Archives of Cardiovascular Disease (2015) **108**, 617—625

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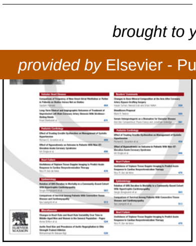

CLINICAL RESEARCH

Electrocardiographic correlates of mechanical dyssynchrony in recipients of cardiac resynchronization therapy devices

Corrélations électromécaniques chez les patients insuffisants cardiaques éligibles à la resynchronisation cardiaque

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Received 15 December 2014; received in revised form 17 June 2015; accepted 18 June 2015
Available online 20 October 2015

KEYWORDS
Heart failure;
Cardiac resynchronization;
Electromechanical dyssynchrony

Summary

Background. — The relationship between electrical and mechanical indices of cardiac dyssynchronization in systolic heart failure (HF) remains poorly understood.

Objectives. — We examined retrospectively this relationship by using the daily practice tools in cardiology in recipients of cardiac resynchronization therapy (CRT) systems.

Methods. — We studied 119 consecutive patients in sinus rhythm and QRS $\geq$ 120 ms (mean: 160 $\pm$ 17 ms) undergoing CRT device implantation. P wave duration, PR, $_{e}$PR (end of P wave to QRS onset), QT, RR—QT, JT and QRS axis and morphology were putative predictors of atrioventricular (diastolic filling time [DFT]/RR), interventricular mechanical dyssynchrony (IVMD) and left intraventricular mechanical dyssynchrony (left ventricular pre-ejection interval [PEI]

Abbreviations: AV, atrioventricular; CI, confidence interval; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; IVMD, interventricular mechanical dyssynchrony; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; LVPEI, left ventricular pre-ejection interval; RV, right ventricular.

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http://dx.doi.org/10.1016/j.acvd.2015.06.007
1875-2136/

and other measures) assessed by transthoracic echocardiography (TTE). Correlations between TTE and electrocardiographic measurements were examined by linear regression.

Results. — Statistically significant but relatively weak correlations were found between heart rate ($r = -0.5$), JT ($r = 0.3$), QT ($r = 0.3$), RR—QT intervals ($r = 0.5$) and DFT/RR, though not with PR and QRS intervals. Weak correlations were found between: (a) QRS ($r = 0.3$) and QT interval ($r = 0.3$) and (b) IVMD > 40 ms; and between (a) ${}_{e}$PR ($r = -0.2$), QRS ($r = 0.4$), QT interval ($r = 0.3$) and (b) LVPEI, though not with other indices of intraventricular dyssynchrony.

Conclusions. — The correlations between electrical and the evaluated mechanical indices of cardiac dyssynchrony were generally weak in heart failure candidates for CRT. These data may help to explain the discordance between electrocardiographic and echocardiographic criteria of ventricular dyssynchrony in predicting the effect of CRT.

MOTS CLÉS
Insuffisance cardiaque ;
Resynchronisation cardiaque ;
Corrélations électromécaniques

Résumé

Introduction. — Les corrélations électromécaniques sont peu connues chez les patients présentant une insuffisance cardiaque avec dysfonction ventriculaire gauche. L'objectif de cette étude est d'essayer de mieux comprendre les relations entre l'activation électrique et l'asynchronisme mécanique dans cette population.

Patients et méthodes. — Cent dix-neuf patients insuffisants cardiaques ayant une indication classique de resynchronisation ont été inclus dans cette étude rétrospective. Les asynchronismes atrioventriculaire (DFT/RR), interventriculaire (IVMD) et intraventriculaire (délai préejectionnel VG [LVPEI] et d'autres mesures) ont été évalués en échographie transthoracique. La fréquence cardiaque, la durée de l'onde p, les intervalles PR, P′R (entre la fin de l'onde p et le début du QRS), RR—QT, JT, QT, QRS, l'axe et la morphologie des QRS ont été définis comme des critères prédictifs possibles de l'asynchronisme mécanique. Les corrélations entre les paramètres échographiques et les mesures électriques ont été analysées sous forme de régressions linéaires.

Résultats. — On observe une corrélation significative entre la fréquence cardiaque ($r = 0{,}50$), le JT ($r = 0{,}40$), le QT ($r = 0{,}30$), l'intervalle RR—QT ($r = 0{,}0$) et le ratio DFT/RR ; cette relation n'est pas observée pour les intervalles PR et QRS. Une corrélation significative mais faible est observée entre les intervalles (a) QRS ($r = 0{,}24$) et QT ($r = 0{,}24$) et (b) IVMD > 40 ms, et entre les intervalles (a) ePR ($r = 0{,}24$), QRS ($r = 0{,}30$), QT ($r = 0{,}24$) et (b) LVPEI. On ne retrouve pas de corrélations significatives avec les autres paramètres d'asynchronisme intraventriculaire gauche.

Conclusion. — Les corrélations électromécaniques sont globalement faibles dans cette population. Ces observations peuvent nous amener à nous poser, d'une part, la question de la validité des critères échographiques utilisés actuellement pour caractériser l'asynchronisme mécanique et, d'autre part, peuvent laisser penser que l'effet bénéfique de la resynchronisation est multifactoriel et ne résulte pas seulement de la correction des anomalies mécaniques.

Background

Cardiac resynchronization is an important means of managing heart failure for patients presenting with a wide QRS complex and a left ventricular ejection fraction (LVEF) < 35%, who remain in New York Heart Association functional classes II—IV despite an optimal pharmaceutical regimen. Cardiac resynchronization therapy (CRT) alleviates symptoms and lowers major heart failure morbidity, all-cause mortality and the risk of sudden death [1—5]. Electrical dyssynchrony on surface electrocardiogram (ECG), manifest in the QRS morphology (left bundle branch block [LBBB] pattern) and duration, is a strong predictor of clinical outcome after CRT [6]. Current guidelines recommend basing patient selection on electrical dyssynchrony criteria [6].

In the past 10 years, several echocardiographic indices of mechanical dyssynchrony have been proposed to prospectively identify responders to therapy. Despite the promising results of observational studies from single centres, most echocardiographic measurements made in large multicentre non-randomized [7] or randomized [8] trials, including analyses by core laboratories, have failed to predict the effect of CRT. In the recent EchoCRT study, the therapy failed to reduce the rates of death from any cause and first hospitalization for management of heart failure in patients presenting with a QRS ≤ 130 ms but echocardiographic signs of left ventricular (LV) dyssynchrony [8]. This discordance between electrical and mechanical dyssynchrony in patients with heart failure remains unexplained, although the attempts made thus far to find electromechanical correlations have been suboptimal.

The aim of the present study was to revisit and try to better understand the relationship between electrical activation and mechanical dyssynchrony in the left heart of heart failure patients who are candidates for CRT, by using the daily practice tools in clinical cardiology (i.e. 12-lead surface ECG and Doppler echocardiography). CRT response was not considered in this study.

Methods

Consecutive patients scheduled to undergo implantation of CRT systems at the Rennes University Medical Centre between March 2009 and March 2012 were retrospectively included in this study. The inclusion criteria were: New York Heart Association functional classes II—IV despite optimal medical therapy; LVEF $\leq$ 35%; stable sinus rhythm; QRS duration $\geq$ 120 ms on 12-lead ECG; and no previous pacemaker or cardioverter defibrillator implantation. The heart disease was considered ischaemic if > 50% stenosis was observed in at least one major epicardial coronary artery or if the patient had a history of myocardial infarction or coronary revascularization.

All patients granted their informed consent to participate in the study, which was reviewed and approved by our institutional ethics review committee.

Electrocardiography

Before CRT implantation, standard 12-lead ECGs were recorded at 25 mm/s paper speed and calibrated at 1.0 mV/cm before recording of the echocardiogram. The method used for ECG analysis has been reported [9]. Heart rate, P wave duration, PR interval, $_e$PR interval (end of P wave to onset of QRS), QRS duration, QT interval, JT interval (end of QRS to onset of T wave) and RR cycle minus QT interval (as a measure of electrical diastole) [10] were measured, and the QRS morphology and axis were analysed. The frontal plane QRS axis was considered normal when between -30° and $+90^\circ$, left deviated when beyond -30°, and right deviated when beyond $+90^\circ$. LBBB was defined as a QRS duration $\geq$ 120 ms, with a broad R wave in leads I, aV_L, V_5 and V_6 and an R peak time > 60 ms in leads V_5 and V_6, according to the practice guidelines issued by major professional societies [11]. Other intraventricular conduction disturbances were classified as right bundle branch block or non-specific intraventricular conduction delays. The intra- and interobserver reproducibility of the measurements were ascertained by comparing the analysis of 20 randomly selected ECGs by two experts unaware of each other's interpretation.

Transthoracic echocardiography

All patients underwent resting two-dimensional Doppler and speckle-tracking transthoracic echocardiography before CRT device implantation, using Vivid 7 or Vivid E9 ultrasound instrumentation (General Electric Medical Systems, Horten, Norway), according to a standardized protocol for image acquisition. LV end-systolic and end-diastolic diameters were measured in the parasternal long-axis view with M-mode; LV volumes indexed to body surface area and LVEF were measured in apical four- and two-chamber views using the biplane Simpson's method [12].

The septal and lateral mitral annular peak systolic velocities were measured from the apical four-chamber view using tissue Doppler imaging. LV strain was analysed by speckle-tracking echocardiography using the four-chamber and mid-LV short-axis views. Images were acquired at end-expiration and analysed off line, using the dedicated automated imaging function of the EchoPAC BT12® software package (GE Healthcare, Chalfont St Giles, UK). We used the echocardiographic indices of mechanical dyssynchrony previously published by Gorcsan et al. [13], and measured according to the recommendations of the American Society of Echocardiography and the Heart Rhythm Society.

Definitions

The diastolic filling time (DFT)/RR interval ratio was used to characterize atrioventricular (AV) dyssynchrony in the left heart. AV dyssynchrony was defined as DFT/RR < 40% [14].

Interventricular mechanical dyssynchrony (IVMD), calculated as the time difference between right ventricular (RV) and LV ejection at the onset of pulsed Doppler flow velocities in the LV and RV outflow tracts, respectively, was used to characterize interventricular dyssynchrony. Interventricular dyssynchrony was defined as IVMD > 40 ms [3,15].

LV pre-ejection interval (LVPEI), the delay between the onset of QRS and the beginning of LV ejection flow by Doppler imaging, was used to characterize left intraventricular dyssynchrony. Intraventricular dyssynchrony was defined as LVPEI > 140 ms [14].

Intraventricular longitudinal dyssynchrony was defined as the maximum delay between opposing septum-to-posterior wall, in colour-coded tissue Doppler imaging in the apical long-axis view, or by the maximum delay between opposing septum-to-posterior wall in speckle-tracking longitudinal strain imaging, in the apical long-axis view [16,17].

Intraventricular radial dyssynchrony was defined as the delay between opposing anteroseptal-to-posterior wall in the mid-LV short-axis view in speckle-tracking radial strain imaging [18,19].

The intrinsic intra- and interobserver reproducibilities of intraventricular dyssynchrony measured by longitudinal strain were ascertained from corresponding repeated measurements, using intraclass correlations. The intra- and interobserver reproducibilities were evaluated by a second measurement of 20 randomly selected transthoracic echocardiograms. The intra- and interobserver reproducibilities of other echocardiography measurements are already known [7,8].

Statistical analysis

A descriptive analysis of pertinent patient characteristics is expressed as means ± standard deviations or counts and percentages, unless specified otherwise. Correlations between indices of mechanical dyssynchrony and electrocardiographic measurements used Spearman's correlation coefficients (and 95% confidence intervals [CIs] through Fisher's Z transformation) and linear regression estimates. 'Good' correlation was considered when the *r* coefficient was ≥ 0.50. Categorical variables were compared between groups using Fisher's exact test, while continuous variables were compared using the non-parametric Kruskall—Wallis test. A multivariable regression analysis included covariates emerging at a $P \leq 0.05$ statistical level in the univariate analysis; we estimated a squared semi-partial coefficient, which represents the proportion of variance in y that is explained by x_1 only. Functional forms of continuous covariates were assessed graphically and statistically, using non-parametric regression and the PROC GAM smoothing technique (SAS Institute, Cary, NC, USA). A two-sided *P* value < 0.05 was considered statistically significant. The data were analysed with the SAS® software package, version 9.3 (SAS Institute, Cary, NC, USA).

Results

The study sample consisted of 119 patients; their baseline demographic, clinical, electrocardiographic and echocardiographic characteristics are presented in Table 1. The disease aetiology was ischaemic in one-third of patients. Over 90% of patients were treated with a beta-blocker and an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker at the highest tolerated doses.

The intra-and interobserver reproducibilities of the intraclass correlations of electrocardiographic intervals and echocardiographic measurements of anteroseptal-posterior delay by two-dimensional strain imaging are shown in Table 2.

'Atrioventricular' dyssynchrony

We studied the correlations between (a) electrocardiographic measurements (expressed as continuous variables), QRS morphology and QRS axis (expressed as qualitative variables) and (b) AV mechanical dyssynchrony (analysed as a continuous variable). We found no correlations between DFT/RR and P wave duration, PR interval, $_e$PR interval, QRS width, QRS morphology or QRS axis. We did, however, find correlations between DFT/RR and heart rate ($P < 0.0001$; $r = -0.5$, 95% CI −0.6 to −0.3), DFT/RR and JT interval ($P = 0.0006$; $r = 0.3$, 95% CI 0.1 to 0.5), DFT/RR and QT interval ($P = 0.0003$; $r = 0.3$, 95% CI 0.1 to 0.5) and DFT/RR and RR—QT interval ($P < 0.0001$; $r = 0.5$, 95% CI 0.3 to 0.6), by univariate analysis (Fig. 1).

We also studied the correlations between (a) electrocardiographic measurements (expressed as continuous variables) and (b) AV mechanical dyssynchrony (analysed as a binary variable) (DFT/RR < 40%; Yes or No). We found no correlations between AV mechanical dyssynchrony and P wave duration, PR interval, $_e$PR interval, QRS width or QRS axis. However, by univariate analysis, correlations were found between DFT/RR < 40% and heart rate ($P < 0.001$), DFT/RR < 40% and JT interval ($P = 0.0036$) and DFT/RR < 40% and QT interval ($P < 0.001$) (Fig. 1).

By multivariable analysis, including all correlates identified by univariate analysis, JT interval ($P = 0.03$) and QT interval ($P = 0.02$) remained independent correlates of DFT/RR (Table 3).

Table 1 Baseline characteristics of 119 study participants.

Characteristic	
Age (years)	64 ± 10
Men	81 (68)
NYHA functional class	2.8 ± 0.4
Ischaemic cardiomyopathy	39 (32)
Distance covered in 6-minute walk (m) (*n* = 62)	400 ± 96
N-terminal B-type natriuretic peptide (pg/mL) (*n* = 89)	2154 ± 2300 [107—13,000]
Drug regimen	
Beta-blocker (*n* = 107)	103 (94.5)
ACE inhibitor or ARB (*n* = 107)	101 (93)
Electrocardiogram	
Heart rate (beats per minute)	66 ± 12
P wave duration (ms)	111 ± 28
PR interval (ms)	202 ± 4
$_e$PR interval (ms)	90 ± 50
QRS duration (ms)	160 ± 17 [130—200]
QT interval (ms)	450 ± 37
JT interval (ms)	289 ± 36
RR—QT interval (ms)	470 ± 188
LBBB	101 (85)
QRS axis within normal range	61 (51)
Transthoracic echocardiogram	
LVEF (%)	26.6 ± 0.6
LV end-diastolic diameter, mm	67.8 ± 8.2
DFT/RR	0.44 ± 0.11
DFT/RR < 0.4	41 (35)
Interventricular mechanical delay (ms)	42 ± 24
Interventricular mechanical delay > 40 ms	54 (45)
LVPEI (ms)	137 ± 35
LVPEI > 140 ms	58 (47)
Septal-lateral delay by Doppler tissue imaging (ms)	97 ± 85
Septal-lateral delay by two-dimensional strain (ms)	240 ± 129
Anteroseptal-posterior delay by two-dimensional strain (ms)	158 ± 131
Overlap	15 (13)
Septal flash	40 (34)

Data are expressed as mean ± standard deviation [interquartile range] or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker; DFT: diastolic filling time; $_e$PR interval: end of P wave to onset of QRS; JT interval: end of QRS to onset of T wave; LBBB: left bundle branch block; LV: left ventricular; LVEF: left ventricular ejection fraction; LVPEI: left ventricular pre-ejection interval; NYHA: New York Heart Association.

Interventricular dyssynchrony

We examined the correlations between (a) electrocardiographic measurements (expressed as continuous variables),

Table 2 Intra- and interobserver reproducibilities of analysis of 20 electrocardiograms and 20 echocardiographic speckle-tracking longitudinal strain recordings.

	Intraobserver	Coefficient of variation	Interobserver	Coefficient of variation
Electrocardiograms				
P wave duration	0.95	1%	0.94	2%
PR interval	0.99	0.2%	0.99	0.7%
QRS duration	0.89	0.6%	0.94	2%
QT interval	0.96	0.5%	0.98	1%
Heart rate	0.99	0.9%	0.99	1%
Echocardiograms				
Septum-to-posterior wall delay	0.88	4%	0.64	12%

QRS morphology and QRS axis (expressed as qualitative variables) and (b) IVMD (analysed as a continuous variable). We found no correlations between interventricular dyssynchrony and heart rate, P wave duration, PR interval, $_{e}$PR interval, JT interval, RR—QT interval, QRS morphology or QRS axis. Weak correlations were found between IVMD and QRS duration ($P = 0.0035$; $r = 0.3$, 95% CI 0.1 to 0.4) and IVMD and QT interval ($P = 0.0015$; $r = 0.3$, 95% CI 0.1 to 0.4).

We also examined the correlations between (a) electrocardiographic measurements (analysed as continuous variables) and (b) interventricular dyssynchrony (analysed as a binary variable) (IVMD > 40 ms: Yes or No). No correlation was found between IVMD > 40 ms and heart rate, P wave duration, PR interval, $_{e}$PR interval, JT interval, RR—QT interval, QRS morphology or QRS axis. We did, however, find correlations between IVMD > 40 ms and QRS duration ($P < 0.0001$) and IVMD > 40 ms and QT interval ($P = 0.0006$), by univariate analysis.

By multivariable analysis, including all correlates identified in the univariate analysis, QRS duration ($P = 0.003$) and QT interval ($P = 0.04$) emerged as independent correlates of IVMD (Table 4).

Left intraventricular dyssynchrony

Finally, we examined the correlations between (a) electrocardiographic measurements (analysed as continuous variables), QRS morphology and axis (expressed as qualitative variables) and (b) echocardiographic indices of left intraventricular mechanical dyssynchrony, including LVPEI > 140 ms (analysed as a qualitative variable) and measures of left intraventricular longitudinal dyssynchrony (by colour-coded tissue Doppler or speckle-tracking longitudinal strain imaging) and left intraventricular radial dyssynchrony (by speckle-tracking radial strain imaging) (both analysed as continuous variables). Correlations were found between LVPEI and $_{e}$PR interval ($P = 0.02$; $r = -0.2$, 95% CI −0.4 to −0.03), LVPEI and QRS duration ($P < 0.0001$; $r = 0.4$, 95% CI 0.2 to 0.5) and LVPEI and QT interval ($P = 0.001$; $r = 0.3$, 95% CI 0.1 to 0.4); between LVPEI > 140 ms and $_{e}$PR interval ($P = 0.02$), LVPEI > 140 ms and QRS duration ($P = 0.0003$) and LVPEI > 140 ms and QT interval ($P = 0.01$); and between QRS morphology and left intraventricular longitudinal dyssynchrony by speckle-tracking longitudinal strain imaging ($P = 0.0004$). Patients with a typical LBBB pattern had the greatest longitudinal dyssynchrony.

By multivariable analysis, QRS duration ($P = 0.0002$) and $_{e}$PR interval ($P = 0.006$) were independent correlates of LVPEI (Table 5).

No significant correlation was found between ECG and qualitative indices of mechanical dyssynchrony, overlap and septal flash in particular.

Discussion

The main observation made in this retrospective study was the weak correlation observed between measurements of

Table 3 Electromechanical correlates: atrioventricular dyssynchrony; diastolic filling time/RR.

	Univariate analysis		Multivariable analysis	
	r	P	Type I semi-partial r^2	P
P wave duration		0.59		
PR interval		0.14		
$_{e}$PR interval		0.30		
QRS duration		0.24		
JT interval	0.3	0.0006	0.13	0.03
QT interval	0.3	0.0003	0.16	0.02
RR—QT interval	0.5	< 0.0001		
LBBB		0.66		
QRS axis		0.44		
Heart rate	−0.5	< 0.001		

$_{e}$PR interval: end of P wave to onset of QRS; JT interval: end of QRS to onset of T wave; LBBB: left bundle branch block.

Table 4 Electromechanical correlates: interventricular dyssynchrony (interventricular mechanical dyssynchrony).

	Univariate analysis		Multivariable analysis	
	r	*P*	Type I semi-partial r^2	*P*
P wave duration		0.57		
PR interval		0.91		
$_e$PR interval		0.61		
QRS duration	0.3	0.0035	0.05	0.003
JT interval		0.70		
QT interval	0.3	0.0015	0.04	0.04
RR—QT interval		0.13		
LBBB		0.11		
QRS axis		0.97		
Heart rate		0.27		

$_e$PR interval: end of P wave to onset of QRS; JT interval: end of QRS to onset of T wave; LBBB: left bundle branch block.

Table 5 Electromechanical correlates: intraventricular dyssynchrony (left ventricular pre-ejection interval).

	Univariate analysis		Multivariable analysis	
	r	*P*	Type I semi-partial r^2	*P*
P wave duration		0.26		
PR interval				
$_e$PR interval	−0.2	0.02	0.06	0.006
QRS duration	0.4	< 0.0001	0.10	0.0002
JT interval		0.55		
QT interval	0.3	0.001		
RR—QT interval		0.29		
LBBB		0.33		
QRS axis		0.08		
Heart rate		0.73		

$_e$PR interval: end of P wave to onset of QRS; JT interval: end of QRS to onset of T wave; LBBB: left bundle branch block.

mechanical versus electrical dyssynchrony, suggesting that the validity of echocardiographic measurements currently applied needs to be reconsidered, and questioning our understanding of differences between mechanical and electrical dyssynchrony.

Several teams — Xiao et al. in particular [20,21] — have investigated the nature of ventricular activation and its relationship with mechanical events in patients with dilated cardiomyopathy. In the present study, we revisited electromechanical correlations, using new echocardiographic measures of mechanical dyssynchrony.

Our results challenge the validity of the echocardiographic criteria currently applied to define mechanical dyssynchrony, particularly with respect to AV dyssynchrony, defined by Cazeau et al. as a mismatch between the end of atrial systole and the onset of ventricular systole, caused by a prolongation of the QRS complex, the PR interval, or both [14]. This mismatch is usually characterized by the DFT/RR ratio, with a 40% cut-off value. Besides the characterization of mechanical dyssynchrony, this index is also used to optimize AV synchrony in standard dual-chamber pacing and in CRT, either manually or automatically [22,23]. Our study detected no correlations between this index and the electrical time intervals in the atria (P wave duration), between the atria and the ventricles (PR and $_e$PR intervals), and in the ventricles (QRS duration). The only correlations we found were with heart rate, with RR—QT considered to reflect the ventricular electrical diastole [10], and, by multivariable analysis, with the QT and JT intervals, which are highly influenced by heart rate. The correlation found between the QT interval and DFT is congruent, given the linear relationship between DFT and the RR—QT interval on the one hand, and the linear relationship between the QT and RR—QT intervals on the other. Ultimately, the best electrical estimation of mechanical diastole in our study was the RR—QT interval, with a correlation approaching 0.8 (Fig. 2) [10,24]. While an increase in diastolic time is physiologically noteworthy, it is probably an oversimplification to consider that a DFT/RR ratio < 40% reflects mechanical AV dyssynchrony [14]. Consequently, the DFT/RR ratio is a poor reflection of AV dyssynchrony, and should not be used alone to assess AV dyssynchrony in the left heart.

As patient selection for CRT was not the purpose of our study, we did not assess the value of multiparametric approaches, which have been shown to slightly improve the sensitivity and specificity, but not the diagnostic

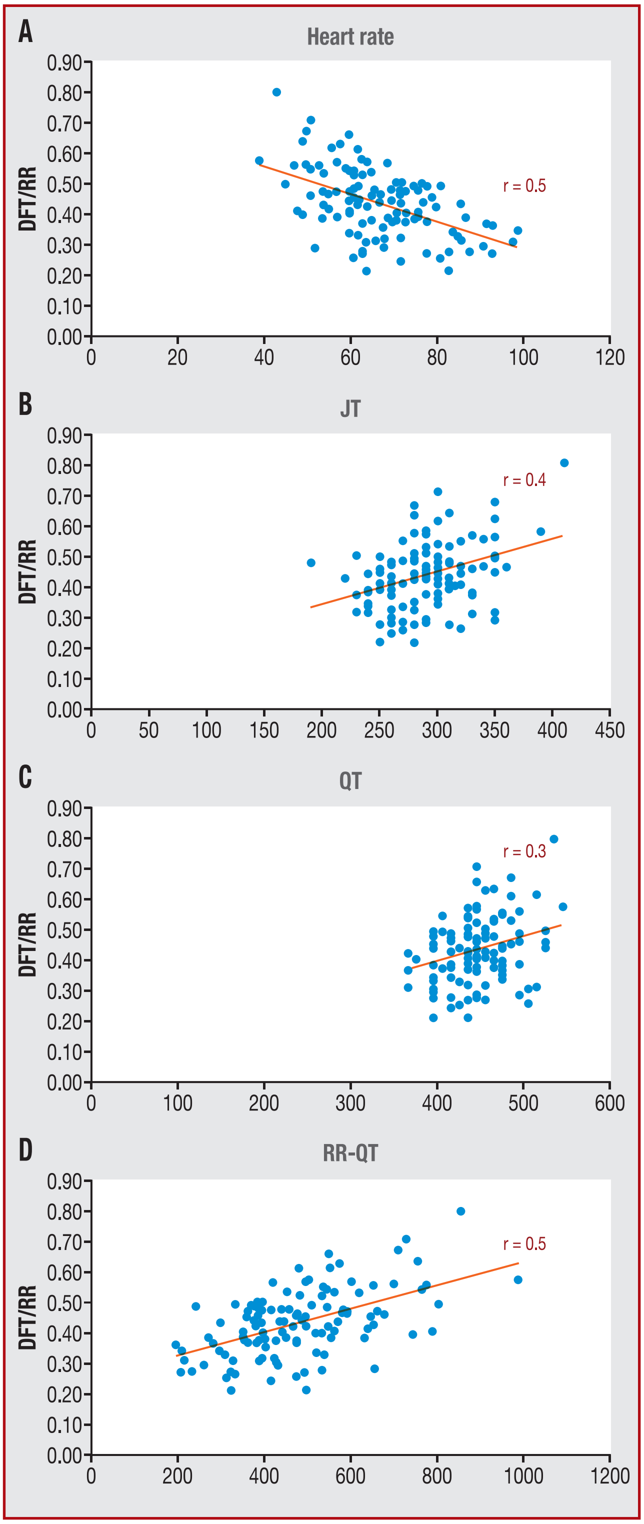

Figure 1. Correlations were observed between (A) DFT/RR and QT interval, (B) DFT/RR and JT interval, (C) DFT/RR and heart rate and (D) DFT/RR and RR–QT. DFT: diastolic filling time.

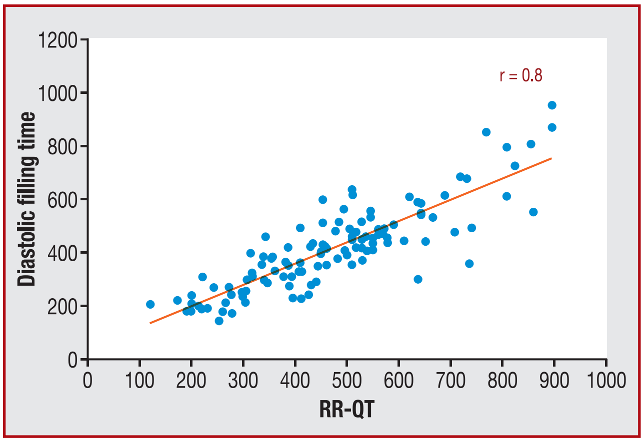

Figure 2. RR–QT was a close electrical correlate of mechanical diastole. The correlation coefficient was 0.8.

accuracy of Doppler echocardiography for selecting potential responders [25]. However, parallel to the limitations of conventional Doppler echocardiography techniques for assessing mechanical dyssynchrony, the value of surface ECGs, and particularly QRS analysis, in the assessment of electrical activation can also be questioned. Correlations between surface ECG and endocardial or epicardial electrical mapping are suboptimal. Using endocardial mapping in CRT candidates, Auricchio et al. [26] showed that a surface ECG was unable to predict the location and extent of specific ventricular delays; the authors showed that patients with LBBB morphology had a specific 'U-shaped' activation sequence that turns around the apex and the inferior wall of the left ventricle. This activation pattern is generated by a functional line of block that is oriented from the base toward the apex of the left ventricle [26]. In a similar way, Ploux et al. showed that ventricular electrical uncoupling measured by noninvasive epicardial mapping predicted the clinical response to CRT better than QRS duration or the presence of LBBB [27].

The absence of strong correlations between electrical and mechanical dyssynchrony raises questions regarding the validity of the basic premise of CRT. The original goal was a mitigation of mechanical dyssynchrony between the right and left ventricles, with a view to improving pump function. A wide QRS was initially considered to reflect mechanical dyssynchrony [28]. In our study, interventricular dyssynchrony, defined as an IVMD > 40 ms, was correlated with QRS and QT interval duration, the latter being strongly influenced by the correlation with the QRS complex. Ultimately, LVPEI was the intraventricular index of dyssynchrony most closely correlated with QRS duration and PR interval on the surface ECG. The other indices of intraventricular mechanical dyssynchrony, including recent ones, such as strain, were not correlated with the electrocardiographic variables that we examined, except longitudinal strain, which was correlated with QRS morphology by univariate analysis. However, these observations must be interpreted cautiously given the relatively low reproducibility of the strain measurements. Similar observations were made with Doppler tissue imaging in the PROSPECT study [7], contrasting with the high reproducibility of standard Doppler indices, such as LVPEI.

These weak correlations suggest that QRS does not solely reflect mechanical dyssynchrony. In fact, QRS width and, more broadly, electrical dyssynchrony are probably the sum of several inputs, which include, in particular, morphological and mechanical factors, the interaction between left and right ventricle [29] and histologic changes, such as fibrosis. For the time being, the quantification of mechanical dyssynchrony involves various measurements, and each considered individually does not allow other factors participating in the haemodynamic alteration to be accounted for. The correction of all or part of the mechanical abnormalities is, therefore, associated with an unidentified multifactorial phenomenon, which explains the therapeutic effects of CRT observed when the patients are selected on the basis of electrocardiographic criteria. Tentatively explaining this phenomenon, Prinzen et al. observed, in an animal study, a higher recruitment of myocardial fibres when stimulating the left ventricle than when stimulating the RV apex [30]. A greater recruitment of healthy tissue could also be one explanation for the beneficial effects of triple site ventricular resynchronization compared with biventricular resynchronization. Finally, in a recent study, Lumens et al. confirmed the importance of the interaction between the left and right ventricles in the response to CRT [29]. All of these plausible explanations should be taken into consideration when explaining all of the beneficial effects of CRT, besides the correction of mechanical dyssynchrony.

Study limitations: besides its retrospective design, the main limitation of this study was its highly homogeneous sample population, consisting of patients with a class I indication for CRT, with electrocardiographic characteristics typical of this population (i.e. > 85% LBBB, very wide QRS complexes and long PR intervals). Consequently, our observations apply only to patients presenting with heart failure and a class I indication for CRT; they do not apply to the general population of patients presenting with heart failure, with or without LV systolic dysfunction. An identical study should, therefore, be conducted in a non-selected population.

Conclusion

The weak electromechanical correlation observed in this study suggests that the validity of our current criteria for mechanical dyssynchrony is poor and that new tools have to be developed.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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