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Echo/Doppler-derived time intervals are able to predict left ventricular reverse remodeling after cardiac resynchronization therapy

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Aim **We evaluated the predictive value of echo/Doppler derived indices, which reflect the duration of the isovolumic phases of the cardiac cycle, in identifying cardiac resynchronization therapy (CRT) responders.**

Methods and results **In 105 patients before and 6 months after CRT the following echo/Doppler parameters were evaluated: myocardial performance index (MPI) as the sum of isovolumic contraction time (IVCT) and isovolumic relaxation time (IVRT) divided by ejection time; total isovolumic time (t-IVT) as the sum of IVCT and IVRT divided by the RR interval; and standard deviation of the time to systolic peak velocity (Ts-SD) as asynchrony index. After 6 months, patients were defined responders according to 15% left ventricle (LV) end-systolic volume reduction or more. At baseline, responders (53.3%) had higher t-IVT and MPI than nonresponders (0.30 ± 0.06 versus 0.22 ± 0.05, $P < 0.0001$ and 1.01 ± 0.27 versus 0.73 ± 0.19, $P < 0.0001$, respectively). Receiving operating characteristic curve analysis showed that both t-IVT (80.3% sensitivity and 83.7% specificity, cut-off = 0.263) and MPI (78.6% sensitivity and 81.6% specificity, cut-off = 0.84) could predict CRT response. Baseline t-IVT correlated well to end-systolic volume reduction ($r = -0.56$, $P < 0.00001$).**

Conclusion **Echo/Doppler derived indices, describing physiologic abnormalities of the isovolumic contraction and relaxation phase, are able to predict CRT-induced reverse remodeling. *J Cardiovasc Med* 11:157–163 © 2010 Italian Federation of Cardiology.**

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Keywords: cardiac resynchronization therapy, isovolumic time, reverse remodeling

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Introduction

Cardiac resynchronization therapy (CRT) is an established therapy in patients with congestive heart failure, low ejection fraction and widened QRS complex. Despite fulfilling the current recommendations [1], 40–50% of patients may not show clinical improvement or left ventricle (LV) reverse remodeling [2–4]. In recent years, several echocardiographic measures of LV dyssynchrony have been proposed as predictors of response to CRT, but, according to the PROSPECT study, none of them can be recommended to improve the patient selection beyond the current guidelines [5]. Moreover, the majority of the proposed echocardiographic techniques require significant operator experience, time-consuming analysis and expensive equipment. Thus, an easier and more effective method for identification of CRT responders is still needed.

The object of CRT is to improve hemodynamics by correcting LV dyssynchrony caused by an altered LV activation. Nonhomogeneous ventricular contraction induced by an altered activation results in decreased rate of rise and fall of ventricular pressure that translates into a prolongation of the total isovolumic periods [6–9]. It has been demonstrated that CRT significantly shortens such isovolumic time, suggesting that improvement of the LV mechanical efficiency is achieved by reducing the ineffective time of cardiac cycle, when the LV is neither ejecting nor filling [10–13].

We hypothesized that the amount of cardiac cycle that is mechanically ineffective, i.e., isovolumic time, could be an effective parameter for simply predicting CRT response.

Methods

Patient selection and study protocol

We prospectively enrolled 108 consecutive patients who underwent biventricular pacing device implantation for chronic heart failure, New York Heart Association (NYHA) class III/IV, ejection fraction 35% or less despite maximum well-tolerated medical therapy and QRS

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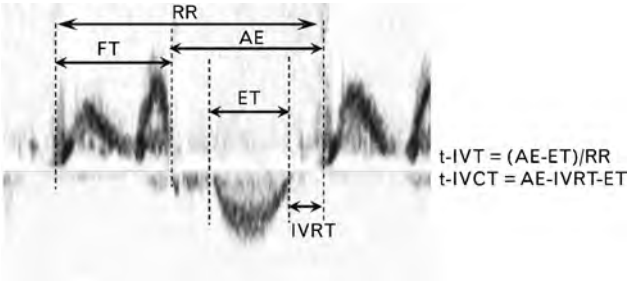
duration 120 ms or more [1]. Exclusion criteria were as follows, atrial fibrillation during preimplant echocardiographic evaluation, previous pacemaker implantation, surgical correctable valvular disease, mechanical or biological prosthetic valve and technically unacceptable echocardiogram. Patients had to remain clinically stable for at least 30 days before enrollment.

Before and 6 months after biventricular pacing device implant, standard and tissue Doppler imaging (TDI) echocardiography were performed, NYHA class and 6-min walking corridor test (WCT) were also evaluated. At the 6-month follow-up, patients were divided into responders or nonresponders according to at least 15% left ventricular end-systolic volume (ESV) reduction [14]. Our institutional review board approved the study and written informed consent was obtained from each patient.

Fig. 1



Schema for measurements of Doppler time intervals. Total isovolumic time (t-IVT) as [(IVCT+IVRT)/RR] was derived by subtracting ejection time from the interval between the cessation and the onset of mitral inflow (AE), divided by RR interval. Isovolumic contraction time (IVCT) was extrapolated by subtracting isovolumic relaxation time (IVRT) and ejection time from AE. AE, interval between the cessation and the onset of mitral inflow; ET, ejection time; FT, filling time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; RR, RR interval.

Biventricular pacemaker implantation

Three transvenous pacing leads were inserted. Right atrial and ventricular leads were positioned conventionally. The left ventricular lead was inserted through either the coronary sinus into the lateral (74 patients) or posterolateral cardiac vein (34 patients). The biventricular devices used were InSync (Medtronic, Inc., Minneapolis, Minnesota, USA) in 66 patients and Contak TR CHFD (Guidant, Inc., St Paul, Minnesota, USA) in 42 patients. The addition of an implantable cardiac defibrillator (ICD) was at the discretion of the physician. Immediately after implantation, the atrioventricular interval was optimized for maximal diastolic filling, by using Doppler echocardiography [15].

Echocardiography

Standard two-dimensional (2D) echo/Doppler and TDI study were performed with patients lying in the left lateral decubitus position, by using a commercially available system (Vivid 7 System; Vingmed-General Electric, Horten, Norway). Left ventricular end-diastolic volumes (EDVs) and ESVs and ejection fraction were calculated using the biplane modified Simpson's rule. The ratio of colour regurgitant jet area to left atrial size in apical four-chamber view was used to define semi-quantitatively the degree of mitral regurgitation [16]. Doppler study included the assessment of transmitral inflow and LV outflow velocities.

For the mitral inflow, the sample volume of pulsed Doppler was placed at the mitral valve tips in the apical four-chamber view. Left ventricular outflow velocity was recorded from the apical long-axis view with the sample volume of pulsed Doppler positioned just below the aortic annulus.

The following time intervals were evaluated as a mean of at least three measurements. Filling time (FT) as the time between the onset of the E wave and the end of the A wave. Ejection time (ET) as the interval between the onset of forward aortic flow and the onset of the aortic valve closure artefact. Isovolumic relaxation time (IVRT), as the interval between the end of aortic flow and the beginning of mitral inflow. Isovolumic contraction time (IVCT), derived by subtracting IVRT and ejection time from the time interval between the cessation and the onset of mitral inflow. All these intervals were corrected by RR interval and expressed as FT_c, ET_c, $IVRT_c$ and $IVCT_c$ respectively. Total isovolumic time of the cardiac cycle (t-IVT) was calculated as IVCT + IVRT/RR. Figure 1 shows the method employed briefly, IVCT + IVRT was extrapolated by subtracting ejection time from the interval between the cessation and the onset of mitral inflow. Myocardial performance index (MPI; IVCT + IVRT/ejection time) was also evaluated, as proposed by Tei *et al.* [17].

TDI was performed with a 2.5 or 3.5 MHz phase array transducer for the long axis motion of the ventricle. At least three consecutive beats were stored, the images were digitized, and computer analyzed offline. Myocardial pulse-Doppler velocity profile signals were reconstituted from the tissue Doppler colour images that provided regional myocardial velocity curves. From the apical four-chamber, two-chamber and long-axis views, a six-basal and six-mid segmental model was obtained in the left ventricle, namely the septal, lateral, anteroseptal, posterior, anterior and inferior segments at both basal and mid levels. The time to systolic peak velocity (Ts) was measured in every segment. For the time to systolic peak velocity, the beginning of the QRS complex was used as the reference point. Standard deviation of time to systolic peak velocity (Ts-SD) was assumed as left ventricular asynchrony index as proposed by Yu *et al.* [18].

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Table 1 Baseline and 6-month follow-up clinical echocardiographic and Doppler parameters in responders and nonresponders

	Responders ($n=56$)			Nonresponders ($n=49$)		
	Baseline	6 months	*P*	Baseline	6 months	*P*
NYHA	3.22 ± 0.48	2.06 ± 0.6	<0.001	3.11 ± 0.47	$2.5 \pm 0.8^{*}$	<0.001
WCT (m)	269.8 ± 156.2	361.7 ± 140.2	<0.01	231.6 ± 185.1	306.1 ± 173.8	0.119
EDV (ml)	204.85 ± 70.02	154.29 ± 56.59	<0.0001	187.26 ± 54.66	$200.09 \pm 65.84^{**}$	<0.01
ESV (ml)	154.50 ± 58.54	101.79 ± 47.46	<0.0001	136.88 ± 43.46	$152.61 \pm 58.49^{**}$	<0.01
EF (%)	25.21 ± 5.81	35.77 ± 8.48	<0.0001	26.60 ± 6.32	$24.63 \pm 7.04^{**}$	0.0600
DT (ms)	199.41 ± 114.67	221.00 ± 85.52	0.1446	197.84 ± 97.53	200.80 ± 81.53	0.8466
E/A	1.54 ± 1.54	1.16 ± 0.77	<0.05	1.29 ± 0.72	1.43 ± 0.99	0.3585
MR	0.27 ± 0.19	0.16 ± 0.13	<0.001	0.22 ± 0.16	0.20 ± 0.14	0.3356

DT, deceleration time of E wave; E/A, peak E wave, peak A wave ratio; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; WCT, 6-min walk corridor test. $^{*}P<0.05$ versus responders. $^{**}P<0.001$ versus responders.

Variations in left ventricular volumes, ejection fraction and filling time from baseline to follow-up were expressed as percentages of the baseline values.

Statistical analysis

Continuous variables are expressed as the mean ± standstandard deviation. Baseline categorical data were compared by means of the χ^2 test. For the comparison of continuous variables the Student's *t*-test for normally distributed paired and unpaired data, and the Mann–Whitney or Wilcoxon test for nonparametric data, when appropriate, were used. Linear regression analysis was used to assess the relationship between the preimplant t-IVT, MPI and changes in ESV, ejection fraction and filling time. Receiving operating characteristics (ROC) curve analysis was used to determine sensitivity and specificity of the prespecified parameters (t-IVT, MPI and Ts-SD) in predicting CRT response. The value corresponding with the highest accuracy (i.e. minimal false-negative and false-positive results) was chosen as the cut-off value. The reliability of the cut-off value was validated by using bootstrap resampling ($n=5000$), 95% confidence intervals (CIs) and estimated standard error are presented. CMDT software (version 1.0 β; Berlin University, Berlin, Germany) was used for the bootstrapping analysis. Sample size for the prospective enrolment was derived considering an area under curve (AUC) for t-IVT of 0.8. This value was derived from a previously studied population [3]. Detection of a significant difference between area under curve of 0.8 and 0.5 required enrolment of at least 54 patients (90% of power given a two-sided α value of 0.05 and a responders/nonresponders ratio of 1 : 1) [3,14,19]. For all tests, a *P*-value less than 0.05 was considered significant.

Results

Among the 108 enrolled patients, one died after 2 months due to abdominal aortic aneurysm rupture, and two did not return to follow-up. Thus, the final analyzed population comprised 105 patients (mean age was 72.3 ± 9.3 years, 20% of patients were in NYHA class IV, 74 were men). The cause of heart failure was ischemic in 54 patients (51.4%) and nonischemic in 51 (48.6%). All patients (100%) received diuretic therapy; 70%, spironolactone; 98%,

Table 2 Doppler derived cardiac cycle intervals in responders and nonresponders at baseline and at follow-up

	Responders ($n=56$)	Nonresponders ($n=49$)	*P* value, responders versus nonresponders
RR (ms)			
Baseline	854.02 ± 145.25	860.27 ± 165.72	0.83
6 months	894.40 ± 108.20	847.22 ± 125.59	0.06
MPI			
Baseline	1.01 ± 0.27	0.73 ± 0.19	<0.0001
6 months	$0.73 \pm 0.24^{**}$	0.74 ± 0.28	0.78
$IVCT_c$			
Baseline	0.16 ± 0.07	0.10 ± 0.05	<0.0001
6 months	$0.07 \pm 0.05^{**}$	$0.08 \pm 0.05^{*}$	0.38
$IVRT_c$			
Baseline	0.14 ± 0.05	0.12 ± 0.04	<0.05
6 months	0.14 ± 0.05	$0.14 \pm 0.06^{*}$	0.87
ET_c			
Baseline	0.30 ± 0.05	0.31 ± 0.05	0.31
6 months	0.30 ± 0.04	0.31 ± 0.04	0.19
FT_c			
Baseline	0.41 ± 0.08	0.45 ± 0.09	0.01
6 months	$0.48 \pm 0.07^{**}$	0.46 ± 0.06	0.21
t-IVT			
Baseline	0.30 ± 0.06	0.22 ± 0.05	<0.0001
6 months	$0.20 \pm 0.07^{**}$	0.21 ± 0.07	0.21

ET_c, ejection time corrected; FT_c, filling time corrected; $IVCT_c$, isovolumic contraction time corrected; $IVRT_c$, isovolumic relaxation time corrected; MPI, myocardial performance index; RR, RR interval; t-IVT, total isovolumic time. $^{*}P<0.05$ versus baseline. $^{**}P<0.0001$ versus baseline.

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angiotensin-converting enzyme (ACE)-inhibitors or angiotensin receptor blockers; 89%, β-blockers; 28%, digoxin; and 20%, amiodarone. At 6-month follow-up, 56 patients (53.3%) were responders according to at least 15% ESV reduction. Percentage of responders was slightly higher in the nonischemic group (55.6%) than in the ischemic group (50.9%, *P* nonsignificant).

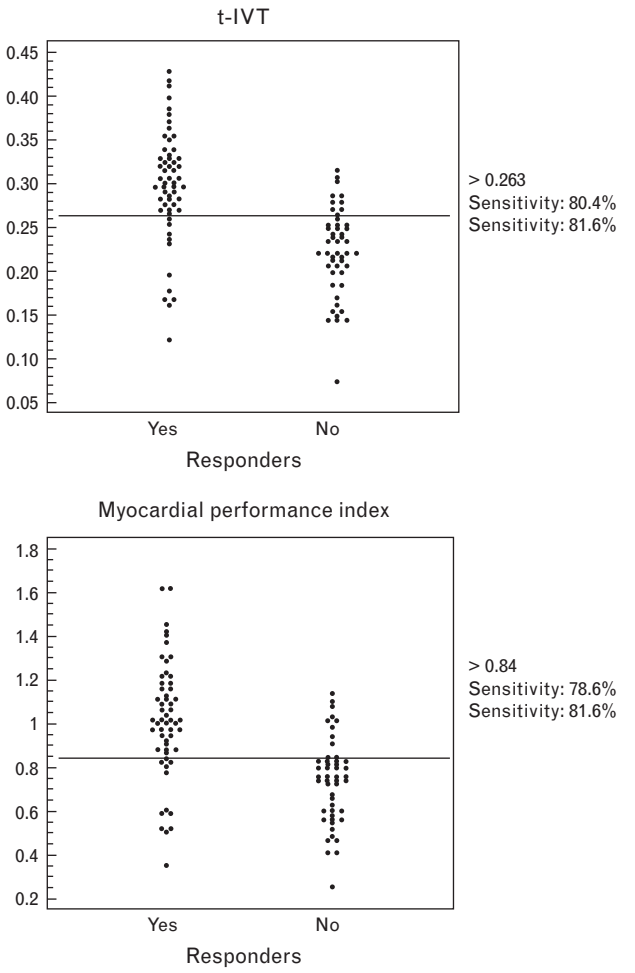
No significant differences were observed between responders and nonresponders in baseline characteristics (sex, age, NYHA class, WCT and medications). Mean QRS duration was 147.4 ± 18.6 ms in responders and 146.9 ± 19.4 ms in nonresponders (*P* nonsignificant). Tables 1 and 2 show clinical, echocardiographic characteristics and Doppler derived measures at baseline and at 6-month follow-up for both responder and nonresponder groups. As compared with nonresponders, patients who responded to CRT had significantly longer $IVCT_c$, $IVRT_c$, shorter FT_c ($P < 0.0001$, $P < 0.05$ and $P = 0.01$, respectively) and significantly higher t-IVT and MPI values ($P < 0.0001$ for both). In responders to CRT the successful reverse remodeling, indicated by the significant reduction of left ventricular volumes ($P < 0.0001$), increase in ejection fraction ($P < 0.0001$) and reduction in mitral regurgitation ($P < 0.001$), was coupled with a significant decrease of $IVCT_c$ ($P < 0.0001$), t-IVT ($P < 0.0001$) and MPI ($P < 0.0001$) and increase of FT_c ($P < 0.0001$) without any changes in $IVRT_c$ and ET_c.

In the nonresponder group, ESV was unchanged in 30 patients (61.2%), and further dilated in the remaining 19 patients (38.8%), ejection fraction, mitral regurgitation, t-IVT, MPI and ET_c were unchanged whereas $IVCT_c$ was reduced and $IVRT_c$ was prolonged ($P < 0.05$ for both). Considering the clinical parameters, NYHA class improved in both responders and nonresponders ($P < 0.001$ for both), whereas WCT performance improved only in responders ($P < 0.01$, Table 1). A more detailed analysis of nonresponder subgroups according to heart failure aetiology, showed that NYHA class showed a significant improvement in both ischemic (3.26 ± 0.45 versus 2.45 ± 0.86, $P < 0.01$) and nonischemic patients (3.25 ± 0.44 versus 2.08 ± 0.83, $P < 0.001$). WCT improved in ischemic nonresponder patients (303.52 ± 119.18 versus 380.65 ± 89.86, $P = 0.01$) and, despite borderline significance, in the nonischemic nonresponder group (330.42 ± 116.17 versus 381.38 ± 117.70, $P = 0.052$). Changes in EDV (-0.21 ± 0.37 versus -0.14 ± 0.42, *P* nonsignificant), ESV (-0.32 ± 0.51 versus -0.28 ± 0.62, *P* nonsignificant) and mitral regurgitation (-0.05 ± 0.16 versus -0.07 ± 0.19, *P* nonsignificant) after CRT were similar in ischemic and nonischemic patients

Prediction of response

The predictive value of t-IVT was assessed by ROC analysis in the overall population and in both the ischemic and the nonischemic group. In the overall population, with an optimal cut-off value of 0.263, t-IVT had 80.4% sensitivity and 81.6% specificity in predicting significant reverse remodeling after CRT (AUC 0.84, 95% CI 0.76–0.90, $P < 0.0001$; Fig. 2).

Fig. 2



Total isovolumic time and myocardial performance index values in responder and nonresponder patients. t-IVT, total isovolumic time.

MPI, with a cut-off of 0.84, had 78.6% of sensitivity and 81.6% of specificity to predict reverse remodeling (AUC 0.81, 95% CI 0.72–0.88, $P < 0.0001$, *P* nonsignificant versus t-IVT; Fig. 2).

Table 3 summarizes the cut-off values with bootstrapped 95% CI in the overall population and in both ischemic and nonischemic groups. In the ischemic patients, maximal sensitivity and specificity was reached with a cut-off of 0.253 (AUC 0.86, 95% CI 0.75–0.96, $P < 0.0001$). In nonischemic patients, the optimal cut-off was slightly higher (0.277) with not significantly different predictive value (AUC 0.84, 95% CI 0.73–0.95, $P < 0.001$; *P* nonsignificant versus ischemic; Fig. 3).

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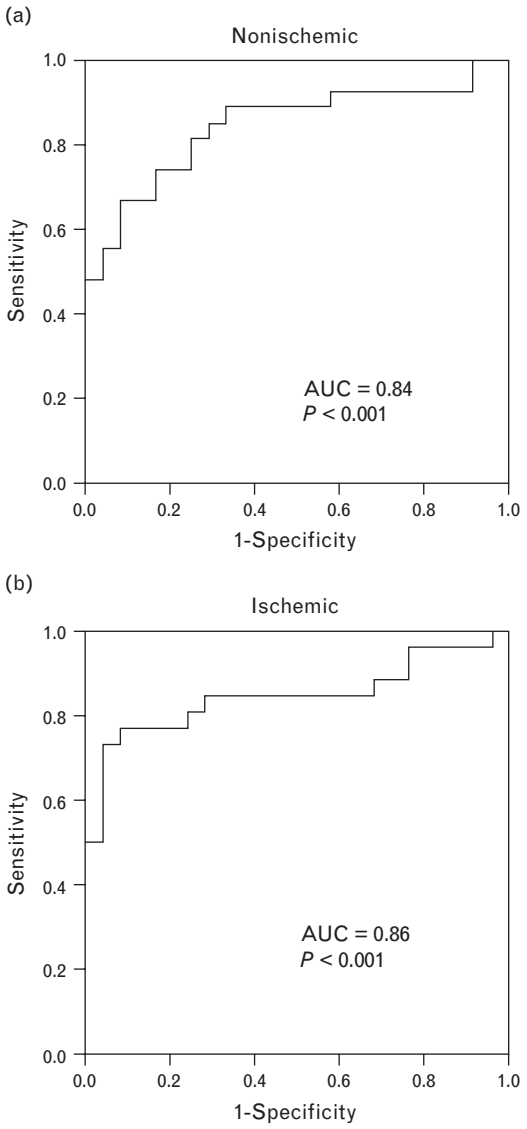
Table 3 Cut-off values, sensitivity and specificity of t-IVT with bootstrapped confidence interval of cut-off

	Cut-off	95% CI by bootstrapping (SE)*	Sensitivity	Specificity
Overall ($n=105$)	0.263	0.255–0.290 (0.008)	80.4	81.6
Ischemic ($n=54$)	0.253	0.230–0.260 (0.008)	75.9	91.7
Nonischemic ($n=51$)	0.277	0.240–0.270 (0.01)	77.8	75

* CIs are bias corrected.

Ts-SD with an optimal cut-off of 32 ms reached 80.8% of sensitivity and 42.2% of specificity (AUC 0.66, 95% CI 0.55–0.75). The AUC of Ts-SD was significantly different from the AUC of both t-IVT and MPI ($P=0.003$ and $P=0.02$ respectively; Fig. 4).

Fig. 3



Receiving operating characteristics curves in nonischemic and ischemic patients (*P* nonsignificant); (a) nonischemic patients, (b) ischemic patients. AUC, area under curve.

The correlation between baseline t-IVT and change in ESV is shown in Fig. 5. Continuous linear relation was observed in the overall population between t-IVT and ESV reduction ($r=-0.56$, $P<0.00001$), ejection fraction increase ($r=0.43$, $P<0.00001$) and filling time prolongation ($r=0.44$, $P<0.001$). These relationships were constant in both ischemic and nonischemic groups.

Relationships between MPI and ESV reduction and ejection fraction improvement were also significant ($r=-0.56$ and $r=0.38$ respectively, $P<0.0001$ for both). Correlation with FT_c prolongation was poorer ($r=0.32$, $P<0.01$).

Reproducibility

The time necessary to calculate t-IVT, as a mean of at least three measurements, was 3 ± 1 min. Reproducibility of t-IVT was assessed in 30 randomly chosen baseline echocardiograms by the Bland–Altman method. The mean $\pm$ standard deviation difference between two expert echocardiographers for t-IVT was 0.002 ± 0.037 ms (95% CI -0.0039 to 0.0074 ms; $r=0.89$).

Discussion

The major findings of our study were that simple indexes, based on time interval measures of cardiac cycle, can predict LV reverse remodeling induced by CRT. These indexes reflect the fraction of cardiac cycle occupied by isovolumic phases when the left ventricle is neither ejecting nor filling.

Since Wiggers [20] in 1926 described the adverse effects induced by anomalous LV activation on mechanical performance, a large number of studies have emphasized the presence of a closed relationship between LV activation, LV mechanical dyssynchrony and LV isovolumic times [6–8]. Abnormal activation, producing mechanical dyssynchrony, decreases peak rates of LV pressure rise and fall, and prolongs isovolumic times. In patients with dilated cardiomyopathies it has been demonstrated that left bundle branch block (LBBB) is associated with increased isovolumic periods and shortened filling time without significant change or shortening of ejection time [21]. CRT principally aims at improving the mechanical dyssynchrony associated with abnormal activation of the failing left ventricle. Changes in time intervals after CRT have been largely described. Consonant with these previous studies [10,22,23], our results show that in responders to LV reverse remodeling, CRT significantly

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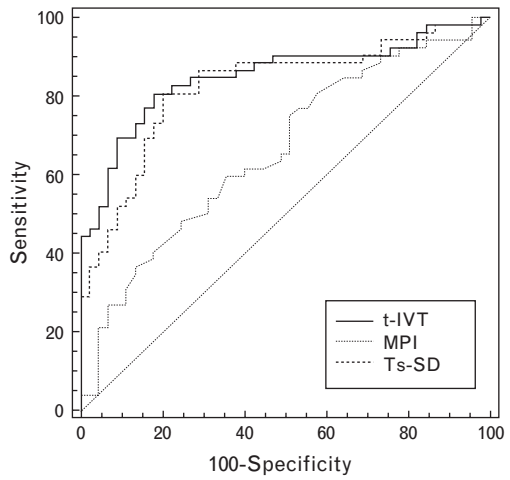
Fig. 4



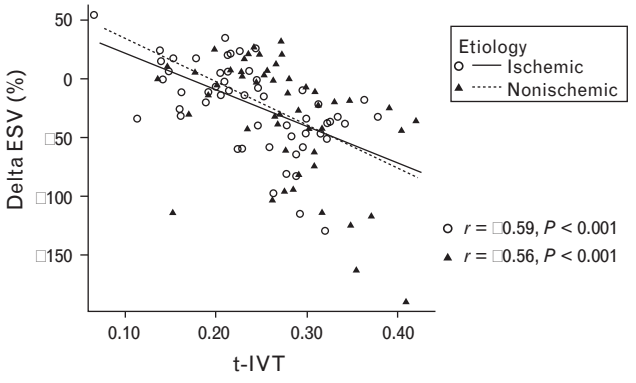
Comparison of receiving operating characteristics curve analysis between standard deviation of the time to the systolic peak velocities, myocardial performance index and total isovolumic time. $P < 0.01$ for t-IVT versus Ts-SD, $P < 0.05$ for MPI versus Ts-SD. MPI, myocardial performance index; t-IVT, total isovolumic time; Ts-SD, time to the systolic peak velocities.

shortens IVCT and lengthens filling time, without significantly changing ejection time. Thus, CRT corrects those alterations in time intervals induced by anomalous electrical activation. This effect precedes LV remodeling and disappears immediately when biventricular pacing is turned off [24].

As t-IVT and MPI reflect the mechanical consequence of altered ventricular activation [9], we hypothesized that high values of these indexes could predict CRT response.

Indeed, our data show that MPI and t-IVT effectively predict reverse remodeling after CRT.

Fig. 5



Scatterplot of change in left ventricular end-systolic volume (delta ESV) as a function of baseline total isovolumic time. ESV, end-systolic volume; t-IVT, total isovolumic time.

The sensitivity and specificity were higher for t-IVT than for MPI. This fits well with the higher sensitivity of t-IVT than MPI in detecting LV altered activation previously shown [9]. Likely, the inclusion of ejection time, which is not significantly influenced by altered activation, in calculation of MPI could be responsible for the lower sensitivity of the latter in predicting CRT response.

ROC curve analysis showed that the area under the curve for both t-IVT and MPI was significantly larger than for Ts-SD, obtained by tissue Doppler imaging, which is currently regarded as the preferred measure of mechanical asynchrony.

Duncan *et al.* [25] have already shown that t-IVT could predict response to CRT in terms of NYHA class reduction and cardiac output gain better than Ts-SD. Recently it has been shown that both gain in peak oxygen uptake (VO_2) and exercise improvement could be predicted by t-IVT [12,13]. Our data support and extend the opinions of these investigators, demonstrating that simple indexes reflecting total isovolumic time are also able to predict CRT response in terms of reverse LV remodeling. Importantly, this effect, rather than clinical improvement, best correlates with long-term survival after cardiac resynchronization therapy [26].

Despite its frequent employment, currently TDI contributes poorly to prediction of CRT responders [5].

Several inherited technical limitations, such as angle dependency, myocardial tethering and cardiac translational movements, could be the reason for the high interobserver variability and poor effectiveness of TDI in predicting CRT response [5].

The recent demonstration that a better prediction can be obtained by combining longitudinal with radial dyssynchrony assessment [27] highlights the three-dimensional (3D) aspect of ventricular dyssynchrony and further complicates the issue of selection of CRT responders. It is possible that the multifaceted nature of asynchrony makes it unlikely for any single parameter to reliably predict CRT response.

As isovolumic times of the cardiac cycle represent the final common pathway of the overall LV ventricular dyssynchrony, irrespective of its nature and of its spatial characteristics, MPI and t-IVT can predict CRT response, overcoming both the methodological difficulties and the need for sophisticated techniques. A second level of imaging techniques, such as magnetic resonance imaging, speckle tracking and 3D echo, might be reserved for those patients with a high probability of response in whom the assessment of scar and localization of the most delayed LV segment could offer a better gain of response.

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Our findings have important practical implications because, by the simple measurement of echo/Doppler time intervals, it is possible to select CRT responders with a diffusible, reproducible and highly cost-effective technique.

Limitations

Our study shows that t-IVT and MPI are effective predictors of response to CRT in both ischemic and nonischemic patients. However, in the ischemic population, we did not perform nuclear magnetic resonance for detection of scar areas, the burden of which can affect the response to CRT [28,29]. However, very recently Jansen *et al.* [30] demonstrated that LV dyssynchrony remains the most important determinant of response to CRT, even in the presence of postero-lateral scar. Moreover, we found that indexes reflecting isovolumic time could also predict CRT response in an ischemic patient. This is likely because isovolumic time reflects the global rather than the regional LV dyssynchrony.

The follow-up, limited to 6 months, could be another limitation. A more extended follow-up could confirm and strongly support the relevance of our method.

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