EDITOR'S CHOICE

Electrical and mechanical dyssynchrony for prediction of cardiac events in patients with systolic heart failure

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ABSTRACT

Background Recent clinical trials have challenged the clinical applicability of mechanical dyssynchrony in predicting cardiac resynchronisation therapy response.

Objective To evaluate whether mechanical dyssynchrony has an additional benefit over QRS duration in predicting cardiac events in patients with systolic heart failure.

Methods A total 167 patients admitted to hospital with heart failure (age 65 ± 12, ejection fraction <35%) were followed up prospectively. Using tissue Doppler imaging (TDI), the time to peak systolic velocity during the ejection phase was measured in the basal septal and lateral segments. A temporal difference between the septal to lateral wall (Ts−l) of ≥65 ms was defined as a mechanical dyssynchrony.

Results After 33 months of follow-up, 70 patients (41.9%) had cardiac events, including 42 (25.1%) with cardiac death. The event-free survival time decreased as Ts−l or QRS duration increased. Patients with QRS ≥120 ms had increased risks of cardiac events by multivariate Cox proportional hazard analysis (HR=1.88, 95% CI 1.07 to 3.29, p = 0.028). The presence of mechanical dyssynchrony also predicted an increased risk of cardiac events (HR=2.37, 95% CI 1.39 to 4.04, p = 0.002). Those with both electrical and mechanical dyssynchrony had a HR of 3.98 (95% CI 2.02 to 7.86, p <0.001) when compared with those with normal QRS duration and absence of mechanical dyssynchrony. The addition of mechanical dyssynchrony significantly improved the prognostic power of a model containing echocardiographic parameters and QRS duration.

Conclusions TDI-derived mechanical dyssynchrony is an important prognosticator and independently associated with QRS duration in predicting adverse events in patients with systolic heart failure.

INTRODUCTION

An intraventricular conduction delay manifested by wide QRS complex in patients with heart failure is associated with advanced myocardial disease, decreased left ventricular (LV) function, and a poor prognosis.[1] Because of this, cardiac resynchronisation therapy (CRT) has been recommended for patients with symptomatic heart failure of New York Heart Association (NYHA) functional class ≥III and who show evidence of electrical dyssynchrony. However, there is a general consensus that a wide QRS complex has only a limited relationship with intraventricular mechanical dyssynchrony and may underestimate intraventricular dyssynchrony.[2–4] Echocardiography has had a key role in evaluating mechanical dyssynchrony, with tissue Doppler imaging (TDI) being the most widely used screening tool.[5–9] However, results of recent clinical trials have challenged the applicability of mechanical dyssynchrony using echocardiography in 'real-world' clinical practice.[10–12] We sought to determine whether mechanical dyssynchrony had an additional benefit over QRS duration in predicting cardiac events in patients with systolic heart failure.

MATERIALS AND METHODS

Study population

Our study is a single-centre, prospective observational study. Patients who were hospitalised for NYHA functional class ≥III heart failure, caused by either ischaemic or non-ischaemic events, and LV ejection fraction (LVEF) ≤35% were consecutively enrolled. Of these, we excluded patients aged ≥80, other than sinus rhythm, cardiac or cerebral ischaemic events within the past 3 months or coexisting serious illnesses. Patients who underwent coronary revascularisation during the study period were also excluded. A total of 167 patients were included in this study. Unless contraindicated, patients were treated with β blockers or ACE inhibitors (or angiotensin receptor blockers) and diuretics at the time of discharge, and the dose of β blocker and ACE inhibitors was increased to maximal tolerable dose. Clinical events included hospitalisation for worsening of heart failure and cardiac death. Cardiac death was verified from hospital records or death certificate from the primary doctors. The study protocol was approved by the institutional review board of our university.

Standard and tissue Doppler echocardiography

Standard echocardiography was performed using a commercially available system (Vivid 5 or 7; General Electric, Norway). LV dimensions were measured by M-mode echocardiography according to the guidelines of the American Society of Echocardiography. LV end-systolic and end-diastolic volumes and LVEF were measured using the modified biplane Simpson rule. Mitral regurgitation was characterised as follows: mild (regurgitation orifice area <0.2 cm^2), moderate (0.2–0.39 cm^2) and severe (≥0.4 cm^2).

For TDI, colour Doppler frame rates varied between 99 and 130 frames/s depending on the sector width. Three cardiac cycles triggered to the QRS complex were stored in digital format on a magneto-optical disk for offline analysis (EchoPac BT07; General Electric).

Ventricular dyssynchrony

To assess regional myocardial velocity, the sample volume was placed in the basal portions of the septum and lateral wall; the time to peak systolic velocity from the R wave on QRS complex during the ejection period was measured and expressed in milliseconds. LV dyssynchrony was derived from the time difference between the septum and lateral wall (Ts–l).[13] If the peak velocity could not be defined because of the noise signal or flat velocity contour, the sample volume was gradually moved to mid-segment until a clear signal intensity could be obtained. We divided patients into four groups based on their QRS duration and the presence or absence of mechanical dyssynchrony; group I: QRS duration <120 ms and Ts–l <65 ms, n = 71, group II: QRS duration ≥ 120 ms and Ts–l <65 ms, n = 25, group III: QRS duration <120 ms and Ts–l ≥65 ms, n = 44, group IV: QRS duration ≥120 ms and Ts–l ≥ 65 ms, n = 27.

Statistics

Summary data are expressed as mean value ± SD or percentage of patients. Comparison of baseline characteristics between the groups was performed with independent t test and χ^2 test. The area under the receiver operating characteristic curve (AUC) was used to compare the predictive validity. A z score was calculated to determine the difference between AUCs. Survival curves were estimated by the Kaplan–Meier method with a log rank test. Predictive variables for cardiac events or cardiac death were examined using the univariate or multivariate Cox proportional hazard regression models. A p value <0.05 was considered statistically significant.

RESULTS

Patients characteristics

Of 167 patients, 52 patients had a QRS ≥ 120 ms (31.1%) and 71 patients had a Ts–l ≥ 65 ms (42.5%). After a mean follow-up of 33.4 ± 19.9 months, 70 patients (41.9%) had cardiac events, including cardiac death in 42 patients (25.1%). Baseline clinical and echocardiographic characteristics are summarised in table 1.

Reproducibility

The reproducibility was determined on a single set of recordings. Variability in the measurement of mechanical dyssynchrony (Ts–l) was evaluated in 20 randomly selected patients. For intraobserver variability, the same observer measured Ts–l for each of the selected patients again 15 days later. For the interobserver variability, a second independent observer repeated the analysis. The coefficients of variations of intra- and interobserver variability were 9.1% and 10.1%, respectively.

Predictors of cardiac events

In univariate analysis, older age, ischaemic aetiology, longer QRS duration, no β-blocker use and longer Ts–l were associated with cardiac events. In multivariate Cox proportional hazard analysis, both QRS duration (HR=1.88, p = 0.028) and Ts–l (HR=2.37, p = 0.002) were independent predictors of cardiac events (table 2). Those with both electrical and mechanical dyssynchrony had a HR of 3.98 (95% CI 2.02 to 7.86, p <0.001) when compared with those with normal QRS duration and an absence of mechanical dyssynchrony. The additional benefit of mechanical dyssynchrony in the prediction of cardiac events is shown in figure 1. The addition of mechanical dyssynchrony significantly improved the prognostic power of a model containing echocardiographic parameters (LVEF and E/e′) and QRS duration. We calculated the AUCs of QRS duration and Ts–l for predicting cardiac events. The AUC of Ts–l was 0.62, which is not statistically different from that of QRS duration (0.60) (z score = 0.31, p = 0.76).

Table 1 Baseline clinical and echocardiographic parameters

	All patients	Clinical event		p Value
		No (n = 97)	Yes (n = 70)	
Age	64.6 ± 11.8	63.3 ± 11.5	66.5 ± 11.9	0.092
Sex (male, %)	65.3	67.0	62.9	0.623
Surface ECG				
QRS duration	112.5 ± 27.1	108.2 ± 23.8	118.5 ± 30.2	0.019
LBBB (%)	16.2	12.4	21.4	0.138
Ischaemic origin	98 (58.7%)	48 (49.5%)	50 (71.4%)	0.007
Diabetes mellitus (%)	39.2	33.3	47.9	0.079
Creatinine (mg/dl)	1.78 ± 1.78	1.44 ± 1.42	2.19 ± 2.07	0.010
Drugs				
β Blocker (%)	79	85.3	72.9	0.075
Dose of carvedilol, (mg)	30.7 ± 13.3	33.3 ± 13.5	27.3 ± 12.4	0.022
ACEI or ARB (%)	92.8	95.8	90.0	0.205
	86.2	84.4	90.0	0.211
LV dimension (mm)				
End-diastole	61.0 ± 8.2	60.7 ± 6.9	61.3 ± 9.8	0.653
End-systole	49.5 ± 9.8	49.4 ± 8.7	49.5 ± 11.1	0.966
LV volume (ml)				
End-diastole	145.5 ± 55.8	139.4 ± 52.2	154.0 ± 59.7	0.103
End-systole	101.8 ± 47.4	102.8 ± 42.1	115.5 ± 53.2	0.101
LV ejection fraction (%)	26.8 ± 6.5	27.2 ± 6.5	26.3 ± 6.3	0.373
Mitral regurgitation (%)				0.032
Mild	46%	51.1%	39.1%	
Moderate	36.8%	38.3%	34.8%	
Severe	17.2%	10.6%	26.1%	
Ts–l (ms)	64.2 ± 48.2	55.0 ± 42.5	76.3 ± 52.8	0.005

Mitral regurgitation: mild (regurgitation orifice area ≤0.2 cm^2), moderate (0.2–0.39 cm^2), and severe (≥0.4 cm^2).
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; LBBB, left bundle branch block; LV, left ventricular; Ts–l, time difference between the septal and lateral wall.

Kaplan–Meier analysis

Cardiac events during follow-up were 23.9% (Kaplan–Meier estimate; 17 events in 71 patients) in group I, 40.0% (10/25) in group II, 59.1% (26/44) in group III, and 63.0% (17/27) in group IV (p <0.001). The mean event-free survival time decreased as QRS duration and Ts–l increased (figure 2).

DISCUSSION

The major finding of this study is that mechanical dyssynchrony has an additional benefit over QRS duration in predicting cardiac events in patients with advanced heart failure. In recently published reports, the use of TDI for the assessment of CRT response has been disappointing.[11 12 14] In the PROSPECT trial, no single echocardiographic measure of dyssynchrony could be recommended to improve patient selection for CRT.[12] There is a poor agreement for evaluating the magnitude of intraventricular dyssynchrony between TDI and real-time, three-dimensional echocardiography.[15] Furthermore, mechanical dyssynchrony based on TDI had a limited role in predicting clinical response in patients with narrow QRS width and mechanical dyssynchrony.[11] In light of these reports, the question remains whether or not TDI is the appropriate diagnostic tool for identifying dyssynchrony in patients with advanced systolic heart failure. Therefore, the QRS duration remains as the dyssynchrony surrogate to identifying patients appropriate for CRT. However, about 10% of patients with heart failure meet the current criteria for CRT.[16] Furthermore, most trials have demonstrated that approximately 30–40% of these

Table 2 Cox-regression hazards ratio (HR) in univariate and multivariate analysis for predicting cardiac events or death

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.03	1.00 to 1.05	0.028			
Sex	1.11	0.68 to 1.80	0.674			
QRS duration (≥120 ms)	1.70	1.05 to 2.76	0.032	1.88	1.07 to 3.29	0.028
Ischaemic aetiology	1.93	1.15 to 3.25	0.013			
Diabetes mellitus	1.43	0.90 to 2.29	0.134			
Serum creatinine	1.14	1.03 to 1.26	0.013	1.24	1.09 to 1.43	0.002
Use of β blocker	0.53	0.31 to 0.89	0.017	0.40	0.22 to 0.74	0.003
End-systole volume	1.01	1.00 to 1.01	0.065			
End-diastole volume	1.00	1.00 to 1.01	0.062			
LV ejection fraction	0.98	0.95 to 1.02	0.286			
E/e'	1.04	1.01 to 1.06	0.005	1.04	1.01 to 1.07	0.009
MR (ERO ≥0.2 cm^2)	1.53	0.94 to 2.45	0.085			
Ts−I (>65 ms)	2.92	1.80 to 4.73	0.000	2.37	1.39 to 4.04	0.002

ERO, effective regurgitation orifice area; MR, mitral regurgitation; LV, left ventricular; Ts−I, time difference between the septal and lateral wall.

patients are considered non-responders clinically or based on echocardiographic remodelling.[2 17 18] Therefore, the actual number of patients who benefit from CRT is quite small relative to that of the number of people with heart failure.[10] Mechanical dyssynchrony itself is associated with a poor prognosis in heart failure[19] and has a greater sensitivity in achieving both clinical and echocardiographic benefits than electrical dyssynchrony after CRT in many studies.[8 20–26] Not all studies are consistent with our study. However, most studies have shown that mechanical dyssynchrony is associated with higher risk of cardiac events, independent of the QRS duration and LVEF in heart failure, or even patients undergoing coronary bypass surgery.[27]

The most basic question that remains unanswered is how exactly to define the marker of dyssynchrony and who will be most likely to respond to CRT. Therefore, the need for better selection criteria for CRT and better imaging modalities to assess more precisely dyssynchrony has been emphasised.[8 17] The prognostic value of a prolonged QRS duration has been known for several years. This electrocardiographic evidence of conduction delay has been considered a marker of ventricular dyssynchrony and associated with a higher incidence of cardiac events or mortality.[28 29] It is generally accepted that the QRS duration alone may not effectively characterise mechanical dyssynchrony.[1] We still have a poor understanding of the interaction between mechanical dyssynchrony and electrical delay. TDI analysis showed that mechanical dyssynchrony was present in nearly half of patients with heart failure with normal QRS duration.[30] In this study, electrical and mechanical dyssynchrony were shown in 31.1% and 42.5%. We previously demonstrated that mechanical dyssynchrony predicts cardiac events, even in patients with a normal QRS duration.[19] Although the prognostic power of mechanical dyssynchrony and the QRS duration assessed by χ^2 and AUCs was not different, mechanical dyssynchrony had an additional benefit and was independently associated with cardiac events in patients with systolic heart failure.

The response to CRT is another point of mechanical dyssynchrony because the response is multifactorial, largely dependent on mechanical dyssynchrony and myocardial scar from a prior infarct, inappropriate lead position and suboptimal device programming. Our study was not designed to assess the

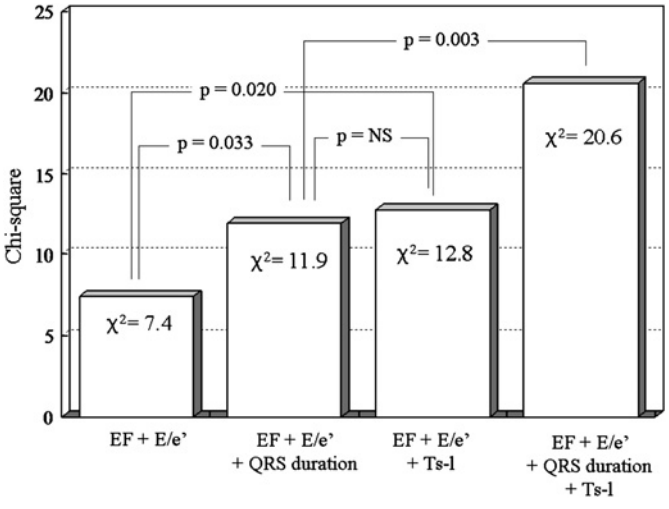

Figure 1 Prognostic power of QRS duration and mechanical dyssynchrony to predict cardiac events. EF, ejection fraction.

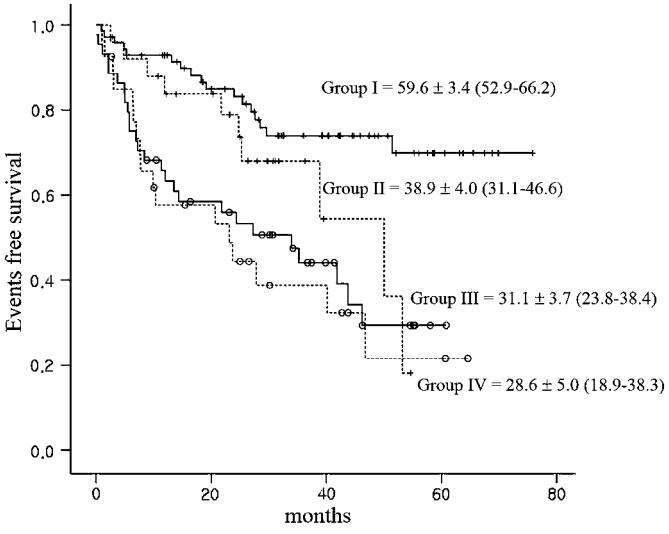

Figure 2 Kaplan–Meier analysis for event free survival. Group I: QRS duration < 120 ms and Ts−I < 65 ms, Group II: QRS duration ≥120 ms and Ts−I <65 ms, Group III: QRS duration <120 ms and Ts−I ≥65 ms, Group IV: QRS duration ≥120 ms and Ts−I ≥65 ms. Data are presented as mean ± SE (CI).

predictive values of dyssynchrony for the response of CRT. Large prospective studies are still needed to determine which parameter of dyssynchrony is best for CRT.

This study has several limitations. The topic is not entirely new. Recent large clinical trials have demonstrated that mechanical dyssynchrony using echocardiography is unsuited for clinical use in CRT selection. In this study, however, echocardiographic techniques in evaluating dyssynchrony are still valuable in predicting adverse events in patients with advanced heart failure. This study is a single-centre, observational study. Furthermore, the number in the study population and the number of patients with hard events was relatively low for identifying various predictors of heart failure.

Competing interests None.

Ethics approval This study was conducted with the approval of the institutional review board of Hallym University.

Provenance and peer review Not commissioned; externally peer reviewed.

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