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Title: Multicenter Study Using Strain Delay Index for Predicting Response to Cardiac Resynchronization Therapy (**MUSIC study**).

Short title: Strain Delay Index and Response to CRT

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Abstract

Aims: Strain delay index (SDI) allows quantification of the wasted contraction or gain of myocardial contractility expected after cardiac resynchronization therapy (CRT). The present multicenter prospective study aimed to assess the accuracy of the SDI in predicting responses to CRT in real life patients that include wide and narrow (<130ms) QRS complexes.

Methods and Results: Implantation of a CRT device was performed in 235 heart failure patients and echocardiography data were analyzable in 80% (n=189) of patients (age 65 ± 12 years, LVEF= $26\pm 8\%$, 63 ischaemic, 51 with narrow QRS complexes). Mechanical dyssynchrony before CRT was quantified by the 12-segment standard deviation of peak longitudinal strain by speckle tracking (12SD- ϵ), and SDI, defined as the sum of difference between end-systolic and peak- ϵ across the 16 segments. Response to CRT was defined as an end-systolic volume reduction (ESVR) at 6 months >15%. After CRT, ESVR>15% was observed in 60% (n=114/189) of patients, and was greater in non-ischaemic (68% vs. 44%, $p=0.003$) and wide QRS patients (65% vs. 49%, $p=0.04$). Correlation between 12SD- ϵ and ESVR was poor ($r=0.18$, $p=0.01$). In contrast, SDI correlated with reverse remodelling ($r=0.61$, $p<0.0001$ for all) in both wide and narrow QRS patients and ischaemic and non ischaemic patients. Decrease in SDI after CRT was greater in responders and correlated with ESVR. Finally, SDI>25% identified responders to CRT (positive and negative predictive value of 80% and 84%, respectively) with 6% inter-observer variability.

Conclusion: The present multicenter study suggests that SDI may identify responders to CRT in ischaemic and non-ischaemic patients.

Keywords: Cardiac resynchronization therapy, strain, speckle tracking, dyssynchrony

INTRODUCTION

Randomized studies have demonstrated that cardiac resynchronization therapy (CRT) has a beneficial impact on reverse remodelling and survival in heart failure (HF) patients with a large QRS interval (1-4). However, up to 40% of patients fail to respond to CRT despite a prolonged QRS duration (2, 5). Observational studies have consistently shown that the main predictor of responsiveness to CRT is mechanical rather than electrical dyssynchrony. Measurement of regional myocardial electrical-mechanical events using velocity data acquired with tissue Doppler imaging (TDI) has been proposed to enhance identification of mechanical dyssynchrony, and to select patients with wide and narrow QRS duration who may better respond to CRT (6, 7). However, myocardial dyssynchrony markers are usually based on time-delay measurements which are inherently limited, as residual myocardial contraction is not taken into account (8-10). Two recent studies demonstrated the limited accuracy of time delay markers to identify responders to CRT in wide (PROSPECT study (5)) and narrow (RETHINQ study(11)) QRS populations. To overcome these limitations, we recently proposed a new method, the strain delay index (12) (SDI) to predict response to CRT by directly assessing the potential for incremental contractility gain after resynchronization rather than by simply quantifying LV dyssynchrony by regional timing. In the present multicenter study, the SDI was assessed in a large cohort of HF patients referred for CRT (that includes wide and narrow QRS duration) and used to predict future reverse remodelling after CRT.

METHODS

Patients

This study was designed as a multicenter observational clinical trial, and aimed to assess the accuracy of the SDI in identifying response to CRT. Four French university centres equipped with GE ultrasound echocardiography systems participated in the study. To test our hypothesis, we enrolled optimally treated heart failure patients who had undergone implantation of a CRT device. Before CRT, all patients underwent a comprehensive echocardiography examination using a GE ultrasound system. Patients with chronic atrial fibrillation were not included. Before enrolment, all patients gave informed consent and our local ethics committee approved the study. Overall, 235 heart failure patients (120 from Creteil, 65 from Bordeaux-Marseilles, 40 from Rennes and 10 from Lyon) who received CRT were enrolled between November 2008 and November 2009. However, 20% of patients were excluded because a limited acoustic window prevented 2D strain analysis (>2 non analyzable segments). Of the 189 analyzable patients (Table I), 51 (27%) had QRS<130ms (narrow) and 138 had a wide QRS complex. In the wide QRS group, all patients had severe LV dysfunction (LVEF \leq 35% by 2D echocardiography, mean $25\pm 8\%$) and had remained symptomatic despite optimal medical treatment (New York Heart Association, NYHA class>II). Medical treatment included beta-blockers (79%), angiotensin inhibitors (87%) and aldosterone antagonists (40%). In the narrow QRS population, the decision to add biventricular pacing to a standard implantable cardioverter defibrillator was taken by the referring cardiologist, following identification of significant mechanical dyssynchrony. For all patients, the medical decision was independent of the strain delay value.

2D echocardiography:

A comprehensive echocardiographic study (GE, Vingmed System 7, Horten, Norway) was performed before and six months after implantation of the CRT device. During the echocardiographic study, apical views (2- 3-, and 4-chamber) with high frame rates (≥ 50 frames/s) were acquired during breath hold and

stored in cine-loop format. All echocardiography data were collected and analyzed in a centralized core lab (Henri Mondor Hospital). The LV volumes and ejection fraction were calculated from the apical 2- and 4-chamber views using Simpson's rule. Speckle tracking analysis was performed by an independent operator unaware of the clinical and echocardiographic data.

Strain delay index and LV dyssynchrony:

The method to compute SDI has been described in detail previously (12). In dyssynchronous ventricles, delayed segments do not contribute fully to end-systolic function. The wasted energy per segment caused by dyssynchrony can be expressed mathematically as the difference between peak (ϵ_{peak}) and ES strain (ϵ_{ES}). Theoretically, this difference ($\epsilon_{\text{ES}} - \epsilon_{\text{peak}}$) increases with the severity of dyssynchrony (Figure 1). The wasted energy is expected to be greater in the segment with preserved contractility than in the segment with minimal or no residual contractility at a similar degree of delayed contraction. The different steps of SDI processing can be summarized as follows: first, a global strain (ϵ) curve representing LV function is obtained by averaging 16 regional LV strain curves. Next, the time to the peak of this global- ϵ curve is used to determine the timing of end-systole (ES) and to compute the strain in ES in the 16 segments. Then, peak and time to peak- ϵ in the 16 segments is defined as the minimum strain value during the cardiac cycle. Finally, the difference ($\epsilon_{\text{peak}} - \epsilon_{\text{ES}}$) in each segment (all 16 segments) is summed to generate the SDI (Figure 2). For segments that exhibit positive strain or biphasic strain with a peak positive strain greater than the maximum absolute negative strain, the term ($\epsilon_{\text{peak}} - \epsilon_{\text{ES}}$) is entered as zero for the calculation of SDI. This methodology is based on previous data demonstrating that dyskinetic segments with a predominant stretching motion are unlikely to contribute to CRT response (13). Time to peak longitudinal strain by speckle tracking is used to calculate the 12-segment (base and mid) SD of time to peak- ϵ (12SD- ϵ). In segments with positive or biphasic strain curves, time to minimum ϵ was chosen to compute 12SD- ϵ . The entire process was computed automatically on an Excel file.

Device implantation:

Implantation of the CRT device was performed in the standard fashion with 3 trans-venous leads inserted. The right atrial and ventricular (apical site) leads were positioned conventionally. The LV lead was inserted through the coronary sinus and positioned into the lateral or posterolateral cardiac vein. Epicardial implantation (n=3) was required when coronary sinus catheterization failed. Biventricular pacing devices used included those manufactured by Medtronic (Minneapolis, MN, USA), St Jude Medical (Sylmar, CA, USA), and Guidant–Johnson & Johnson (Boston, MA, USA). After implantation, the atrioventricular interval was adjusted for optimal diastolic filling (by pulsed mitral Doppler): no VV delay setting was performed. In all patients, a device control was performed at 6 months to confirm the appropriate biventricular pacing (pacing time >80% in all patients included).

Follow-Up:

Clinical characteristics at baseline and 6-months follow-up were obtained from medical reports. The echocardiographic examination was repeated 6 months after CRT. Response to CRT was defined by significant LV reverse remodelling (LVES volume reduction [ESVR] >15%) 6 months after CRT. Changes in SDI and mechanical dyssynchrony after CRT were available in 82 patients that underwent the 6-month follow-up echocardiography with the GE system.

Statistical analysis:

All continuous variables are presented as mean \pm SD and dichotomous data as percentages. To compare numerical data between two groups paired and unpaired Student t-tests were used as appropriate. Correlations between variables were assessed using a Pearson's linear correlation. Inter and intra-observer reproducibility was expressed as the difference between 2 measurements divided by the mean of these measurements. Sensitivity, specificity and positive and negative predictive values of the SDI were computed using a previously validated cut-off value (SDI >25%). To identify predictors of CRT response,

multivariate analysis using the logistic regression model was performed with the inclusion of variables with p value <0.1 by univariate analysis. Statistical significance was considered when the p value was <0.05.

RESULTS

Characteristics of the whole population are summarized in the Table 1. During the 6 month follow up, 65% of patients were clinically improved (change in NYHA score ≥ 1), while 35% remained stable or worsened their symptoms (3 died, 5 underwent heart transplantation, 5 were hospitalized for recurrent HF and 4 had severe ventricular arrhythmia). The increase in LVEF averaged $11 \pm 20\%$ and mean ESVR was $18 \pm 25\%$. Response to CRT (ESVR > 15%) was observed in 114 (60%) patients, and was less in ischaemic (44% vs. 68%, $p=0.001$, Table 2) and narrow QRS patients (49% vs. 65%, $p=0.04$, Table 3). Responders to CRT had more preserved global strain ($-8 \pm 3\%$ vs. $-7 \pm 3\%$, $p=0.01$), more dyssynchrony ($12SD-\epsilon = 112 \pm 37\text{ms}$ vs. $97 \pm 30\text{ms}$, $p=0.005$) and had greater SDI ($39 \pm 10\%$ vs. $24 \pm 9\%$, $p<0.0001$, Table 1). A poor correlation with reverse remodelling after CRT was observed for baseline QRS duration ($r=0.17$ $p=0.02$), $12SD-\epsilon$ ($r=0.18$, $p=0.01$) and global strain ($r=0.20$, $p=0.005$). In contrast, SDI correlated with LVEF improvement ($r=0.45$, $p<0.0001$), ESVR ($r=0.61$, $p<0.0001$, Figure 3) and was greater in patients who were clinically improved ($36 \pm 12\%$ vs. $30 \pm 12\%$, $p=0.01$). Multivariate analysis adjusted to QRS duration, LV dyssynchrony, global strain, and cardiac aetiology showed that only SDI (OR=1.8, $p<0.001$) was predictive for response to CRT. Using the cut-off value previously reported, SDI > 25% identified 92% of responders with a positive predictive value of 80% and a negative predictive value of 84% (Figure 4).

Strain delay index in ischaemic patients:

Compared to the non-ischaemic group, ischaemic patients responded less to CRT despite a similar level of dyssynchrony and QRS duration (Table 2). However, compared to the non-ischaemic group, SDI was lower in ischaemic patients ($30 \pm 11\%$ vs. $35 \pm 12\%$, $p=0.01$) and differed between responders and non-responders (Figure 5), while LV dyssynchrony failed to predict response to CRT. Importantly, SDI

similarly correlated with ESVR in both the ischaemic ($r=0.55$, $p<0.001$) and non-ischaemic group ($r=0.61$, $p<0.0001$, Figure 3).

Strain delay index in narrow QRS patients:

Despite a similar level of LVEF impairment, narrow QRS patients in comparison to wide QRS patients had a less dilated ventricle, less severe myocardial dyssynchrony ($97\pm30\text{ms}$ vs. 110 ± 37 , $p=0.02$) and lower SDI value ($30\pm10\%$ vs. $34\pm13\%$, $p=0.01$) (Table 3). Response to CRT was observed in 49% of patients in the narrow QRS group vs. 65% in the wide QRS group ($p=0.04$). Response to CRT was not associated with LV dyssynchrony (Figure 5) and baseline follow-up QRS duration. In contrast, SDI was greater in responders and correlated with ESVR similarly in the narrow and wide QRS populations (Figure 3).

Changes in dyssynchrony and strain delay index:

In responders, decrease in LV dyssynchrony ($-13\pm48\text{ms}$ vs. $+9\pm49\text{ms}$, $p=0.05$) and in SDI ($-7\pm18\%$ vs. $4\pm11\%$, $p=0.002$) was more marked than in non responders. Changes in SDI correlated with ESVR ($r=0.35$, $p=0.001$) and LVEF improvement after CRT ($r=0.27$, $p=0.01$). In non responders, LV dyssynchrony ($+9\pm49\text{ms}$) and SDI ($4\pm11\%$) remained unchanged despite efficient pacing.

Reproducibility:

Intra and inter-observer variability performed in 10 random subjects was 8% and 12%, respectively for automatic 12SD-ε and 5% and 6%, respectively for automatic SDI.

DISCUSSION

Reverse remodelling of the LV after CRT provides an objective measurement of CRT response, that correlates with improved survival and LV function. In this multicenter non randomized study which included a large number of patients, CRT response ($\text{ESVR}>15\%$) was observed in 65% of patients with

prolonged QRS duration, and in 49% of patients with narrow QRS duration ($p<0.05$). Left ventricular mechanical dyssynchrony (12SD- ϵ) derived from time-delay measurement with speckle tracking analysis was lower in non-responder patients but its accuracy is limited to identifying responders to CRT. In contrast, SDI, which quantifies the amount of wasted energy due to LV dyssynchrony, was found to correlate closely with LVEF improvement and reverse remodelling after CRT in both narrow ($r=0.59$, $p<0.001$) and wide QRS patients ($r=0.66$, $p<0.0001$, Figure 3).

Most CRT studies have demonstrated that up to 40% of patients are non-responders, presumably because mechanical dyssynchrony was absent despite a wide QRS duration (1, 5). Several methods based on the time-delay measurement of regional wall motion have been proposed to quantify LV dyssynchrony. Single-centre studies have demonstrated that the 12SD of peak velocity by TDI (14) (SD-TDI) and opposing-wall delay (15) by radial strain or longitudinal velocity, correlate to the clinical response to CRT. However, in the PROSPECT (5) study, neither the SD-TDI (AUC=0.55, sensitivity=0.77, specificity=0.31) nor the opposing-wall delay by TDI (AUC=0.61, sensitivity=53%, specificity=69%) was predictive of response to CRT. Current updated European Society of Cardiology guidelines do not recommend the use of echocardiographic markers of dyssynchrony for selecting patients for CRT (16). The suboptimal accuracy of echocardiographic markers to predict response to CRT has been attributed to the limited accuracy and reproducibility of the Doppler technique in HF patients (17, 18) and/or the use of a single marker approach. To overcome these limitations, Lafitte et al (19) proposed a multi-parametric approach using conventional echocardiographic markers to improve identification of responders. In the same way, several authors (20) have suggested that it may be possible to better predict response to CRT by quantifying myocardial dyssynchrony with the use of speckle tracking (21, 22) that provides a more accurate assessment of myocardial deformation. However, neither the predictive value of mechanical dyssynchrony derived from speckle tracking (23) for responsiveness to CRT nor the multi-parametric (24) approach have been confirmed. The controversial accuracy of time delay measurement using either TDI or speckle tracking

may be explained by the fact that delayed contraction is a nonspecific marker of myocardial dysfunction that can be seen in scar (8, 10), fibrosis (25, 26), and viable (27) myocardium and may be further impacted by loading conditions (28, 29). This limitation particularly affects ischaemic patients but may be overcome by investigating myocardial viability and contractile reserve (9, 30-32) as a complement to LV dyssynchrony to better identify responders.

In a recent study (12), we proposed a new method, the SDI that combines within a single marker mechanical dyssynchrony measurement and myocardial contractility, to predict response to CRT. Strain delay index is not a simple measurement of contractility or time delay but a combination (and relative weighting) of both of these parameters (Figure 1). The importance of considering contractility and dyssynchrony to predict responsiveness to CRT is particularly crucial in ischaemic patients (13, 33). Indeed, ischaemic patients respond less to CRT despite a similar level of dyssynchrony and QRS duration than non-ischaemic patients. This may be explained by the presence of extensive scar in delayed segments that prevents efficient biventricular pacing (9, 30-32). In ischaemic and non ischaemic patients, leads positioned in scar (31) or non desynchronized segments (34) and severe myocardial dysfunction related to myocardial fibrosis and remodelling may also limit the beneficial effects of CRT. Reant et al (33) recently demonstrated that responders and super responders to CRT had greater longitudinal global strain than non responders. Scar and fibrosis in delayed segments may be investigated by stress echocardiography or magnetic resonance and nuclear imaging. However, the physiological approach of SDI may provide a simple alternative to these complex and costly investigations. The SDI incorporates the degree of impaired contractility related to myocardial dyssynchrony rather than dyssynchrony alone. This explains the close correlation between strain delay index and reverse remodelling after CRT in ischaemic and non- ischaemic patients. In the present study, we demonstrated that SDI and decrease in SDI after CRT was greater in responders. In addition, decrease in SDI after CRT appears to be correlated with reverse remodelling and

LVEF improvement. These results suggest that the SDI may be inferred as the gain of contractility expected after optimal resynchronization therapy.

Narrow QRS patients may respond to CRT when mechanical dyssynchrony exists (35). In the present study, we found that narrow QRS patients who responded to CRT had a similar SDI to wide QRS patients despite lower mechanical dyssynchrony. This can be explained by the fact that the narrow QRS patients had less advanced heart disease and more preserved contractility in delayed segments. Indeed, the wasted energy in segments with limited dyssynchrony (5-10% of RR interval) and preserved contractility can reach a similar level to severely desynchronized segments (>10% delay from ES, Figure 6). Finally, these results highlight the concept of mechanical dyssynchrony by demonstrating that limitation of time delay markers is not simply related to the accuracy of the method used to quantify timing but rather to the need to consider contractility. The SDI may overcome this limitation by quantifying the wasted energy related to dyssynchrony that can be recruited by biventricular pacing. The wasted energy is expected to be higher in less advanced heart failure patients (NYHA I-II or/and LVEF>35%) with wide QRS complex. In this population, recent studies have demonstrated a substantial benefit of CRT (36, 37). The use of SDI may be particularly useful for selecting patients who will most benefit from CRT, especially when the QRS complex is moderately enlarged (<150ms).

Study Limitations: Despite the large number of patients included in the study, only a limited number of patients with a narrow QRS duration underwent CRT. The size of the study is a limitation to firmly concluding that the SDI in narrow QRS patients is an accurate method for identifying responders to CRT. A randomized study should be performed in this setting to confirm our results. In addition, the follow up period should be extended to fully understand reverse remodelling related to CRT and its association with SDI. Further studies should be performed to assess the impact of myocardial scar extent and lead position relative to scar, on the accuracy of SDI in predicting response to CRT. Radial and circumferential strains

were not used to quantify SDI because their values cannot be computed from the whole myocardium and reproducibility remains limited. Finally, the study excluded 20% of patients with limited acoustic windows to provide the real accuracy of SDI.

Conclusions: The present multicenter prospective study, that included non-selected patients referred for CRT suggests that SDI, which considers LV dyssynchrony and residual contractility, may identify responders to CRT.

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Conflict of Interest Disclosures: none

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Figure legends

Figure 1: Changes in wasted energy ($\epsilon_{\text{peak}} - \epsilon_{\text{ES}}$) according to myocardial dyssynchrony and contractility. Panel A shows the increase in wasted energy relative to dyssynchrony in two segments with preserved contractility. Panel (B) shows how the wasted energy is affected by the residual contractility. The scar segment with depressed contractility (dotted line) has lower wasted energy than segment with preserved contractility. Panel (C) shows that moderately delayed segments with preserved contractility have greater wasted energy than delayed segments with impaired contractility.

Figure 2: Strain delay index is defined as the sum of the wasted energy ($\epsilon_{\text{ES}} - \epsilon_{\text{peak}}$) caused by LV dyssynchrony across the 16 myocardial segments of the LV (coloured curves). After CRT, the increase (Δ) of global strain curve (white dashed curve) appears to be proportional to the strain delay index.

Figure 3: Correlation between strain delay index and ESVR according to cardiac aetiology (A) and to QRS complex (B). DCM = dilated cardiomyopathy, CAD = coronary artery disease

Figure 4: ROC curves showing the accuracy of strain delay index in predicting response to CRT. SDI = strain delay index, 12SD- ϵ = 12 standard deviation of time to peak strain by speckle tracking.

Figure 5: Left ventricular dyssynchrony was greater in responders with a wide QRS duration and non ischaemic aetiology (A). In contrast, strain delay index (B) was greater in responders independently of QRS duration and cardiac aetiology.

Figure 6: Data from wide (A) and narrow (B) QRS patients demonstrating that the wasted energy per segment ($\epsilon_{\text{peak}} - \epsilon_{\text{ES}}$) is related to the severity of dyssynchrony (x-axis) and to the residual contractility (z-axis).