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CLINICAL RESEARCH

Revisiting diastolic filling time as mechanistic insight for response to cardiac resynchronization therapy

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Aims Intraventricular dyssynchrony and commonly associated prolonged atrioventricular conduction both reduce diastolic filling time (DFT), which can be improved by cardiac resynchronization therapy (CRT). Our aim was to investigate whether change in DFT corrected for RR interval (DFT_C) after CRT might serve to assess the mechanistic response to CRT.

Methods and results Echocardiography data of consecutive patients in sinus rhythm ($n = 91$) were studied before and 6 months after implantation. Mortality and heart failure hospitalization data were collected. Patients with vs. without DFT_C increase after 6 months were compared. The programmed atrioventricular delay, percentage of biventricular pacing, and change in PR interval were similar in both groups. DFT_C increase after 6 months reflected favourable reverse left ventricular remodelling and was significantly associated with freedom from death or heart failure admission ($P = 0.008$). In multivariate analysis including guideline criteria for CRT (i.e. QRS width, presence of left bundle branch block, and ejection fraction), interventricular mechanical delay, and Tei index, baseline DFT_C was the strongest predictor of adverse outcome. Notably, while patients with impaired relaxation had a large and highly significant reduction in all-cause mortality and heart failure admissions when DFT_C increased [hazard ratio (HR), 95% confidence interval (CI) = 0.24, 0.08–0.73; $P = 0.012$], this benefit was less pronounced and did not reach statistical significance in patients with pseudonormal or restrictive filling (HR, 95% CI = 0.64, 0.23–1.77; $P = 0.388$).

Conclusion DFT_C increase after CRT reflects favourable reverse remodelling and is associated with better clinical outcome.

Keywords Cardiac resynchronization therapy • Diastolic filling time • Heart failure • Outcome • Reverse remodelling

Introduction

Cardiac resynchronization therapy (CRT) restores the coordination of contraction and relaxation among the cardiac chambers, which leads to reverse remodelling, improved exercise tolerance, less heart failure admissions, and decreased mortality in patients with heart failure, reduced ejection fraction, and evidence of ventricular conduction delay, under optimal medical therapy.[1–5] However, with current selection criteria for CRT, up to one-third of patients may not experience any improvement in terms of reverse remodelling and/or clinical status. Multiple echocardiographic indices of mechanical systolic dyssynchrony have been proposed to better predict CRT response, but they often rely on difficult, off-line techniques, which are time-consuming, have poor reproducibility in less experienced hands, and therefore are not adopted in routine clinical practice.[6–8]

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What's new?

- An increase in diastolic filling time relative to RR interval after cardiac resynchronization therapy reflects favourable reverse left ventricular remodelling and is associated with better clinical outcome.
- Long diastolic filling time before implantation is associated with worse response to cardiac resynchronization therapy.
- Adding a parameter for diastolic dyssynchrony to current selection criteria for cardiac resynchronization therapy might improve response rates.

From a physiological point of view, diastolic filling might be interesting to assess the mechanistic response to CRT.[9] Transmitral pulsed-wave Doppler (PWD) analysis is easy, highly reproducible, and together with other Doppler parameters provides information on left ventricular relaxation, stiffness, and filling pressure.[10,11] Importantly, intraventricular mechanical dyssynchrony and commonly associated prolonged atrioventricular (AV) conduction both result in a shorter diastolic filling time (DFT), which can be corrected by CRT.[9] The former impedes ventricular relaxation during early diastole, while the latter often results in superposition of the late diastolic filling phase on the early filling (i.e. 'fusion'). Even before the CRT era, DDD pacing with short AV delay has been demonstrated to beneficially influence reverse ventricular remodelling and clinical status in selected patients with short DFT and refractory heart failure.[12–14] Furthermore, ventricular remodelling and improvements in left ventricular systolic function after CRT are correlated with improvements in left ventricular filling.[15,16] Therefore, we hypothesized that increased DFT corrected for RR interval (DFTc) after 6 months of CRT would reflect reverse remodelling and would be associated with better clinical outcome.

Methods

Study design

In a retrospective, exploratory design, we studied all CRT patients implanted between October 2008 and April 2011 in a single tertiary care centre (Ziekenhuis Oost-Limburg, Genk, Belgium). Patients needed to be in sinus rhythm and to have complete echocardiography data before implantation. Patients had a left ventricular ejection fraction (LVEF) $\leq$35%, QRS duration $\geq$120 ms, and were in New York Heart Association (NYHA) functional class II–IV despite optimal medical treatment, consistent with current guideline recommendations for CRT.[17] All patients underwent a multidisciplinary CRT optimization protocol after implantation, as previously described by our group.[18,19] Briefly, patients received echocardiography-guided AV optimization, based on the transmitral PWD signal, which was repeated afterwards with each visit at our dedicated CRT clinic. The standard VV interval was programmed at 0 ms and was only changed if the interventricular mechanical delay (IVMD), measured by echocardiography, remained >40 ms. Patients received a first follow-up appointment 6 weeks after implantation, a second one after 6 months, with subsequent follow-up intervals at the discretion of the treating physician. The study complied with the Declaration of Helsinki. Our locally appointed ethics committee approved the research protocol and waived the need for informed consent, as this was a retrospective, observational study. The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and agreed to the report as written.

Baseline characteristics and echocardiography measurements

Demographics, clinical data, and medical therapy at the time of implantation were obtained for all patients by searching the electronic health record of the hospital. The percentage of biventricular pacing, as well as programmed AV intervals, QRS width, and PR interval were collected after 6 months. Comprehensive two-dimensional echocardiography exams were performed with a commercially available system (Philips Healthcare, iE33®) by experienced cardiac sonographers at the time of device implantation and after 6 months of follow-up. Images were acquired in the left lateral decubitus position, triggered to QRS complex, and digitally stored in cine loops in DICOM format. All reported echocardiography measurements were averaged from three consecutive cycles and assessed as recommended by the American Society of Echocardiography.[20]

Left atrial diameter, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD), were measured from the parasternal long-axis view. Left ventricular ejection fraction was obtained by Teichholz method or Simpson's biplane formula if volumetric measurements were available. Diastolic function was assessed in a standardized manner by use of the transmitral PWD signal and the isovolumetric contraction and relaxation time.[10,11] Diastolic dysfunction (DDF) was then categorized as grade 1 (impaired relaxation), grade 2 (pseudonormal filling), or grade 3 (restrictive filling). Mitral and tricuspid valve regurgitation were assessed by colour Doppler flow mapping.[21] Right ventricular systolic pressure was calculated from the maximal continuous wave Doppler velocity if tricuspid valve regurgitation was measurable. The IVMD was measured as the difference between the start of left and right ventricular ejection on the electrocardiographically triggered PWD signal through the left and right ventricular outflow tract, respectively.[22] Tei index was calculated as isovolumetric contraction plus relaxation time divided by ejection time.[23,24] Diastolic filling time was measured from the start of the E-wave to the end of the A-wave on the transmitral PWD signal obtained at the coaptation point of the mitral valve leaflets and divided by the RR interval duration to correct for the length of the cardiac cycle. Resulting DFT_C was expressed as percentage and used for all subsequent analyses. Intra-observer and inter-observer variability for DFT_C were 2 and 3%, respectively, when stored images were read by two experienced cardiac imaging specialists.

Echocardiography and clinical endpoints

Reverse left ventricular remodelling was assessed by measuring the changes in LVEDD and LVESD after 6 months. Patients with DFT_C increase $\geq$1% were compared with subjects with no change or a decrease (*Figures 1* and *2*). As the cut-off for a clinically meaningful increase in DFT_C remains yet undetermined, we chose the 1% cut-off for its simplicity. We repeated the analyses, however, using a 2 or 3% cut-off (the upper limit of intra-observer and inter-observer variability for DFT_C, respectively). The pre-specified clinical endpoint was time to a composite endpoint of all-cause mortality or first hospitalization for heart failure (defined as a hospital admission because of signs or symptoms of low cardiac output or congestion warranting treatment with parenteral drugs). Data were censored at 31 October 2011, yielding at least 6 months of follow-up for every patient.

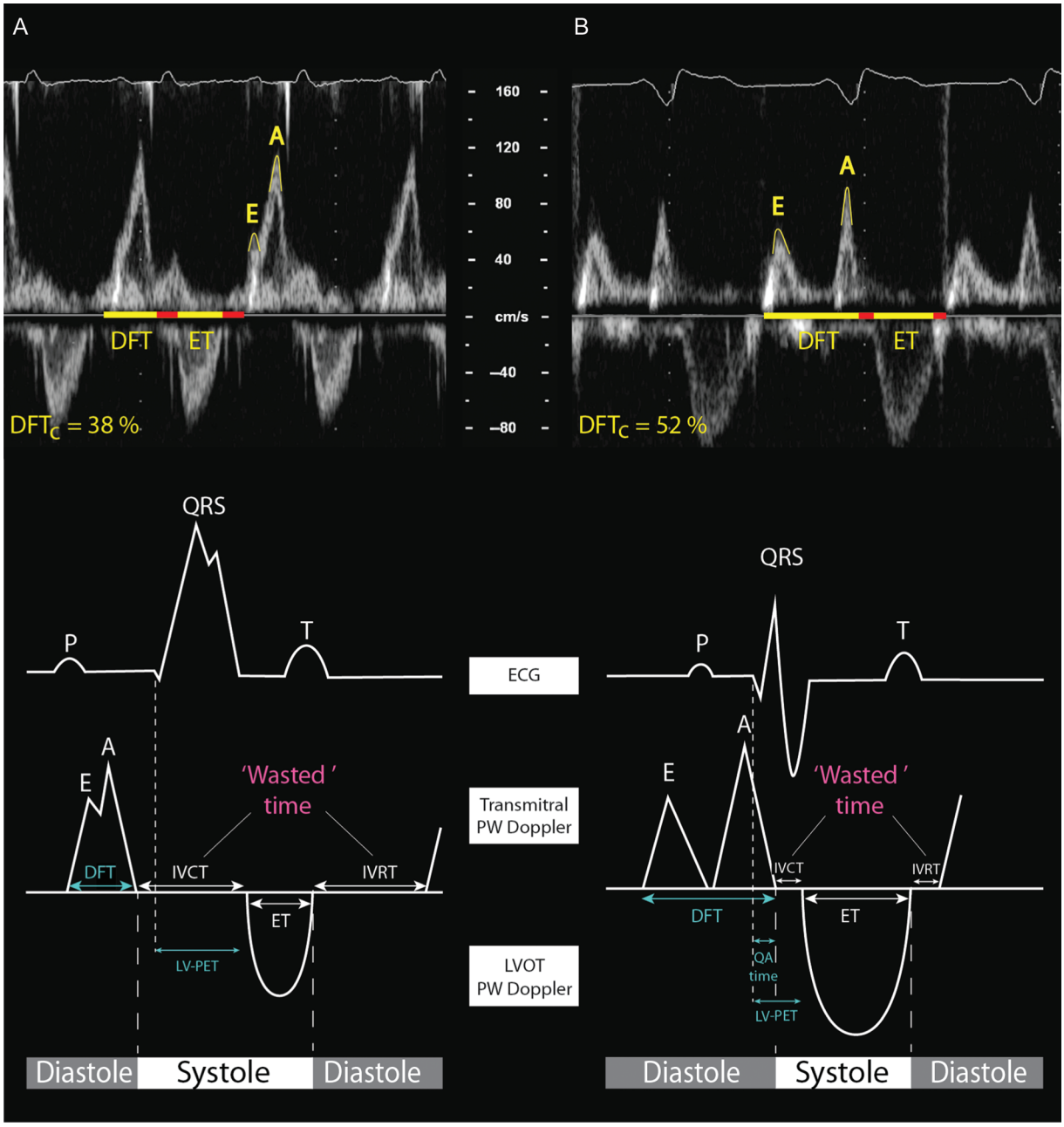

Figure 1 A typical patient with DFT$_C$ increase after CRT. (*A*) There is an obvious diastolic component of dyssynchrony before CRT, as illustrated by the short DFT and E–A fusion on the transmitral pulsed-wave (PW) Doppler signal. Importantly, left ventricular pre-ejection time (LV-PET) is long and left ventricular filling ends well before the onset of the QRS complex. Isovolumetric contraction time (IVCT) and relaxation time (IVRT) are long with much 'wasted time', defined as intrinsic cardiac work without blood displacement. (*B*) After 6 months of CRT, there is a nice separation of E- and A-wave on the transmitral PW Doppler signal, which corresponds to a longer DFT. PR interval and LV-PET are shorter. Importantly, left ventricular filling now continues even after the start of the QRS complex (QA time). IVCT and IVRT are short with less 'wasted time', while ejection time (ET) is also prolonged. Note that the absolute velocity–time integral of left ventricular filling as well as ejection is increased after CRT, as a surrogate for higher stroke volume.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), if normally distributed, or otherwise by median and interquartile range. Normality was assessed by the Shapiro–Wilk statistic. Data were compared by the Student's *t*-test or Mann–Whitney *U* test, when appropriate. Categorical data were expressed as percentages and compared with Fisher's exact test or the Pearson χ^2 test in case of a non-binary response. Correlations were described by using Spearman's ρ. Statistical significance was set at a two-tailed

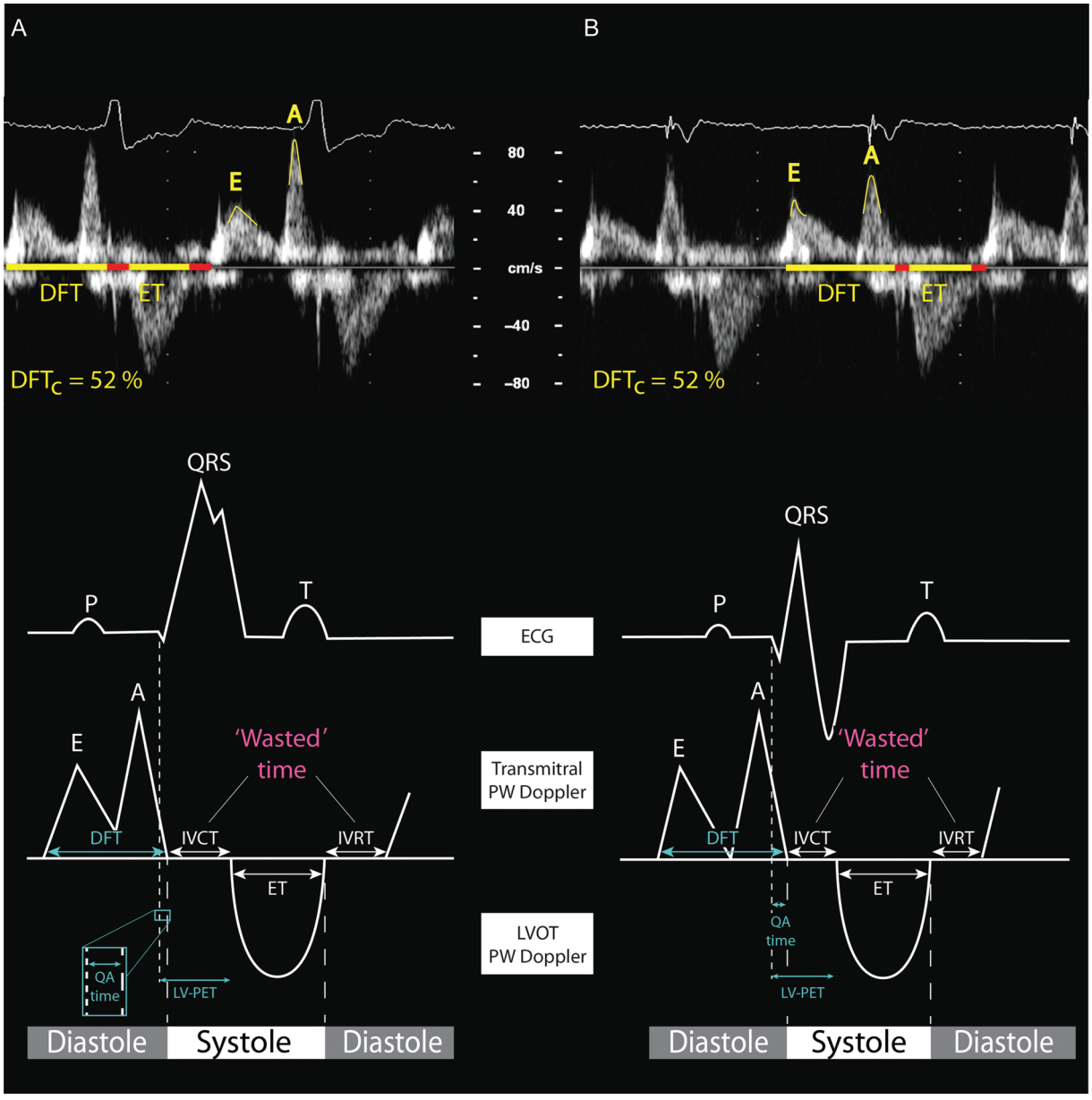

Figure 2 A typical patient without DFT$_C$ increase after CRT. (*A*) Diastolic dyssynchrony is not obvious before CRT, as illustrated by the fairly long DFT and separated E- and A-waves on the transmitral pulsed-wave (PW) Doppler signal. Left ventricular pre-ejection time (LV-PET) is rather short and left ventricular filling ends right after the beginning of the QRS complex (minimal QA time). Isovolumetric contraction time (IVCT) and relaxation time (IVRT) are relatively short, indicating only a limited amount of 'wasted time'. (*B*) After 6 months of CRT, diastolic filling has not changed much. There is still a nice separation of E- and A-wave on the transmitral PW Doppler signal. Diastolic filling time corrected for RR interval is equally long with only a small increase in QA time. IVCT and IVRT are only slightly shorter, while no clear benefit on ejection time (ET) is observed. Note that the absolute velocity–time integral of left ventricular filling as well as ejection is almost identical before and after CRT.

probability level of <0.05. Cumulative, actuarial survival rates were calculated according to the Kaplan–Meier method with the log-rank test used for comparisons between groups. The Cox proportional hazards model was used to calculate hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs). All statistics were performed using (IBM® SPSS®, New Orchard Road, Armonk, New York, USA) (version 20.0) for Windows.

Results

Baseline characteristics of the study population

A study flowchart is presented in *Figure 3*. Baseline characteristics of the study population are summarized in *Table 1*. Baseline DFT was

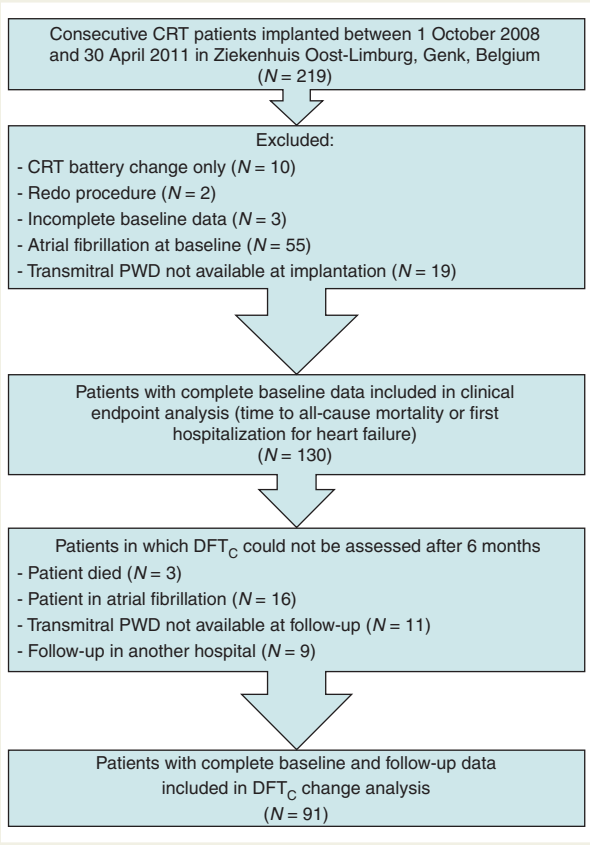

Figure 3 Study flowchart.

393 ± 159 ms overall. When corrected for RR interval, baseline DFT_C was 42 ± 11%. Ejection time corrected for RR interval was 31 ± 5%, while isovolumetric contraction and relaxation made up the remaining 27 ± 10% of the cardiac cycle.

Diastolic filling time corrected for RR interval change and reverse remodelling response

After 6 months of CRT, 61 patients demonstrated a ≥1% increase of DFT_C compared with baseline (mean ± SD = +13 ± 9%). In 30 other patients DFT_C did not change or even decreased (mean ± SD = −8 ± 7%). Compared with patients without DFT_C increase, subjects with an increase had a significantly higher heart rate (71 vs. 62 b.p.m.; $P = 0.003$), lower LVEF (27 vs. 32%; $P = 0.017$), and more intraventricular dyssynchrony assessed by Tei index (1.00 vs. 0.65; $P = 0.001$) at baseline. The sensed and paced AV intervals were programmed at 101 ± 24 and 125 ± 26 ms, respectively, with similar settings in both groups. The percentage of biventricular pacing was 100% (99–100%) in both groups. Only patients with increased DFT_C had favourable reverse left ventricular remodelling reflected by a significant decrease in LVEDD and LVESD (*Figure 4*). Moreover, the improvement in LVEF 6 months after CRT was significantly greater in the group with an increase in DFT_C (+15 ± 14 vs. +7 ± 13% in the group without increase, $P = 0.018$). Electrocardiography and echocardiography measurements at baseline compared with 6 months are presented in *Table 2*. Neither QRS width, PR interval nor IVMD differed at baseline or at follow-up between patients with or without DFT_C increase. Patients with increased DFT_C had

Table 1 Baseline characteristics of the study population (*n* = 91)

Age (years)	71 ± 9
Gender (%)	
Male	67
Female	33
QRS width (ms)	155 ± 25
Typical left bundle branch block (%)	84
Ischaemic aetiology for heart failure (%)	56
NYHA functional class (%)	
II	32
III	61
IV	7
VO_2max (mL/kg/min)	14.4 ± 5.0
Blood pressure (mmHg)	
Systolic	120 (110–129)
Diastolic	70 (65–80)
Heart rate	68 ± 14
Diabetes mellitus (%)	24
COPD (%)	32
eGFR (mL/min/1.73m^2)	65 ± 22
LVEF (%)	28 ± 9
LVEDD (cm)	6.6 ± 1.0
LVESD (cm)	5.7 ± 1.1
Left atrial diameter (cm)	4.2 ± 0.8
Diastolic dysfunction (%)	
Grade 1—impaired relaxation	59
Grade 2—pseudonormal filling	16
Grade 3—restrictive filling	25
RVSP (mmHg)	25 (25–35)
Mitral valve regurgitation (/4)	1 (0.5–1.5)
Tricuspid valve regurgitation (/4)	0.5 (0.5–1)
Tei index	0.85 (0.62–1.11)
Interventricular mechanical delay (ms)	40 ± 29
Pharmacological treatment	
ACE-I or ARB (%)	85
β-Blocker (%)	96
Aldosterone antagonist (%)	71
Loop diuretic (%)	46
Digoxin (%)	11
Amiodarone (%)	18
Antiplatelet agent (%)	66
Anticoagulation therapy (%)	23
Statin (%)	66

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate by the MDRD formula; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; VO_2max, maximal aerobic capacity.

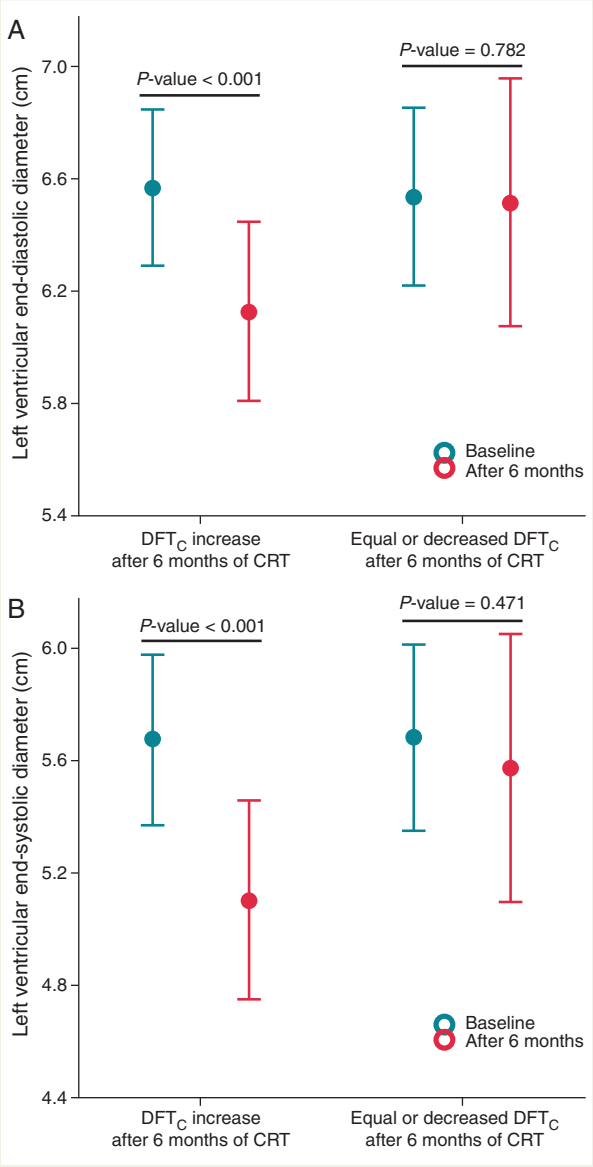

Figure 4 DFT_C change and left ventricular remodelling response. Only patients with increased DFT_C after 6 months of CRT demonstrated favourable reverse left ventricular remodelling, assessed by the change in LVEDD (*A*) or LVESD (*B*).

a significant decrease in the duration of isovolumetric contraction and relaxation phases, while ejection time remained unchanged. This resulted in a significant improvement of Tei index in this group compared with patients without DFT_C increase ($P < 0.001$). The correlations between change in DFT_C, more traditional echocardiography measurements of dyssynchrony, and ventricular remodelling are presented in *Table 3*. Changes in dyssynchrony parameters, including DFT_C, according to ventricular remodelling and clinical response are provided in Supplementary material online, *Tables S1* and *S2*. When analyses were repeated using a 2 or 3% cut-off for a meaningful increase in DFT_C, this yielded similar results (data not shown).

Diastolic filling time corrected for RR interval and clinical outcome

During mean follow-up of 16 ± 9 months, 10 patients died (8%), 30 were admitted because of worsening heart failure (23%), while 95 had an event-free survival (73%). Event-free survival was significantly better in patients with a DFT_C increase after 6 months of CRT (*Figure 5*). In multivariate analysis including guideline criteria for CRT (i.e. QRS width, presence of left bundle branch block, and LVEF), IVMD as a marker for interventricular dyssynchrony and Tei index as a marker for intraventricular dyssynchrony, baseline DFT_C was the strongest predictor of adverse outcome (*Table 4*).

Diastolic filling time corrected for RR interval and diastolic dysfunction grade

DFT_C values at baseline varied according to DDF grade: 44 ± 10% in grade 1 DDF, 43 ± 13% in grade 2 DDF, and 36 ± 11% in grade 3 DDF ($P = 0.012$ between groups). Patients with impaired relaxation vs. pseudonormal or restrictive filling had a similar chance of increasing DFT_C (69 vs. 65%; $P = 0.444$). However, while patients with grade 1 DDF had a large and highly significant reduction in all-cause mortality and heart failure admissions when DFT_C increased (HR, 95% CI = 0.24, 0.08–0.73; $P = 0.012$), this benefit was less pronounced and did not reach statistical significance in patients with pseudonormal or restrictive filling (HR, 95% CI = 0.64, 0.23–1.77; $P = 0.388$). Overall, patients with grade 2–3 DDF had a significantly worse clinical outcome compared with patients with grade 1 DDF (HR, 95% CI = 2.26, 1.16–4.43; $P = 0.017$).

Discussion

The key finding of this study, involving CRT patients in sinus rhythm, is that DFT_C, which can easily be measured by echocardiography in a straightforward and highly reproducible manner, is a useful parameter to assess the mechanistic response to CRT. Increase of DFT_C after CRT reflects more favourable reverse left ventricular remodelling, and is associated with better clinical outcome (i.e. lower mortality and less heart failure admissions). Moreover, baseline DFT_C is significantly associated with adverse outcome, even after correction for guideline criteria for CRT (QRS width, presence of left bundle branch block, and LVEF), IVMD (i.e. interventricular dyssynchrony), and Tei index (i.e. intraventricular dyssynchrony). This *might* indicate that patients who already have reached their physiological maximum for DFT_C benefit less from CRT. Our results reinforce the paramount importance of better understanding the (patho)physiological mechanisms characterizing electromechanical dyssynchrony, to better predict response to CRT.

From a physiological point of view, DFT might be an important marker of electromechanical efficiency of the ventricle. In sinus rhythm, diastolic filling of the left ventricle normally occurs in two phases. The rapid, early filling phase (E-wave on transmitral PWD signal) starts with the opening of the mitral valve and is highly dependent on efficient and complete ventricular relaxation (creating diastolic suction and allowing the left ventricle to fill at low atrial pressure). In addition, early diastolic filling is also determined by the strength and coordination of the previous systole, which is the driver for ventricular suction.[25] After the period

Table 2 Electrocardiography and echocardiography measurements at baseline and after 6 months of CRT

	DFT_C increase ($n = 61$)	No DFT_C increase ($n = 30$)	*P* value
QRS width at baseline (ms)	154 ± 26	157 ± 23	0.563
QRS width after 6 months (ms)	153 ± 25	155 ± 29	0.707
QRS width change from baseline (ms)	−1 ± 32	−2 ± 27	0.877
PR interval at baseline (ms)	186 ± 32	197 ± 45	0.243
PR interval after 6 months (ms)	128 ± 27	135 ± 37	0.342
PR interval change from baseline (ms)	−58 ± 41	−58 ± 51	0.999
LVEDD at baseline (cm)	6.6 ± 1.1	6.5 ± 0.9	0.882
LVEDD after 6 months (cm)	6.1 ± 1.2	6.5 ± 1.2	0.158
LVEDD change from baseline(cm)	−0.5 ± 0.8	0 ± 0.8	0.021
LVESD at baseline (cm)	5.7 ± 1.2	5.7 ± 0.9	0.974
LVESD after 6 months (cm)	5.1 ± 1.4	5.6 ± 1.3	0.124
LVESD change from baseline (cm)	−0.6 ± 1.0	−0.1 ± 0.9	0.038
LVEF at baseline (%)	27 ± 8	32 ± 10	0.017
LVEF after 6 months (%)	41 ± 12	38 ± 11	0.200
LVEF change from baseline (%)	+15 ± 14	+7 ± 13	0.018
Mitral valve regurgitation at baseline (/4)	1 (0.5–1.8)	1 (0.5–1.6)	0.889
Mitral valve regurgitation change from baseline(/4)	−0.30 ± 0.60	−0.05 ± 0.93	0.121
Tricuspid valve regurgitation at baseline (/4)	0.5 (0.5–1)	0.5 (0.5–1.1)	0.859
Tricuspid valve regurgitation change from baseline(/4)	−0.22 ± 0.70	+0.10 ± 0.70	0.043
RVSP at baseline (mmHg)	25 (21–29)	25 (17–33)	0.923
RVSP change from baseline (mmHg)	−2 ± 9	2 ± 12	0.085
DFT_C at baseline (%)	37 ± 9	51 ± 7	<0.001
DFT_C after 6 months (%)	50 ± 7	43 ± 9	<0.001
ET_C at baseline (%)	31 ± 8	28 ± 7	0.075
ET_C after 6 months (%)	32 ± 5	33 ± 5	0.557
$IVCT_C$+$IVRT_C$ at baseline (%)	31 ± 10	20 ± 6	<0.001
$IVCT_C$+$IVRT_C$ after 6 months (%)	18 ± 7	24 ± 9	<0.001
Tei index at baseline	1.00 (0.71–1.22)	0.65 (0.49–0.85)	0.001
Tei index after 6 months	0.52 (0.43–0.71)	0.67 (0.55–0.94)	0.003
Tei index change from baseline	−0.44 ± 0.46	+0.06 ± 0.43	< 0.001
IVMD at baseline (ms)	41 ± 29	39 ± 30	0.852
IVMD after 6 months (ms)	30 ± 23	32 ± 25	0.768
IVMD change from baseline (ms)	−12 ± 32	−14 ± 37	0.854

CRT, cardiac resynchronization therapy; DFT_C, diastolic filling time corrected for RR interval; ET_C, ejection time corrected for RR interval; $IVCT_C$, isovolumetric contraction time corrected for RR interval; IVMD, interventricular mechanical delay; $IVRT_C$, isovolumetric relaxation time corrected for RR interval; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RVSP, right ventricular systolic pressure.

of diastasis and following the P-wave on the electrocardiogram, indicating electrical activation of the atria, ventricular filling occurs by atrial contribution (A-wave on the transmitral PWD signal). This process is dependent on normal atrial function and left ventricular stiffness. Because of the electromechanical delay, ventricular filling by atrial contribution normally continues well after the start of the QRS complex and thus during electrical systole (i.e. QA time). As left ventricular pre-ejection time is physiologically short because of efficient conduction through the His–Purkinje system, little time is needed for isovolumetric contraction and relaxation. Thus, 'wasted time' of intrinsic cardiac work (i.e. time without blood displacement in or out of the ventricle) is limited to a minimum.

As ventricular relaxation and contraction are part of a continuous cycle, dyssynchronous systolic contraction will prolong isovolumetric relaxation and further impair diastolic function. In heart failure with reduced LVEF, diastolic dyssynchrony is reported being even more prevalent than systolic dyssynchrony.[26] In combination with commonly associated AV conduction delay, diastolic dyssynchrony might markedly affect ventricular filling. First, because of inefficient myocardial relaxation of the ventricle, the rapid, early filling phase will be impaired. Secondly, delayed electromechanical activation of the left ventricle because of first-degree AV block causes premature ending of left ventricular filling well before the start of the QRS complex, sometimes even leading to diastolic mitral valve regurgitation.[27] As a result, fusion of both ventricular filling phases often

Table 3 Correlation between change in DFT_C and traditional echocardiography parameters of CRT response after 6 months

	ΔPR interval	ΔIVMD	ΔTei index	ΔLVEDD	ΔLVESD	ΔLVEF
ΔDFT_C	$\rho = -0.173$ $P = 0.128$	$\rho = 0.056$ $P = 0.695$	$\rho = -0.745$ $P < 0.001$	$\rho = -0.208$ $P = 0.052$	$\rho = -0.216$ $P = 0.043$	$\rho = 0.192$ $P = 0.073$
ΔPR interval	$\rho = 1$	$\rho = -0.111$ $P = 0.485$	$\rho = 0.125$ $P = 0.307$	$\rho = -0.071$ $P = 0.505$	$\rho = -0.174$ $P = 0.101$	$\rho = 0.206$ $P = 0.052$
ΔIVMD		$\rho = 1$	$\rho = 0.160$ $P = 0.268$	$\rho = -0.109$ $P = 0.440$	$\rho = -0.018$ $P = 0.899$	$\rho = -0.179$ $P = 0.205$
ΔTei index			$\rho = 1$	$\rho = 0.035$ $P = 0.759$	$\rho = 0.082$ $P = 0.471$	$\rho = -0.190$ $P = 0.092$
ΔLVEDD				$\rho = 1$	$\rho = 0.869$ $P < 0.001$	$\rho = -0.328$ $P = 0.001$
ΔLVESD					$\rho = 1$	$\rho = -0.498$ $P < 0.001$

CRT, cardiac resynchronization therapy; DFT_C, diastolic filling time corrected for RR interval; IVMD, interventricular mechanical delay; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

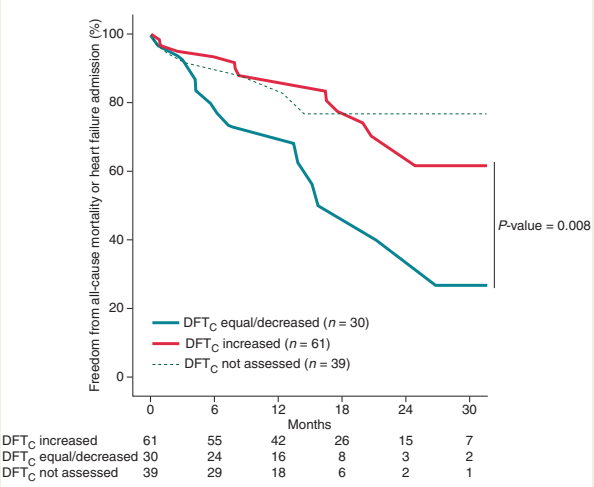

Figure 5 DFT_C change and clinical outcome. DFT_C increase after 6 months of CRT was associated with higher freedom from all-cause mortality or heart failure admission.

arises and 'wasted time' for isovolumetric contraction and relaxation, in which no blood enters or leaves the ventricles, is significantly prolonged. Conclusively, DFT might be a relevant marker of global myocardial performance. Importantly, as absolute DFT is significantly influenced by the heart rate in normal physiological conditions, it is important to correct for RR interval.[28] As illustrated by the results of the present study, a potentially good responder to CRT has a short baseline DFT_C (*Figure 1*), while less obvious benefits can be expected for a patient with an already normal left ventricular filling time (*Figure 2*).

Markers of electrical dyssynchrony already have been demonstrated to portend prognostic value in CRT patients. More prolonged QRS duration (≥150 ms) before implantation is associated with better response rates in terms of reverse remodelling and clinical outcome.[29] However, QRS width is merely a rude marker for left ventricular electromechanical dyssynchrony as it lacks an underpinning mechanistic substrate. Therefore, one should not be surprised that patients with wide QRS complex, but pure right bundle branch block benefit less from CRT.[29–31] Despite these findings, a significant amount of patients with QRS width <150 ms and/or non-left bundle branch block also respond beneficially to CRT, so response cannot be explained by QRS width or type alone.[32] A recent study has demonstrated that left ventricular electrical delay, measured as the time from onset of the QRS complex from the surface electrocardiogram to the first peak of the left ventricular electrogram during left ventricular lead placement (Q-LV time), might be a stronger predictor of reverse remodelling with CRT than QRS width and/or type.[33] However, reliance on periprocedural measurements and dependency of anatomical considerations of the coronary sinus may hamper the use of this approach.

Clinical implications

Our study adds important new evidence about the value of DFT_C as an easy and reproducible parameter to assess positive response after implantation. First, our data clearly point out that patients with DFT_C increase after CRT have more favourable reverse left ventricular remodelling and better clinical outcome free from death or heart failure admission. Secondly, as device settings and change in PR interval after implantation were similar both in patients with or without DFT_C increase, AV optimization was probably not the main reason behind a DFT_C increase. Rather, the potential for improvement of global myocardial performance with less intraventricular dyssynchrony, elimination of diastolic fusion, and possibly lower diastolic filling pressures, is a more likely contributor. Indeed, by using diastolic strain rate during the isovolumetric relaxation period as a marker for left ventricular relaxation, Shanks *et al.*[34] have reported an improvement in 'CRT responders' with a 15% reduction in left ventricular end-systolic volume and non-ischaemic aetiology for heart failure. Strain echocardiography is strongly dependent on left ventricular relaxation and can

Table 4 Multivariate analysis of predictors of adverse outcome (all-cause mortality or heart failure admission)

	Hazard ratio	95% Confidence interval	*P* value
Baseline DFT_C (%)[a]	1.06	1.01–1.11	0.022
Baseline QRS width (ms)[a]	1.00	0.99–1.02	0.740
Presence of left bundle branch block	0.43	0.16–1.13	0.085
Baseline left ventricular ejection fraction (%)[a]	0.96	0.92–1.01	0.079
Interventricular mechanical delay (ms)[a]	0.99	0.98–1.01	0.433
Tei index[a]	3.66	1.05–12.7	0.041

DFT_C, diastolic filling time corrected for RR interval.
[a]Hazard ratios per unit increment.

predict left ventricular filling pressures with reasonable accuracy.[35–37] However, DFT_C might be an easier and readily available technique in most clinical centres. Thirdly, in multivariate analysis, baseline DFT_C was superior to current guideline criteria for CRT to predict clinical outcome. We believe that this finding calls into question the lack of attention for diastolic components of cardiac dyssynchrony in current guideline recommendations for CRT, which are based solely on QRS width and morphology, systolic function (i.e. LVEF), and NYHA functional class. Fourthly, we demonstrated that absolute values of DFT_C depend on DDF grade. This could explain why a single measurement before implantation only had moderate sensitivity and specificity to predict CRT response in the Predictors of Response to CRT (PROSPECT) study. Unlike PROSPECT, our study looked at dynamic improvements of DFT_C, suggesting a physiological maximum at which no further benefit could be obtained. Fifthly, we found that while patients with more advanced DDF (i.e. pseudonormal or restrictive filling) had a similar chance of improving DFT_C, their net clinical benefit was lower, possibly because their prognosis was reserved anyway. However, because no control group without CRT was present, these findings should only be considered hypothesis-generating.

Study limitations

Some study limitations should be taken into account. First, the retrospective study design might have led to differences in the study population subgroups that could also account for the observed differences. However, LVEF and heart rate were the only baseline characteristics that differed significantly between patients with and without DFT_C increase. Moreover, LVEF was lower and HR higher in the group with an increase of DFT_C after 6 months, which would be expected to result in a less beneficial outcome in this group. Nevertheless, our findings should be considered hypothesis-generating and ask for confirmation in a prospective study design. Secondly, in 39 patients (30%) DFT_C could not be measured after 6 months of follow-up because of two main reasons. Some patients were followed in another centre and therefore had no transmitral PWD signal available at follow-up. However, baseline characteristics of these patients were similar compared with patients with complete follow-up data. Secondly, an important number of CRT patients had atrial fibrillation. These patients lack an atrial contribution to left ventricular filling and therefore have a significantly shorter DFT_C. Accordingly, differences between DFT_C pre- and post-implantation values are expected to be smaller, which might limit the applicability of the parameter. The lack of evidence-based medicine for CRT in patients with atrial fibrillation is also reflected in the weaker class IIb (Level of evidence: C) recommendation for CRT in current guidelines.[17] Thirdly, we used left ventricular diameters to assess left ventricular remodelling instead of volumetric measurements, which are more representative of global remodelling but are prone to a higher error rate. For instance, the intra- and inter-observer variability for left ventricular end-systolic volume were 3.8 and 14.5% in the PROSPECT study.[8] Fourthly, we assessed reverse left ventricular remodelling after 6 months of CRT and the results might have been different with another follow-up window. However, the time interval was prespecified to observe the maximal benefits of CRT, allowing for aggressive uptitration of neurohumoral blockers during dedicated follow-up in our multidisciplinary CRT clinic. Overall, in 56 patients (43%), the dose of neurohumoral blockers could be increased after implantation, which was also similar among groups. Fifthly, we had no information on myocardial scar burden and left ventricular lead location, which are also known to influence CRT response. Finally, we do not feel any cut-off value for DFT_C should be used as a sole prognosticator to predict response, but rather might help in better understanding the physiological mechanisms through which CRT affects electromechanical dyssynchrony.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: F.H.V. and W.M. are researchers for the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk (LSM), Hasselt University, Ziekenhuis Oost-Limburg, and Jessa Hospital. No grants, contracts, or other forms of financial support were given to support publication of this manuscript. W.H.W.T. and W.M. are consultants to Medtronic Inc. and St Jude Inc. The other authors have no conflict of interest to declare.

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