Chapter 7

Tissue Doppler velocity is superior to strain imaging in predicting long-term cardiovascular events after cardiac resynchronization therapy

Zhang Q, **van Bommel RJ**, Fung JW, Chan JY, Bleeker GB, Ypenburg C, Yip G, Liang YJ, Schalij MJ, Bax JJ, Yu CM

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ABSTRACT

Background: Aim of this study was to examine the predictive value of systolic dyssynchrony measured by tissue Doppler velocity vs. tissue Doppler strain imaging on long-term outcome after cardiac resynchronization therapy (CRT).

Methods: The time to peak systolic velocity during ejection phase (Ts) and the time to peak systolic strain (Tε) were assessed for dyssynchrony, i.e. the maximal delay in Ts and the maximal delay in Tε among the 4 left ventricular basal segments in 239 patients (65±12 years, 76% males) who underwent CRT. Occurrence of cardiovascular end-points between patients with and without dyssynchrony was compared by Kaplan-Meier curves, followed by Cox regression analysis for potential predictor(s).

Results: There were 78 (33%) deaths, with cardiovascular causes in 64 (27%) patients, while 136 (57%) patients were hospitalized for cardiovascular events, including decompensated heart failure in 87 (36%) patients. Patients with the maximal delay in Ts ≥65ms showed a lower event rate for cardiovascular mortality (19% vs. 38%, Log-rank χ^2=7.803, p = 0.005) and other prognostic end-points. In Cox regression analysis, the maximal delay in Ts (HR: 0.463, 95% CI: 0.270-0.792, p = 0.005) and ischemic etiology (HR: 2.716, 95% CI: 1.505-4.901, p = 0.001) were independent predictors of cardiovascular mortality. In contrast, the maximal delay in Tε ≥80 ms failed to predict any cardiovascular event.

Conclusions: Echocardiographic evidence of pre-pacing systolic dyssynchrony measured by TDI velocity, but not TDI strain, predicted lower long-term cardiovascular events after CRT.

INTRODUCTION

It has already been shown in large clinical trials that patients with advanced heart failure, depressed left ventricular (LV) function and wide QRS complex benefit from cardiac resynchronization therapy (CRT). These benefits include improvement in cardiac function, exercise capacity, quality of life and long-term prognosis.[1-5] Despite this, about one-third of patients receiving CRT do not respond when evaluated by composite clinical and/or echocardiographic end-points.[2,6] In the past few years, although the results of studies were not uniform, mechanical dyssynchrony measured by echocardiography, in particular tissue Doppler imaging (TDI) and its post-processing approaches, were shown to be able to predict LV reverse remodeling and other favorable responses after CRT.[7-13] However, the prognostic implication of systolic dyssynchrony in CRT remains unknown when using some hard end-points, such as cardiovascular mortality and/or hospitalization. In the CARE-HF study, there was a trend for a greater reduction of the primary end-point in patients with a higher degree of interventricular mechanical delay (IVMD) at baseline, i.e. death from any cause or an unplanned hospitalization for a major cardiovascular event.[14] In contrast, the pre-existing intraventricular dyssynchrony was suggested to be predictive of death or heart failure hospitalization in 2 small-scaled studies with shorter follow up durations.[12,15] Therefore, the main objectives of the present study were to: 1) investigate the prognostic values of baseline dyssynchrony on major cardiac events during long-term follow up; 2) compare the 2 post-processing modalities of TDI, i.e. velocity vs. strain, for their predictive values of long-term outcome.

METHODS

Patients

The study population consisted of 239 heart failure patients (aged 65±12 years, 76% males) from 2 cardiac centers who received CRT and regular follow-up for at least 3 months. They had comprehensive echocardiographic examination including TDI at baseline while the exclusion rate was about 10% due to inadequate image quality for TDI and/or volumetric analysis. Inclusion criteria for CRT were compatible with current guidelines which included New York Heart Association (NYHA) class III or IV heart failure despite optimal pharmacological therapy, evidence of LV systolic dysfunction (ejection fraction <35%) and QRS duration >120 ms. CRT devices were implanted as previously described.[16] One hundred and eighteen patients (49%) received CRT pacemaker (CRT-P) while the other 121 (51%) had CRT plus defibrillator (CRT-D). The protocol was approved by the Ethics Committees of the 2 institutions and written informed consents were obtained from all patients.

Echocardiography with TDI

Echocardiography with TDI was performed at baseline (Vivid 5 and Vivid 7, Vingmed-General Electric, Horten, Norway). The 2 centers had the same echocardiographic facilities for image acquisition and offline analysis. The LV volumes and ejection fraction were assessed by modified Simpson's rule using the apical 4- and 2-chamber views where the length of the ventricular image was maximized.

Two-dimensional color-coded TDI was performed in the apical 4- and 2-chamber views for offline analysis. Depth, frequency, sector width and angle were adjusted to ensure a higher frame rate (minimally >100frames/sec) and a better wall/segment alignment with Doppler signals. Using different post-processing modalities, myocardial velocity (sampling window: 6x12 mm) or strain (sampling window: 12 mm) curves were reconstituted at basal septal, basal lateral, basal anterior and basal inferior segments (EchoPac PC, version 6.1.0, Vingmed-General Electric, Horten, Norway).

For velocity imaging, the time to peak systolic velocity during ejection phase (Ts), as denoted by aortic valve opening and closure timings, was measured. On the other hand, the time to peak systolic strain (Tε), i.e. maximal negative value throughout the whole cardiac cycle, was measured for strain imaging. Systolic dyssynchrony was computed by the maximal delay in Ts and the maximal delay in Tε among the 4 LV basal segments, as in previous studies.[12,17] The operators who performed the echocardiographic assessment were blinded to the clinical results. Variability analyses were performed by offline reconstitution of myocardial velocity or strain curve rather than repeated calculation on the preloaded curve. For measuring the Ts, the interobserver variability ranged 5-10% while the intraobserver variability was 4-5%. For measuring the Tε, these figures were 13-21% and 10-15%, respectively.

Documentation of cardiovascular events during clinical follow up

All patients were followed up in the heart failure clinics for every 3 months, with documentation on clinical assessment, surface ECG and device interrogation to ensure the maintenance of biventricular pacing. The occurrence of cardiovascular events was adjudicated by 2 cardiologists blinded to echocardiographic and other clinical investigations as well. The causes of death or hospitalization were ascertained by reviewing the clinical records, report of the close relatives and/or post-mortem findings, based on the current guidelines.[18]

Statistical analysis

Unpaired *t*-test or Pearson χ^2 analysis was used where appropriate to compare between the survivors and non-survivors of cardiovascular events, as well as between patients with and without baseline systolic dyssynchrony. Differences in cardiovascular event rate between patients with and without dyssynchrony were compared by Kaplan-Meier survival curves where the Log-rank χ^2 values were presented. Cox regression multivariable survival analysis was used to evaluate potential predictor(s) for cardiovascular mortality. Continuous variables were expressed as mean±SD. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of patients and clinical outcome during long-term follow up

Before device implantation, 208 (87%) patients were in NYHA class III heart failure while the other 31 (13%) were in class IV despite optimal medical therapy. The etiologies of heart failure were ischemic in 131 (55%) and non-ischemic in 108 (45%) patients. The QRS duration on surface ECG was prolonged (148±32ms). Echocardiography showed enlarged LV end-diastolic (212±86cm^3) and end-systolic (162±77cm^3) volume with severely impaired ejection fraction (25.0±8.2%).

The mean duration of follow up after CRT was 37±20 months. There were 78 (33%) deaths, with cardiovascular causes in 64 (27%) patients. The cardiovascular deaths included heart failure in 34 patients, sudden cardiac death in 17, myocardial infarction in 4, cardiogenic shock in 1, ventricular fibrillation in 3, and cerebrovascular accident in 5. Whereas non-cardiac deaths occurred in 14 patients, mainly due to malignancy and infections. During the long-term follow up, 136 (57%) patients were hospitalized for fatal and non-fatal cardiovascular events, which included decompensated heart failure in 87 (36%) patients.

Comparison of baseline characteristics between survivors and non-survivors of cardiovascular events

When clinical and echocardiographic characteristics before CRT were compared between survivors (Group I, n = 175) and non-survivors (Group II, n = 64) of cardiovascular events, there was a significant difference in age (65±12 vs. 68±10 years, p = 0.04) and prevalence of ischemic heart failure (50% vs. 67%, p = 0.016) (Table 1). The QRS duration on the surface

ECG was prolonged in both groups with similar width (147±34 vs. 150±29 ms, p = 0.555). The proportion of CRT-D implant seemed to be higher in Group I than Group II (54% vs. 42%, p = 0.105), though it was not statistically significant. On echocardiography, the maximal delay in Ts was significantly larger in Group I than Group II (76±41 vs. 61±41ms, p = 0.014), whereas no inter-group difference was found in maximal delay in Tε (110±78 vs. 117±93 ms, p = 0.607) (Table 1).

Furthermore, significant systolic dyssynchrony was observed in 60% of the study population, by using a cut-off value of ≥65ms for the maximal delay in Ts as formerly described,[12] which was found in 117 (67%) patients of Group I and 28 (44%) of Group II respectively (χ^2=10.486, p = 0.001). In order to compare tissue Doppler velocity and strain side by side for their predictive values in prognosis after CRT, a cut-off point of the maximal delay in Tε should be defined though no reference value had been found in previous reports. Therefore, the maximal delay in Tε of ≥80 ms was used where 60% of the study population would have shown systolic dyssynchrony. That was similar to the prevalence measured by the maximal delay in Ts criterion. Subsequently, systolic dyssynchrony was noted in 109 (62%) Group I patients and 38 (60%) Group II patients (χ^2=0.078, p = 0.780).

Table 1. Baseline clinical and echocardiographic characteristics of survivors and non-survivors of cardiovascular death after cardiac resynchronization therapy

Parameters	Survivors (n = 175)	Non-survivors (n = 64)	p-value
Age (years)	65 ± 12	68 ± 10	**0.040**
Gender (%)			
Male	75	81	χ^2 = 1.156
Female	25	19	p = 0.282
NYHA class (%)			
III	88	83	χ^2 = 3.087
IV	12	17	p = 0.214
Quality of life score	35 ± 19	37 ± 21	0.585
Etiology of heart failure (%)			
Ischemic	50	67	χ^2 = 5.768
Non-ischemic	50	33	**p = 0.016**
CRT-P	46	58	χ^2 = 2.622
CRT-D	54	42	p = 0.105
LVEDV (cm^3)	211 ± 84	213 ± 92	0.867
LVESV (cm^3)	160 ± 74	167 ± 85	0.563
LV ejection fraction (%)	25.5 ± 7.5	23.5 ± 9.8	0.091
QRS duration (ms)	147 ± 34	150 ± 29	0.555
LV dyssynchrony (ms)			
Maximal delay in Ts	76 ± 41	61 ± 41	**0.014**
Maximal delay in Tε	110 ± 78	117 ± 93	0.607

CRT-D = cardiac resynchronization therapy pacemaker plus defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; Ts = the time to peak systolic velocity; Tε = the time to peak systolic strain

Differences in cardiovascular events between systolic dyssynchrony detected by Ts and Tε

The occurrence of various cardiovascular events during follow up was compared by Kaplan-Meier survival analysis between patients with and without baseline systolic dyssynchrony, based on Ts or Tε (Table 3). Patients with the maximal delay in Ts of ≥65ms showed a better event-free survival than those without dyssynchrony (Ts <65ms), for cardiovascular mortality (19% vs. 38%, Log-rank χ^2=7.803, p = 0.005), cardiovascular hospitalization (p = 0.032), as well as the composite end-point of heart failure hospitalization or cardiovascular mortality (p = 0.037) (Table 3 and Figure 1A). There was no difference in heart failure hospitalization between the 2 groups. On the other hand, patients with baseline dyssynchrony defined by the maximal delay in Tε of ≥80 ms failed to demonstrate a favorable long-term prognosis when compared to those without dyssynchrony, for cardiovascular mortality or other composite end-points (Table 3 and Figure 1B).

Table 2. Comparison of cardiovascular events between patients with and without systolic dyssynchrony defined by tissue Doppler velocity and strain parameters

Cardiovascular events	**Maximal delay in Ts**				**Maximal delay in Tε**			
	<65 ms (n = 94)	*≥65 ms (n = 145)*	*Log-rank χ^2*	*p-value*	*<80 ms (n = 92)*	*≥80 ms (n = 147)*	*Log-rank χ^2*	*p-value*
Cardiovascular mortality	38%	19%	7.803	**0.005**	28%	26%	0.433	0.506
Fatal and non-fatal heart failure hospitalization	42%	34%	1.416	0.234	32%	40%	1.617	0.203
Fatal and non-fatal cardiovascular hospitalization	66%	52%	4.606	**0.032**	50%	62%	5.223	**0.022**
Heart failure hospitalization or cardiovascular mortality	55%	39%	4.330	**0.037**	40%	48%	1.584	0.208

Abbreviations as listed in Table 1

Table 3. Prediction of cardiovascular mortality after cardiac resynchronization therapy using Cox regression multivariate analysis

Parameters	**Cardiovascular mortality**		
	HR	*95% CI*	*p-value*
		Model I	
Maximal delay in Ts (ms)	0.993	0.986-1.000	0.045
Maximal delay in Tε (ms)	0.998	0.994-1.002	0.375
QRS duration (ms)	0.997	0.987-1.007	0.549
Age (years)	1.019	0.993-1.045	0.152
Female gender	0.679	0.329-1.399	0.294
Ischemic etiology	2.696	1.487-4.889	**0.001**
Quality of life score	1.002	0.989-1.015	0.807
LV ejection fraction (%)	0.983	0.951-1.016	0.311
CRT-D	0.672	0.380-1.187	0.171
		Model II	
Maximal delay in Ts ≥65ms	0.463	0.270-0.792	**0.005**
Maximal delay in Tε ≥80 ms	0.739	0.393-1.388	0.347
QRS duration (ms)	0.998	0.987-1.008	0.635
Age (years)	1.021	0.994-1.048	0.127
Female gender	0.674	0.326-1.391	0.286
Ischemic etiology	2.716	1.505-4.901	**0.001**
Quality of life score	0.999	0.987-1.012	0.916
LV ejection fraction (%)	0.981	0.949-1.014	0.260
CRT-D	0.716	0.405-1.266	0.251

Abbreviations as listed in Table 1

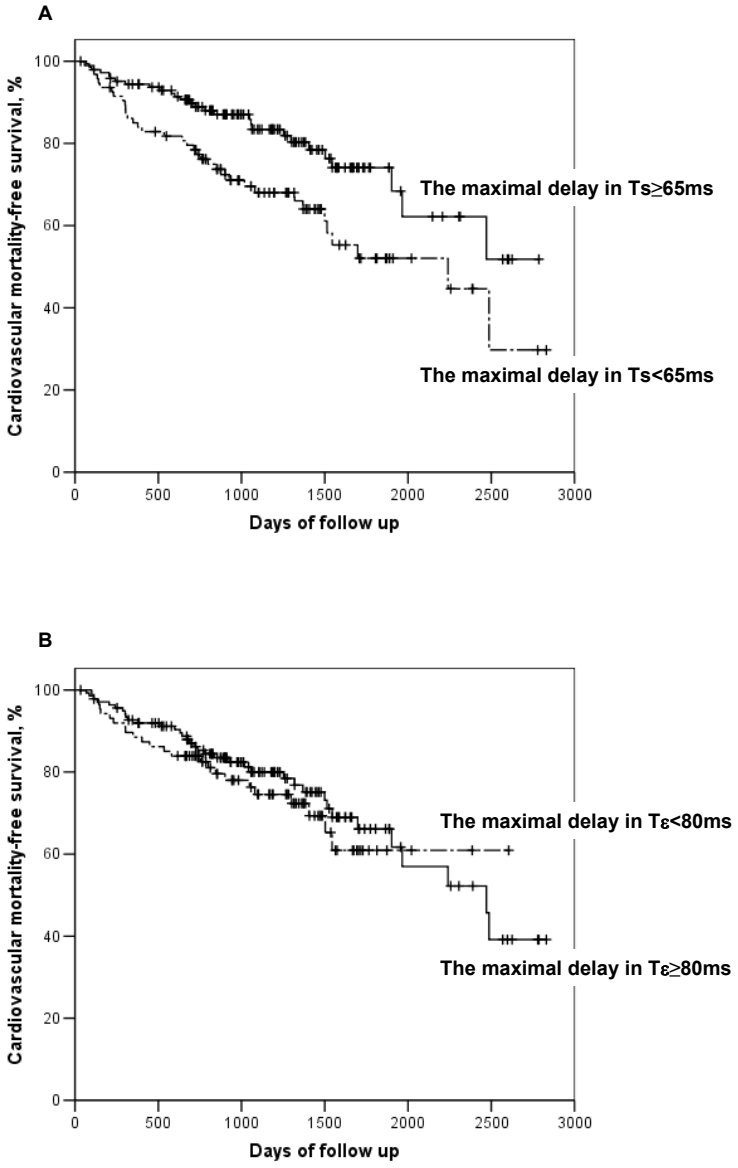

Figure 1. Kaplan-Meier survival curves showing (A) lower cardiovascular mortality in patients with significant systolic dyssynchrony defined by the maximal delay in Ts of ≥65ms; (B) comparable cardiovascular mortality between patients with and without systolic dyssynchrony, as measured by the maximal delay in Tε of ≥80ms.

Tissue Doppler velocity vs. strain imaging in predicting cardiovascular events after CRT

By using Cox regression multivariate analysis to predict cardiovascular mortality after CRT, a group of covariates were selected into the models as shown in Table 3, which included clinical characteristics, conventional echocardiographic parameters, as well as systolic dyssynchrony by velocity and strain analyses. Both the maximal delay in Ts and the maximal delay in Tε, as continuous variables, were included in Model I, whereas the maximal delay in Ts of ≥65ms and the maximal delay in Tε of ≥80 ms were adopted in Model II, when other covariates remained unchanged between the 2 models. The results showed that systolic dyssynchrony measured by the maximal delay in Ts, in the form of either a continuous (HR: 0.993, 95% CI: 0.986-1.000, p = 0.045) or categorical (HR: 0.463, 95% CI: 0.270-0.792, p = 0.005) parameter using 65ms as a cut-off value, was found to be an independent prognosticator of cardiovascular mortality after CRT. On the contrary, its counterpart in Tε, i.e. the maximal delay in Tε itself (HR: 0.998, 95% CI: 0.994-1.002, p = 0.375) or the maximal delay in Tε of ≥80 ms (HR: 0.739, 95% CI: 0.399-1.388, p = 0.347), was unable to predict long-term outcome. In addition, ischemic etiology of heart failure (HR: 2.716, 95% CI: 1.505-4.901, p = 0.001) was another independent predictor of cardiovascular death.

DISCUSSION

This study is the largest with longest duration of follow up to date that illustrated the prognostic value of intraventricular systolic dyssynchrony on clinical outcome after CRT, with data collected from 2 experienced centers on dyssynchrony analysis. Furthermore, the current study compared tissue Doppler velocity and strain parameters of dyssynchrony in the same study population. Patients with significant dyssynchrony at baseline, defined by the maximal delay in Ts of ≥65ms, were associated with significantly lower cardiovascular mortality and occurrence of other composite end-points than those without dyssynchrony when followed up for a mean period of over 3 years. On the contrary, the maximal delay in Tε of ≥80 ms failed to show the beneficial differences between patients with and without dyssynchrony.

Baseline systolic dyssynchrony is associated with better long-term clinical outcome after CRT

Although the benefit of CRT on mortality and hospitalization has been demonstrated in large, multicenter trials, the observation that at least 33% of patients were non-responders prompted further work to identify potential predictors of response.[6,19] Previous studies have

identified pre-pacing factors which correlated with prognosis including NYHA class, etiology of heart failure, systolic blood pressure, LV diameter, mitral regurgitation, interventricular delay as well as N-terminal pro-brain natriuretic peptide (NT-proBNP) level.[14, 20-22] In the CARE-HF study, (with 813 patients randomized to medical therapy or CRT plus medical therapy and followed up for a mean of 29.4 months) ischemic etiology, more severe mitral regurgitation and increased NT-proBNP independently predicted the primary composite end-point, i.e. death or unplanned cardiovascular hospitalization, in heart failure patients irrespective of CRT. In the CRT group, patients with increasing systolic blood pressure or less severe interventricular delay showed less benefit from CRT.[14] Our recent publication observed that cardiovascular mortality and hospitalization after CRT were higher in ischemic patients than non-ischemic patients, implicating the progressive nature of coronary heart disease may lead to worse outcome.[20] Similarly, the INSYNC/INSYNC ICD Italian Registry demonstrated that patients with ischemic cardiomyopathy or NYHA class IV before device implantation had a higher all-cause mortality during 3-year follow up.[21] In addition, patients receiving CRT-D was found to have more survival benefits than those receiving CRT-P in COMPANION study.[5] It is understandable that the CRT-P population would be less protected from sudden cardiac death, though the trend of inferior survival did not reach statistical significance in the current study.

Previous studies observed that baseline systolic dyssynchrony is a useful predictor of early CRT response after treatment for 3-6 months.[7-12,23,24] It has also been demonstrated that intraventricular dyssynchrony was more predictive of response to CRT as compared to interventricular dyssynchrony.[25] However, assessment of intraventricular dyssynchrony is a relatively complex and advanced echocardiographic examination, which is usually excluded in multicenter device studies. Two small, single center studies suggested that the presence of baseline intraventricular dyssynchrony predicted favorable outcome in 60 and 85 patients when followed up for 6 and 14 months, respectively.[12,15] The current study included comprehensive assessment of tissue Doppler velocity and strain parameters of dyssynchrony in a large group of 239 patients for a mean follow up period of more than 3 years, and confirmed the independent predictive value of maximal delay in Ts of ≥65ms on long-term cardiovascular outcome measures including mortality and hospitalization. Therefore, the presence of baseline intraventricular delay by Ts measurement appeared to be helpful to predict long-term cardiovascular outcome, apart from improvement of cardiac function.

It should be acknowledged that systematic training and substantial experience is needed to provide reproducible measurements of systolic dyssynchrony. Such an approach is analogous to the training of experienced electrophysiologists leading to successful implantation of CRT, and a learning curve exists for dyssynchrony analysis similar to for CRT implantation. Indeed, the recently published PROSPECT study reported that pre-pacing dyssynchrony assessment by Doppler echocardiography, M-mode or tissue Doppler imaging had only limited value for predicting 6-month response to CRT.[26] This might mainly be due to suboptimal data acquisition and offline analysis resulting in limited reproducibility of echocardiographic dys-

synchrony results. It appears thus essential to provide substantial training and gain extensive experience on LV dyssynchrony assessment to obtain optimal results.

Systolic dyssynchrony by velocity parameter is superior to strain to predict major cardiac events after CRT

TDI is an advanced echocardiographic technology that has been used for assessment of longitudinal myocardial function and dyssynchrony. Parameters of dyssynchrony derived from velocity and other post-processing modalities, such as strain, strain rate and displacement imaging, have been undergoing continuous exploration to predict responses to CRT. In predicting short-term LV reverse remodeling, the superiority of velocity imaging was established, whereas the role of strain imaging remained controversial.[17,27] However, comparative data on their abilities in predicting long-term cardiovascular outcome were not included in previous reports. The current study has demonstrated that long-axis tissue Doppler velocity, but not strain imaging, predicts long-term cardiovascular outcome after CRT. In current post-processing modalities, tissue Doppler strain technology has a lower signal-to-noise ratio and more angle-dependency than tissue Doppler velocity, which results in a higher variability in measurement of 25%.[28] This problem of low reproducibility would be even worse in dilated and spherically shaped left ventricle (as often encountered in the CRT population), where the angle of incidence of the scan line may not be aligned with the direction of LV shortening.[17] A more recent approach to assess regional strain and dyssynchrony based on the angle-independent 2D speckle-tracking has overcome these issues and appears useful in predicting 6-month response to CRT.[13,29,30] However, the ability of this new technology to predict long-term clinical outcome remains to be determined.

Limitations of the study

Although this study focused on the prognostic value of pre-pacing systolic dyssynchrony measured by TDI modalities as well as other major baseline parameters, it would be more comprehensive to include long-term reverse remodeling and cardiac function data. The good reproducibility of TDI velocity present in this study may lead to an underestimate of the difficulties in dyssynchrony assessment. It was in fact achieved by systematic training and substantial practice in experienced centers.

Conclusion

The current study illustrates that echocardiographic evidence of pre-pacing systolic dyssynchrony measured by tissue Doppler velocity, but not tissue Doppler strain, predicted long-term outcome after CRT.

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