^{8,21,22} This discrepancy can be explained by the fact that these studies used dyssynchrony parameters which are less closely related to mechanical dyssynchrony or applied less strict definitions of CRT response. In line with this, a recent multicentre trial concluded that rise in LVEF of >5% during DSE increases the chances of CRT response, but could not explain why a remarkable number of patients (54%) without significant increase in LVEF (or even with a drop in LVEF) also responded to CRT.⁸

In addition, the clinical feasibility of the previously proposed cut-off values for LVEF changes in the range of 5–8% must be questioned, given the normal variability of echocardiographic biplane EF measurements which is in the same range.²³

Dynamic left-ventricular dyssynchrony and response to cardiac resynchronization therapy

In previous studies, stress tests have been reported to increase, decrease, or have no effect on LV dyssynchrony.^{7,18,19,24} These differences may be explained by different stressors (exercise vs. pharmacological), the different definitions of dyssynchrony and different measurement approaches. Based on apical rocking, our data show that dobutamine-induced increase of LV contractility may unmask or potentiate mechanical LV dyssynchrony and improve the predictive value of dyssynchrony parameters for CRT response, although sensitivity of apical rocking for predicting CRT response was already high at rest.

Long-term survival

Our data add to the growing body of evidence that the absence of mechanical dyssynchrony is associated with significantly less favourable survival after CRT. A number of recent trials have demonstrated the relationship between several echocardiographic measures of dyssynchrony and long-term event-free survival following CRT.^{25–28} In our study, patients in whom apical rocking was corrected by CRT had better survival than those without apical rocking or uncorrected rocking despite CRT. Furthermore, in contrast to LVEF changes which could not predict long-term survival, the amplitude of apical rocking both at rest and peak stress was associated with improved survival. It is noteworthy that a recent multicentre trial also showed similar mortality between CRT candidates with and without significant dobutamine-induced increase in LVEF during 15 months follow-up.²⁹

Clinical implications

Our data indicate that the commonly used clinical definition of contractile reserve as an increase of LVEF under low-dose-dobutamine does not apply to all patients with conduction delays. Cardiac resynchronization therapy candidates should therefore not be denied

resynchronization therapy based on the failure to increase EF during a dobutamine challenge. Furthermore, incremental value of low-dose DSE in this patient population seems to be limited. All patients with resting LV dyssynchrony should be referred to CRT implantation without prior stress testing, since the impact of beta-blocker withdrawal on heart failure stability may outweigh the added clinical value of DSE. According to our data, low-dose dobutamine challenge can be considered in patients without apical rocking at rest, as an attempt to uncover mechanical dyssynchrony.

Our data underline further the importance of assessing mechanical dyssynchrony before CRT implantation. The good predictive value of apical rocking may be explained by the integration of both, temporal and spatial information on myocardial function, which is different to most peak-velocity-based parameters. This explanation is supported by the good performance of other parameters which are able to detect the typical characteristics of an LBBB-induced motion pattern.^{4,7,30}

Study limitations

Our measurements of ATM and its changes during low-dose DSE were based on tissue Doppler data which were processed with a custom made software. The coefficient of variation, however, limits the feasibility of the quantitative approach for decision making in a single patient. Since the incremental predictive value of stress-induced ATM changes for CRT success was shown to be limited, a precise quantification of ATM at rest may not be needed. As shown previously, a simple visual assessment of apical rocking at rest is as effective as its quantification and may serve as highly feasible clinical approach.¹³ Further, other recently proposed dyssynchrony parameters which are able to detect the characteristic LBBB-induced motion pattern can complement the assessment: visual or M-mode-based assessment of septal flash,⁷ regional strain pattern analysis,⁴ or anteroapical to posterior time to peak radial strain difference.³⁰

Conclusions

In CRT candidates with mechanical dyssynchrony, dobutamine-induced changes in ejection fraction do not reliably reflect contractile reserve in all patients and should not be used as a selection criterion for CRT. Scar burden and LV mechanical dyssynchrony were shown to be the two determinants of CRT outcome. Apical rocking integrates information on mechanical dyssynchrony and scar burden in CRT candidates and is predictive of response and long-term survival following CRT.

Funding

I.S. received a research grant from the European Association of Cardiovascular Imaging. A.N.N. is partly supported by grant no. 175099 of the Ministry of Science, Republic of Serbia. J.-U.V. holds a personal research mandate (No. 1832912) of the Flemish Research Fund (FWO).

Conflict of interest: none declared.

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