Peak longitudinal strain delay is superior to TDI in the selection of patients for resynchronisation therapy

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Background. Mechanical dyssynchrony has proven to be superior to QRS duration in predicting response to cardiac resynchronisation therapy (CRT). Whether time to peak longitudinal strain delay between the mid-septum and mid-lateral left ventricular wall better predicts CRT response than tissue Doppler imaging (TDI) is unclear. This study compares the value of the two methods for the assessment of mechanical dyssynchrony and prediction of CRT responders.

Methods. 66 clinical responders and 17 nonresponders to CRT with severe systolic heart failure (LVEF <35%), New York Heart Association classification III or IV and a wide QRS >130 ms with left bundle branch block were evaluated by peak longitudinal strain and TDI. Doppler echocardiograms and electromechanical time delay (EMD) intervals were acquired before and after pacemaker implantation.

Results. In all responders EMD measured by peak longitudinal strain was >60 ms before implantation, compared with 76% of the patients measured by TDI. Nonresponders had EMD <60 ms measured by both techniques. Only peak longitudinal strain delay showed shortened values in every responder postimplantation and demonstrated the most significant reduction and could

predict responders to CRT. However, EMD measured by TDI did not diminish in 30% of the positive clinical responders. Nonresponders showed worsening of the EMD with peak longitudinal strain, but not with TDI.

Conclusions. Responders to CRT can be excellently predicted if EMD before implantation determined by peak longitudinal strain delay is >60 ms. Peak longitudinal strain delay appears to be superior to TDI to predict the response to CRT. (Neth Heart J 2010;18:574-82.)

Keywords: Cardiac Resynchronization Therapy; Heart Failure; Echocardiography; Strain Rate Imaging

Large randomised multicentre trials have proven that cardiac resynchronisation therapy (CRT) improves symptoms, quality of life and left ventricular systolic function. In addition, CRT also positively influences morbidity and mortality in selected patients with severe heart failure.¹⁻⁵ Selection criteria for resynchronisation therapy¹⁻³ are New York Heart Association (NYHA) functional class III-IV congestive heart failure, left ventricular ejection fraction (LVEF) <35% and a wide QRS complex with left bundle branch block (LBBB) morphology >130 ms. Later QRS width showed to be poorly correlated with the presence and degree of intraventricular electromechanical dyssynchrony,⁸ whereas the type of bundle branch block does not predict the location and degree of intraventricular dyssynchrony.^{9,10}

In search of predictors of CRT, other markers for the assessment of intraventricular dyssynchrony have been explored.^{11,12} Novel Doppler echocardiographic methods correctly identify mechanical dyssynchrony and likely provide a better marker to identify responders to CRT than QRS width.^{12,13} Tissue Doppler imaging (TDI) proposed by Bax and Yu¹⁴⁻¹⁶ can measure the electromechanical delay and predicts reverse remodelling during cardiac resynchronisation therapy. Sogaard¹⁷ suggested de-

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layed lateral wall contraction as a superior predictor of CRT efficacy. As yet neither of the methods have been standardised and reports undermining their diagnostic power have recently appeared.^{18,19} The recent Prospect study²⁰ showed that none of the 12 examined echocardiographic parameters of dyssynchrony had sufficient diagnostic power to predict responsiveness to CRT.

Strain rate imaging should potentially be superior to TDI to measure mechanical dyssynchrony because the former represents regional deformation whereas TDI only measures movement of the cardiac walls. Therefore strain rate imaging informs about true local contractility of the walls and enables to calculate the correct time difference of mechanical wall contractility between separate parts of the left ventricle. This approach obviously contrasts with TDI, which measures time differences of movements between separate parts of the walls.

In this echocardiographic study we compared the value of electromechanical time delay (EMD) mea-

sured by TDI and strain rate imaging in patients selected for CRT. In addition other Doppler echocardiographic parameters were studied to determine the best marker of CRT response.

Methods

Patient group

In 83 patients selected for CRT with dilated ischaemic and nonischaemic cardiomyopathy a pacemaker (PM) for electrical resynchronisation was implanted because of LBBB pattern with a QRS width >130 ms and an LVEF <35%. Despite optimal medical treatment, all patients had been in NYHA class III-IV heart failure for several years.

Patients with a deficient echocardiographic study or a poor TDI signal or strain rate imaging with a poor signal-to-noise ratio were excluded from this study.

Pacemaker implantation

Of the three pacing leads one was inserted in the right atrium, usually in the interatrial septum, a sec-

Figure 1. Preimplantation peak longitudinal strain curves from the mid-septum and mid-lateral wall showing a mechanical delay measured from the onset of aortic valve opening to peak strain of 260 ms minus 90 ms is 170 ms. Postimplantation is the mechanical delay between the mid-septum and the mid-lateral wall diminished from 260 ms minus 250 ms to 10 ms.

Table 1. Clinical characteristics of 66 responders and 17 nonresponders to CRT.

Parameter	Responders to CRT (n=66)	Nonresponders to CRT (n=17)
Age	68.8±10 years	71.6±10 years
Gender, male (%)	41 (62)	12 (70)
Dilated cardiomyopathy (%)	27 (41)	8 (46)
AF (%)	13 (19.7)	4 (23.5)
NYHA class	3.2±0.4	3.3±0.4
LVEF (%)	22.2 ±6.7	22.4±6.7
MR grade	2.3±0.8	2.6±0.8
LV dP/dt (mmHg/s)	470.8±128.1	608±128

AF=atrial fibrillation, NYHA class=New York Heart Association class, LVEF=left ventricular ejection fraction, MR =mitral regurgitation; LV=left ventricular.

ond in the high/mid-septum of the right ventricle (RV) or apex and the coronary sinus (CS) lead was placed in one of the side branches at the posterolateral area of the left ventricle, depending on the place of latest activation.²¹ In 16 patients the posterior branch, in 56 a posterolateral branch and 11 a

lateral or anterolateral branch of the coronary sinus was the site of insertion of the left ventricular lead. The leads were connected to a biventricular pacemaker (Medtronic 8042, Insync III) with separated ventricular channels, enabling programming of the interventricular pacing interval (V-V interval). The

Table 2. Baseline echocardiographic parameters from 66 responders and 17 nonresponders to CRT, before and after implantation of a CRT device.

Parameter	Responders (n=66)			Nonresponders (n=17)		
	Baseline	Post-CRT	P value vs. baseline	Baseline	Post CRT	P value vs. baseline
AF (%)	13 (19.7)	6 (9)		4 (23.5)	4 (23.5)	
NYHA class	3.2±0.4	2.0±0.2	<0.0001	3.3±0.4	3.8±0.2	0.07
LVEF (%)	22.2±6.7	33.8±11.5	<0.0001	22.4±6.7	19.7±11.5	0.007
MR grade	2.3±0.8	1.6±0.6	<0.0001	2.6±0.8	2.8±0.6	0.086
LV dP/dt (mmHg/s)	470.8±128.1	784.8±250.3	<0.0001	608±128	473±250	0.005
LA dimension (mm)	48.8±6.8	48.3±6.8	0.57	51.1±6.8	52.9±6.8	0.20
AO dimension (mm)	33.4± 3.4	33.7±3.6	0.08	33.6±2.7	33,6±3.4	0.50
LVED dimension (mm)	73.8±9.7	69.5±9.5	<0.0001	71.0±9.7	71.1±9.5	0.88
LVES dimension (mm)	63.3±9.5	58.3±11.4	<0.0001	61.6±9.5	62.1±11.4	0.70
AO TVI (cm)	18.3±4.2	21.3± 4.6	<0.0001	16.3±3.9	13.6±4.3	0.024
AO flow (m/s)	1.2± 0.3	1.3±0.3	0.13	1.3±0.3	1.0±0.3	0.025
Mitral TVI (cm)	17.4±4.6	19.3±4.8	<0.0001	15.5±2.9	14.2±2.2	0.16
E flow (m/s)	0.81±0.3	0.76±0.3	0.07	0.85±0.3	0.95±0.2	0.11
A flow (m/s)	0.75±0.3	0.71±0.3	1.67	0.56±0.3	0.36±0.2	0.05
Deceleration time (s)	169.9±60.2	204.5±74.5	0.007	181.9±60.2	160.5±74.5	0.31
TR max velocity (m/s)	2.5±0.5	2.7±0.5	0.008	2.8±0.5	2.8±0.5	0.18

AF=atrial fibrillation, NYHA class=New York Heart Association class, LVEF=left ventricular ejection fraction, MR=mitral regurgitation, LV=left ventricular, LA=left atrium, AO=aorta, LVED=left ventricular end-diastolic, LVES=left ventricular end-systolic, AO TVI=aorta time velocity integral, E=early diastolic velocity, A=atrial contraction, TR=tricuspid regurgitation.

Table 3. Electromechanical echo-timing variables from 66 responders and 17 nonresponders to CRT, before and after implantation of a CRT device.

Parameter	Responders (n=66)			Nonresponders (n=17)		
	Baseline	Post CRT	P vs. baseline	Baseline	Post CRT	P vs. baseline
Aortic pre-ejection time (ms)	156.3±31.6	153.6±32.217	0.68	125.4±29.7	128.1±28.2	0.85
Pulmonary pre-ejection time (ms)	108.6±29.2	120.5±33.7	0.01	101.7±17.6	102.5±24.9	0.97
IVMD (ms)	47.9±29.5	33.6±25.6	0.0004	25.7±27.1	26.6±18.8	0.95
SLWD on TDI (ms)	79.5±37.6	59.2±35.1	0.0049	34.7±16.1	47.6±29.8	0.07
Peak longitudinal strain, SLWD (ms)	180.5±74.8	36.7±28.9	<0.0001	30.7±11.3	94.1±46.7	0.002
Programmed A-V delay (ms)		104.3±21			92.3±21	
Programmed V-V delay (ms)		LV20 (-12- +80)			LV10 (-4- +28)	

IVMD=Interventricular mechanical delay, SLWD=Septal to lateral ventricular wall delay, TDI=tissue Doppler imaging, A-V delay=atrioventricular delay, V-V delay=interventricular delay between right to left ventricular lead, RV=right ventricle, LV=left ventricle.

biventricular pacemaker was programmed in the DDD mode in patients with sinus rhythm and in the VVIR mode in patients with chronic atrial fibrillation. All patients with atrial fibrillation had an atrial lead inserted in case sinus rhythm could be obtained after implantation. Adjustment of the A-V delay was performed using the iterative method to ensure ventricular capture with the longest possible atrioventricular filling time evaluated by the pulsed Doppler (PD) method. Adjustment of the V-V timing was performed with the time velocity integral (TVI) of the aorta to optimise cardiac output.²²

Echocardiographic examinations

The System Seven (GE Vingmed Ultrasound, Horten Norway) with a 2.5 and 3.5 MHz multi-phase transducer was used. The two-dimensional and M-mode echocardiography examinations were obtained according to the guidelines of the American Society of Echocardiography²³ the day before and two days after pacemaker implantation and repeated after three to six months. LVEF was assessed using the modified biplane Simpson rule. Doppler echocardiography was applied to measure transmitral, aortic, pulmonary and tricuspid flow velocities with pulsed or continuous wave (CW) Doppler. The LV pre-ejection interval (Q-Ao flow), RV pre-ejection interval (Q-P flow) were measured. Their difference gives the interventricular mechanical delay (IVMD). Time velocity integral from the aorta flow and the diastolic flow properties were determined. Mitral regurgitation is used to calculate DP/dt and tricuspid regurgitation for the right ventricular pressures.

Dyssynchrony markers

Colour TDI was used to assess the timing of the systolic mechanical event (onset S wave) with reference to the onset of electrical activity (QRS complex). TDI from the basal part of the septum and the basal part of the left lateral ventricle wall was used to calculate intraventricular mechanical dyssynchrony, as used by Bax.^{14,15}

An interval >60 ms was considered dyssynchronous contraction.¹⁴ Colour Doppler myocardial images were stored digitally from the apical four-chamber view to allow postprocessing image analysis. In this study peak longitudinal strain was derived from strain rate imaging.¹³

Strain rate imaging (SRI) was performed using an apical four-chamber view with the image sector width as narrow as possible and an angle of only 10 to 20° in the mid-regions of the septum and lateral wall separately to achieve the highest acquisition frame rates at 200-250 fps and the pulse repetition was set to avoid aliasing.¹³ Regional strain rates were estimated from the spatial gradient of the myocardial velocity profile over a user defined sample volume with a computational area of 10 mm. The regional strain rate profiles were integrated over time to obtain the natural systolic strain profile. Data from PD on aortic and mitral flow were incorporated to identify the timing of aortic and mitral valve opening and closure. This allowed the exact measurement from the onset of aortic valve opening to maximal peak strain from the mid-septal wall and also the mid-lateral wall and the difference between the two is used as the marker of

intraventricular mechanical delay measured by SRI (figure 1). We know that a delay of up to 40 ms is found in normal individuals.^{13,24}

Device programming

After implantation the A-V and V-V delay were optimised, followed by a second optimisation three to six months later to improve systolic left ventricular function. The most optimal setting was selected in the further follow-up.

Clinical evaluation

All patients were referred from the heart failure outpatient clinic and followed by a heart failure practitioner to optimise medical treatment and evaluate NYHA classification before and after implantation.

Responders to CRT

1. Improvement in NYHA classification of >1 class;
2. An increase in the left ventricular ejection fraction;
3. A raise in dP/dt;
4. Reduction in left ventricular end-diastolic and end-systolic dimensions were used as discriminators of response.

However, all Doppler echocardiographic parameters were evaluated preimplantation and post-implantation and compared with changes in EMD and not used as markers for CRT response.

Statistical analysis

Data analysis was performed with the SAS System for Windows 8.2 Statistical Software (SAS Institute, Inc). Data are expressed as mean $\pm$ SD unless stated otherwise. Continuous variables were verified to have equal variances by Bartlett's test, and to be normally distributed by a D'Agostino and Pearson omnibus K2 normality test. They were compared using Student's T test. Categorical variables were compared by a Fisher's exact test. A two-sided significance level of 5% was deemed appropriate to document difference between groups.

Results

Clinical data

The demographic and clinical findings of 66 responders and 17 nonresponders to CRT before implantation are depicted in table 1. Their baseline characteristics did not differ except for LV dP/dt with a lower value in responders than in nonresponders.

The responders showed that after PM implantation (table 2) the functional condition measured by NYHA classification improved from 3.2 ± 0.4 to 2.0 ± 0.2 ($p < 0.0001$), dP/dt increased from 470.8 ± 128.1 to 784.8 ± 250.3 mmHg/s ($p < 0.0001$) and LVEF improved by 11.6% ($p < 0.0001$). Mitral

valve regurgitation diminished significantly. A significant reduction in right ventricular pressure was found, measured by the tricuspid regurgitation.

Before implantation atrial fibrillation persisted in 19.7%, while afterwards in 9% of the patients atrial fibrillation was recorded at their latest follow-up visit. In the nonresponder group NYHA classification, dP/dt and LVEF decreased significantly and the prevalence of AF remained unchanged (table 2).

Echocardiographic results

Significant reverse LV remodelling appeared in responders, as shown by the reduction in LVED and LVES dimension (table 2). LA dimension was unchanged after CRT despite the reduction in mitral incompetence. Left ventricular systolic performance measured by TVI from the aorta improved from 18.3 ± 4.2 cm to 21.3 ± 4.6 cm ($p < 0.0001$); the TVI from the mitral valve also improved significantly. The nonresponders showed no change in LA and LV dimensions and worsening in left ventricular systolic performance seen in a reduction of the TVI from the aorta and deterioration of mitral regurgitation.

EMD results

Aortic pre-ejection time did not predict any response in contrast to the interventricular delay, because pulmonary pre-ejection time increased in responders. The EMDs measured by peak longitudinal strain and TDI were obtained in all 83 patients before and after CRT. In all responders a preimplantation EMD >60 ms (mean 180.5 ± 74.5 ms) between mid-septum and mid-lateral wall was found with peak longitudinal strain (table 3).

In contrast, TDI showed a preimplantation EMD of >60 ms (mean 79.5 ± 37.6 ms) in only 50 of 66 responders (76%). In all 66 responders the mean EMD measured by TDI and peak longitudinal strain showed definite electromechanical dyssynchrony before implantation with a significant improvement after CRT. However, peak longitudinal strain delay between mid-septum and mid-lateral wall showed the greatest reduction in EMD after implantation (mean 36.7 ± 28.9 ms) and this outcome was consistent in all responders. On the other hand, the EMD measured by TDI after implantation diminished much less (mean 59.2 ± 35.1 ms) and did not become shorter or even prolonged in 20 of the 66 responders (30%) (figure 2). All nonresponders showed preimplantation EMDs of <60 ms measured by peak longitudinal strain and TDI (figure 3). In the nonresponders EMD after implantation measured by TDI remained unchanged (34.7 ± 16.1 ms to 47.6 ± 29.8 ms) and in 5 of 17 (29%) of the nonresponders dyssynchrony could be observed after implantation. However, EMD measured by peak longitudinal strain after implantation worsened significantly (30.7 ± 11.3 ms

Figure 2. Pre- and postimplantation electromechanical delays in 66 clinical responders to CRT measured by peak longitudinal strain between the mid-septum and mid-left lateral wall showing a reduction of EMD in every patient, while EMD measured by TDI preimplantation shows no reduction or even an increase postimplantation. In contrast to what one would expect, this is accompanied by a good clinical response. A cut-off line of more than 60 ms marking patients with dyssynchrony shows that even patients with a lesser EMD measured by TDI are good clinical responders. The red lines represent mean EMD pre- and postimplantation.

to 94.1 ± 46.7 ms) through which dyssynchrony appeared in 13 of 17 (76%) of the nonresponders.

Reproducibility of measurements

All electromechanical parameters were measured off line which allows post-process image analysis of the data. The intraobserver variability for TDI and for peak longitudinal strain between the mid-septum and mid-lateral left ventricular wall was 2 to 5%. The interobserver variability for TDI was 15 to 20% and for SRI 5 to 8%.

Discussion

Strain rate imaging is a new echocardiographic technique that processes velocity data of colour

Doppler myocardial imaging and thereby can discern between healthy, ischaemic and viable cardiac segments^{13,25} and can also determine left ventricular mechanical dyssynchrony.²⁶ Preliminary reports showed that LV dyssynchrony measured by strain rate imaging improved after CRT²⁷ but the results are conflicting.²⁸ This study shows domination of peak longitudinal strain derived from SRI over TDI in the selection and outcome to CRT.

In the follow-up of this study, we observed that peak longitudinal strain was capable to detect a true reduction of EMD in all responders, whereas TDI missed the reduction of delays in 30% of the patients responsive to CRT.

Figure 3. Pre- and postimplantation electromechanical delays in 17 clinical nonresponders to CRT, measured by peak longitudinal strain between mid-septum and mid-left lateral wall and with TDI show a preimplantation EMD of 60 ms or less in all patients. The mean EMD measured by peak longitudinal strain shows worsening postimplantation, while EMD measured by TDI hardly changed. The cut-off line of 60 ms marking patients with dyssynchrony is seen in 13 patients, when peak longitudinal strain is used, while EMD measured by TDI showed a different behaviour in each patient and only four patients were dyssynchronous postimplantation. The red lines represent the mean EMD pre- and postimplantation.

Superiority of strain rate imaging to TDI

After initial superiority of TDI for quantifying mechanical dyssynchrony as selecting method for candidates to CRT, several negative reports have challenged this supremacy and advocated other techniques.^{18,19,29} The recently published Prospect study²⁰ was disappointing for TDI as well as for the other methods tested as dyssynchrony markers and therefore predictors for CRT. This outcome was not expected because the main therapeutic mechanism of CRT is correction of this mechanical dyssynchrony of the left ventricle. Our study shows that peak longitudinal strain delay defines mechanical dyssynchrony much better than TDI.

By examining the interval between time to peak longitudinal strain of the mid-septum and that of the left ventricular lateral wall the degree of dyssynchronous contraction of the LV walls could be precisely assessed (figure 1).

We emphasise that measurement of peak longitudinal strain delay from strain rate imaging does differ strongly with that of measurements of translational movement recorded with TDI.

Reduction in EMD after implantation predicts more synchronous contraction and better left ventricular systolic performance.

In responders, the left ventricular intraventricular EMD measured by peak longitudinal strain

showed a mean reduction >140 ms during CRT in contrast to a mean reduction of 20 ms measured by TDI. This difference can be attributed to the fact that TDI underestimates the degree of dyssynchrony, particularly in patients with ischaemic heart disease.^{26,27} It is noteworthy to mention that peak longitudinal strain delay was reduced in all patients.

These findings contrast with the observations in 20 of 66 patients (30%) in whom TDI did not show changes in EMD, despite the fact that these patients were identified as clinical responders. In the nonresponder group TDI did not show a change in EMD either, while peak longitudinal strain showed deterioration in EMD >60 ms after implantation, predicting more dyssynchronous contraction and hence a poorer left ventricular systolic performance.

Standardisation of EMD markers

In the presence of delayed electromechanical conduction the dissociation between regional motion and regional contraction becomes important.

EMD measured by TDI is restricted to regional motion, which is affected by neighbouring segments and the overall motion of the heart. Strain rate imaging is not affected by motion at all and can measure the true regional contraction sequence, which allows estimating the recruitable contractile reserve. Furthermore, there is no standardised method for measuring EMD with TDI. In diverse studies different ways to measure EMD with TDI are employed. No consensus has been derived about the use of the onset of the S wave or top of the S wave and in case of several tops, which top should be measured. In contrast, if an accurate peak strain curve can be obtained, it is easy to measure and there will be no discussion on how to measure the EMD, improving intra and interobserver variability.

CRT response

The responder group consisted of only patients with EMD of >60 ms measured by peak longitudinal strain and nonresponders of EMDs <60 ms. The clinical improvement of the responders paralleled reversed LV remodelling by various echocardiographic parameters, including interventricular and intraventricular EMDs.

If EMD measured by TDI had been used as a marker for positive CRT response, 24% (16 patients) of the responders in this study would not have received a CRT device and would be undertreated. Furthermore an EMD <60 ms measured by TDI is seen in responders and nonresponders, which troubles the selection for CRT. By optimising the CRT device, clinical improvement of NYHA classification, dP/dt and EF could be obtained; this was accompanied with a reduction in EMD measured by peak longitudinal strain in all responders. On the other hand in 30% (20 patients)

EMD measured by TDI could not be reduced or even increased, although these patients did improve in NYHA classification, dP/dt and EF (figure 2).

Deterioration in EMD in the nonresponder group measured by peak longitudinal strain was far more pronounced than with TDI: 82 vs. 30% (figure 3).

These findings made peak longitudinal strain a superior technique to use as a marker of EMD in the selection and outcome for CRT implantation. If EMD is >60 ms, improvement in NYHA classification, dP/dt, EF and other echocardiographic parameters was always present and accompanied by a strong reduction in EMD after implantation.

Limitations

This study was carried out in one institution and was not randomised but outcome-oriented. Only the NYHA classification was used as a marker for CRT response.

Conclusions and perspectives

As in the Prospect trial we found that TDI was not sufficiently accurate in predicting response to CRT. Peak longitudinal strain has obvious advantages to TDI and therefore merits application.^{24,26} However, randomised studies are needed to specify the cut-off value of strain rate imaging in various settings of congestive heart failure regarding selection and follow-up, its contribution to the fast programming of stimulation algorithms of the implanted device and the role of strain rate imaging when CRT fails to produce a positive clinical response. ■

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