CARDIOVASCULAR MEDICINE

Tissue Doppler velocity is superior to displacement and strain mapping in predicting left ventricular reverse remodelling response after cardiac resynchronisation therapy

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Objective: To compare the values of three different forms of tissue Doppler imaging (TDI) processing in predicting left ventricular (LV) reverse remodelling—namely, tissue velocity, displacement and strain mapping.

Design: Standard echocardiography with TDI was performed before and 3 months after cardiac resynchronisation therapy (CRT).

Setting: University teaching hospital.

Patients: 55 patients with heart failure who received CRT and were followed up for at least 3 months were recruited.

Interventions: During off-line analysis, the time to peak systolic velocity in the ejection phase, time to peak positive displacement and time to peak negative strain were measured in the six basal, six mid-segmental model. Parameters of systolic asynchrony derived by velocity, displacement and strain mapping were correlated with percentage reduction in LV end systolic volume (LVESV) and absolute gain in ejection fraction (EF).

Results: Among the three TDI processing technologies, all parameters of tissue velocity correlated with LV reverse remodelling ($r = -0.49$ to $r = -0.76$, all $p < 0.001$), but the predictive value was strongest in models with 12 LV segments. For displacement mapping, only the two parameters that included 12 LV segments correlated modestly with reduction in LVESV ($r = -0.36$, $p < 0.05$) and gain in EF. However, none of the strain mapping parameters predicted a favourable echocardiographic response. The receiver operating characteristic (ROC) curve areas were higher for parameters of tissue velocity based on 12 LV segments (ROC areas 0.88 and 0.94) than the corresponding areas derived from displacement mapping (ROC areas 0.72 and 0.71).

Conclusion: Tissue velocity parameters of systolic asynchrony are superior to those of displacement and strain mapping in predicting LV reverse remodelling response after CRT.

The establishment of cardiac resynchronisation therapy (CRT) for patients with advanced heart failure and prolonged QRS complex duration was based on the positive results of multicentre trials.^{1–4} Recently, left ventricular (LV) reverse remodelling after CRT was also found to predict long-term cardiovascular morbidity and mortality.⁵ However, lack of a clinical or reverse remodelling response of the left ventricle has been observed in about one third of patients. In the past few years, the role of echocardiography in assessing mechanical dyssynchrony in patients receiving CRT has been explored continually.^{6–9} In particular, tissue Doppler imaging (TDI) that extracts tissue velocity data from regional walls of the ventricles has proved to be useful to predict LV reverse remodelling.^{6–10} The method based on TDI examined the time to peak systolic velocity from which parameters of systolic mechanical asynchrony were calculated. In previous studies, the measurement of an “asynchrony index” from 12 LV segments predicted LV reverse remodelling and a favourable increase in ejection fraction (EF).^{11–12} Recently, other imaging modalities derived from post-processing of TDI technology have been assessed for their ability to quantify systolic dyssynchrony and predict a favourable response to CRT, in particular strain and

displacement mapping.¹³ This study compared parameters of systolic asynchrony derived from tissue velocity, strain and displacement mapping in predicting LV reverse remodelling and improvement of EF.

METHODS

Patients

Fifty-five patients with heart failure (mean age 66 (SD 12) years, 72% men), who received CRT and were followed up for at least three months, were recruited in the study. Inclusion criteria of CRT were New York Heart Association functional class III ($n = 43$) or IV ($n = 12$) heart failure despite optimal drug treatment, evidence of LV systolic dysfunction with an EF $< 40\%$ and a QRS duration > 120 ms. The aetiologies of heart failure were ischaemic in 28 (51%) and non-ischaemic in 27 (49%) patients. The study protocol was approved by the ethics committee and written informed consent was obtained from all the patients.

Abbreviations: CRT, cardiac resynchronisation therapy; EF, ejection fraction; LV, left ventricular; LVESV, left ventricular end systolic volume; ROC, receiver operating characteristic; TDI, tissue Doppler imaging

Device implantation

Biventricular devices were implanted as previously described.¹⁻⁶ The LV pacing lead was inserted by a transvenous approach through the coronary sinus into either the lateral or posterolateral cardiac vein. Only three patients had CRT plus defibrillator devices (InSync ICD, Medtronic Inc, Minneapolis; or Contak CD, Guidant Inc, St Paul, Minnesota, USA), and all the others received biventricular pacemakers (InSync, InSync III, Contak TR or Contak TR II).

Echocardiography

Standard two-dimensional and Doppler echocardiography was performed as previously described.⁶ The atrioventricular interval was optimised by Ritter's method by using Doppler echocardiography on the first day after implantation,¹⁴ and the devices were all programmed to simultaneous biventricular pacing mode. TDI was performed (Vivid 5 or Vivid 7; Vingmed-General Electric, Horten, Norway) before and three months after CRT.⁶⁻¹¹ At least three cardiac cycles were analysed and the average value was taken. LV volumes and EF were assessed by biplane Simpson's equation in the apical four-chamber and two-chamber views. Two-dimensional colour TDI was performed in three apical views (apical four-chamber, two-chamber and long-axis) for evaluating the long-axis motion of the ventricles as previously described.⁶ Images were analysed offline (EchoPac-PC 3.1.3; Vingmed-General Electric) by using the six basal and six mid-segmental model of the LV as previously described.⁶⁻¹¹ For tissue velocity mapping, myocardial velocity curves were reconstituted. The time to peak myocardial systolic velocity during the ejection phase was measured with reference to the QRS complex.⁶⁻¹¹⁻¹⁵ For displacement mapping, the velocity-time integral of tissue velocity was computed and the regional long-axis movement curve was displayed. The time to peak positive displacement was measured. Strain was mapped by programming the sampling points to 12 mm apart in a certain myocardial segment. Tissue strain (ϵ) was calculated by the formula $\epsilon = (L - L_0) / L_0 \times 100\%$, where L_0 refers to the original length of myocardial fibre and L refers to the length and deformation. The time to peak negative strain was measured.

Parameters of systolic asynchrony based on tissue velocity, displacement or strain mapping were as follows:

- SD of measured timing of the 12 LV segments
- Maximum difference of measured timing between any two of 12 LV segments
- SD of measured timing of the six basal LV segments

Figure 1 Analyses of tissue velocity in a patient who received cardiac resynchronisation therapy (CRT). Images were captured by two-dimensional tissue Doppler imaging signals and analysed offline. In the apical four-chamber view, the signal was sampled at septal and lateral segments at both basal and mid-levels. In this patient, improvement of systolic asynchrony is illustrated by the reduced dispersion of the time to peak myocardial tissue velocity in the ejection period. (A) Before CRT; (B) 3 months after CRT. AVC, aortic valve closure; AVO, aortic valve opening.

Table 1 Relationship between Δ LVESV or Δ EF and parameters of systolic asynchrony measured by tissue velocity, displacement and strain mapping

	SD-12	SD-6	Dif-12	Dif-6	Sept-lat	Sept-post
Time to peak tissue velocity						
Δ LVESV	-0.76**	-0.63**	-0.64**	-0.62**	-0.54**	-0.49**
Δ EF	0.65**	0.55**	0.61**	0.56**	0.42*	0.37*
Time to peak displacement						
Δ LVESV	-0.36*	-0.26	-0.36*	-0.26	-0.16	-0.07
Δ EF	0.28*	0.21	0.31*	0.22	0.07	-0.04
Time to peak strain						
Δ LVESV	-0.17	-0.13	-0.20	-0.13	0.11	0.08
Δ EF	0.23	0.22	0.24	0.21	0.03	-0.02

* $p < 0.05$; ** $p < 0.001$.

Δ EF, change in ejection fraction; Δ LVESV, change in left ventricular end systolic volume; Dif-6, maximum difference of measured timing between any two of six basal left ventricular (LV) segments; Dif-12, maximum difference of measured timing between any two of 12 LV segments; SD-6, SD of measured timing of the six basal LV segments; SD-12, SD of measured timing of the 12 LV segments; Sept-lat, absolute difference in measured timing between the basal septal and basal lateral segments; Sept-post, absolute difference in measured timing between the basal septal and basal posterior segments.

Figure 2 Analyses of displacement imaging in the same patient as in fig 1. Improvement of systolic asynchrony is illustrated by the reduced dispersion of the time to peak positive displacement. (A) Before CRT; (B) 3 months after CRT. AVC, aortic valve closure; AVO, aortic valve opening.

- Maximum difference of measured timing between any two of six basal LV segments
- Absolute difference in measured timing between the basal septal and basal lateral segment
- Absolute difference in measured timing between the basal septal and basal posterior wall.

Statistics

For statistical comparison of parametric variables before and after CRT, the paired sample *t* test was used. Pearson correlation analysis was used to compare the relationship between parameters of systolic asynchrony and the change of LV end systolic volume (LVESV) or EF after pacing, and the correlation coefficient was compared. Receiver operating characteristic (ROC) curves were analysed to compare and determine the cut-off values of parameters of systolic asynchrony. Differences between the ROC curves were compared by the Delong test. All parametric data were expressed as mean (SD). A value of $p < 0.05$ was considered significant.

Figure 3 Analyses of strain imaging in the same patient as in fig 1. Improvement of systolic asynchrony is illustrated by the reduced dispersion of the time to peak negative strain. (A) Before CRT; (B) 3 months after CRT. AVC, aortic valve closure; AVO, aortic valve opening.

RESULTS

Reverse remodelling response after CRT

LV end diastolic volume ($179 (75) \nu 156 (72) \text{ cm}^3$, $p < 0.001$) and LVESV ($136 (68) \nu 107 (61) \text{ cm}^3$, $p < 0.001$) decreased and EF improved ($25.9 (9.1)\% \nu 33.9 (10.8)\%$, $p < 0.001$) at the end of three months after CRT. Successful LV reverse remodelling was defined as a reduction of LVESV of $> 15\%$,^{7 11 16} which was observed in 29 (53%) patients, regarded as volumetric responders. The other 26 (47%) patients who had a reduction of LVESV $\leq 15\%$ were regarded as volumetric non-responders.

Predictive values of TDI parameters

Among the three TDI-derived imaging techniques for systolic asynchrony, all the parameters of tissue velocity correlated significantly with LV reverse remodelling ($r = -0.49$ to $r = -0.76$, all $p < 0.001$) (table 1, figs 1–3). Similarly, all these parameters correlated with the gain in EF ($r = 0.37$ to $r = 0.65$, all $p < 0.01$). The correlation coefficient decreased gradually when the number of segments of the parameters decreased from 12 to six, and further to two. For the displacement mapping, only those parameters that encompassed the measurement of 12 LV segments significantly

Table 2 ROC curve areas for parameters of systolic asynchrony that predict LV reverse remodelling

Parameter	ROC area (95% CI)	p Value	Cut-off value (ms)	Sensitivity (%)	Specificity (%)
Tissue velocity					
SD-12	0.94 (0.88 to 1.00)*	<0.001	31.4	96	78
Dif-12	0.88 (0.78 to 0.98)*	<0.001	98.5	90	76
Displacement					
SD-12	0.71 (0.57 to 0.85)	0.009	75	66	73
Dif-12	0.72 (0.58 to 0.85)	0.005	205	62	62

Dif-12, maximum difference of measured timing between any two of 12 left ventricular (LV) segments; ROC, receiver operating characteristic; SD-12, SD of measured timing of the 12 LV segments.

* $p < 0.01$ v SD-12 or Dif-12.

correlated with LV reverse remodelling and gain in EF (table 1). In contrast, none of the parameters derived from strain mapping correlated with the changes in LVESV or EF.

Table 2 shows the cut-off values, sensitivity and specificity derived from the ROC curves of the displacement mapping parameters that predicted LV reverse remodelling, compared with similar tissue velocity parameters. The parameters based on tissue velocity have higher sensitivity and specificity than the corresponding displacement mapping parameters. Figure 4 shows the ROC curve for identification of LV reverse remodelling.

Figure 4 Receiver operating characteristics for identification of left ventricular (LV) reverse remodelling in patients who received cardiac resynchronisation therapy. (A) Standard deviation of the time to peak segmental displacement of the 12 LV segments, and (B) maximum difference in time to peak segmental displacement between any two of the 12 LV segments. The area under the curve is provided for each graph.

DISCUSSION

Although CRT is an established therapy for advanced heart failure with electromechanical delay, the consistent finding of non-responders is an emerging issue that prompts the use of non-invasive imaging tools to evaluate mechanical asynchrony, as well as to guide optimisation of the treatment.^{7–12 17 18} Two major factors determine the response to CRT: the selection of patients on the basis of the ECG criterion of prolonged QRS duration, which has included patients without obvious systolic mechanical asynchrony; and the suboptimal location of LV leads at a region other than the free wall.^{9 18} In our study we had a relatively high prevalence of non-responders. This may be explained by the rigorous criterion of an LV volumetric reduction of $\leq 15\%$ evaluated echocardiographically. In fact, previous studies that used similar criteria had reported a non-responder rate of $> 40\%$, which is generally greater than the rate obtained by the clinical definition of non-responders.^{7 12 19} On the other hand, there is no consensus on the definition of clinical response, which varies between studies. Furthermore, some clinical end points are subject to the placebo effect in multicentre trials.^{1 20} We used echocardiographic evidence of LV reverse remodelling to define a favourable response to CRT, as early volumetric improvement also predicted a good long-term clinical outcome.⁵

Optimisation of a CRT device is another important aspect of the therapy. Optimisation of the atrioventricular delay after CRT has been suggested to improve atrioventricular synchrony by abolishing the late diastolic ventriculoatrial gradient and “diastolic” mitral regurgitation, and by increasing the LV filling time and hence cardiac output.^{21 22} In our laboratory, the atrioventricular delay was optimised by Doppler echocardiography within 24 h after device implantation, which was repeated during intermediate (three months) and long-term follow up. The interventricular interval is not optimised routinely in our current practice. Although two recent papers have suggested that optimisation may further improve LV performance,^{23 24} such benefit has not been shown by large, randomised studies that compared sequential with simultaneous biventricular pacing. Furthermore, methods of optimising interventricular intervals have been highly variable, such as aortic velocity time integral, myocardial performance index and TDI, and a consensus method has yet to be identified.^{23 25 26}

Over the past few years, the use of echocardiographic parameters to assess pre-pacing systolic mechanical asynchrony has been reported to be useful to predict a favourable response, especially LV reverse remodelling and improvement of systolic function.^{6–9} Among various echocardiographic methods, the tissue velocity signal derived from TDI has been found useful by virtue of its ability to examine regional myocardial function quantitatively.^{6 8–10} However, a few other post-processing mapping modalities from TDI are available, which provide further opportunity to examine systolic asynchrony in different ways. These include displacement

mapping (time-velocity integration of myocardial velocity curve), strain mapping (deformation of myocardium) and strain rate mapping (rate of deformation of myocardium). We previously observed that strain rate mapping is not useful to predict LV reverse remodelling.¹² However, little is known about whether displacement and strain mapping are useful, and comparison with tissue velocity will provide insight about their relative strengths for such a purpose.

The present study focused on assessment of systolic asynchrony by different post-processing technologies of TDI and compared their predictive values for cardiac structural and functional improvement after CRT. Tissue velocity was observed to be superior to both displacement and strain mapping in predicting LV reverse remodelling and gain in EF. In fact, only parameters of displacement mapping that included 12 LV segments were found useful, and none of the parameters of strain imaging correlated with either reduction of LVESV or increase in EF. For similar parameters, tissue velocity remains superior to displacement mapping as reflected by the higher correlation coefficients. In a normal and synchronously contracting heart, long-axis displacement and negative strain peak at the time of end systole—that is, during aortic valve closure. In the failing heart, which exhibits systolic asynchrony, this may happen during isovolumic contraction, the ejection phase or even after aortic valve closure—that is, after systolic shortening.¹² However, such redistribution of timing can be a consequence of severe myocardial disease per se rather than a manifestation of systolic asynchrony. For example, patients with coronary heart disease may have post-systolic shortening, signifying myocardial ischaemia or viability.^{27–28} A previous study showed that measuring the time to peak post-systolic shortening has a significantly lower predictive value for LV reverse remodelling and gain in EF than does measuring the ejection phase.²⁹ Parameters of strain and displacement mapping in the current study also sampled the time delay beyond aortic valve closure (if present), which is contributed by post-systolic shortening; this may significantly reduce the predictive value for a favourable volumetric response to CRT.

In conclusion, tissue velocity is superior to displacement and strain mapping in predicting a favourable LV reverse remodelling response and improvement of EF. Displacement mapping was useful only when systolic asynchrony was comprehensively evaluated by including all 12 LV segments.

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