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A reduction in total isovolumic time with cardiac resynchronisation therapy is a predictor of clinical outcomes

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ABSTRACT

Background: Total isovolumic time (t-IVT) reflects left ventricular (LV) asynchrony (when the ventricle is neither ejecting nor filling). It is prolonged in left bundle branch block (LBBB). Cardiac resynchronisation therapy (CRT) is a treatment for patients with heart failure, reduced LV ejection fraction and LBBB. CRT shortens t-IVT, but the long-term clinical benefit of such reduction after CRT has not been studied in this patient group.
Methods: Seventy-three patients who underwent CRT had t-IVT measured before and after CRT implantation. The study end-point was a composite of unplanned heart failure hospitalisation and all-cause mortality.
Results: Baseline t-IVT showed considerable scatter: 30 patients had t-IVT values longer than 15 s/min (upper 95% limit of normal). The change in t-IVT with CRT was also variable: t-IVT shortened in 50 patients (from 16.2 ± 4.8 s/min to 11.7 ± 3.7 s/min: group A), and lengthened in 23 patients (from 11.7 ± 4.2 s/min to 14.5 ± 4.33 s/min: group B). The magnitude of change in t-IVT with CRT negatively correlated with baseline t-IVT ($r = -0.619$, $p<0.001$); thus t-IVT (significantly longer in group A than group B before CRT: 16.2 ± 4.8 s/min vs. 11.7 ± 4.2 s/min, $p<0.001$) became significantly shorter in group A compared to group B after CRT (11.7 ± 3.7 s/min vs. 14.5 ± 4.3 s/min, $p = 0.005$). After follow-up of 30 months, 70% group A patients had event-free survival compared to 39% group B patients. The presence of any fall in t-IVT after CRT was an independent predictor of event-free survival.
Conclusion: T-IVT is a marker of global cardiac asynchrony that has predictive capacity on functional, symptomatic, and mortality endpoints in patients with advanced heart failure.

1. Introduction

In selected patients with heart failure, cardiac resynchronisation therapy (CRT) provides symptomatic relief, improved exercise tolerance and beneficial effects on mortality [1,2]. However there is a well reported 30% non-response rate, which is important, since device implantation is potentially hazardous with a small but significant risk of complication(s) to the patient. To aid with patient selection, several single-centre limited studies have evaluated a series of complex echocardiographic markers, reported to be reliable indicators of regional ventricular asynchrony, that suggest the possibility of favorable resynchronisation [3–5]. Major prospective studies to date however demonstrate that these measures are so poorly reproducible as to be unreliable [6,7].

Total isovolumic time (t-IVT), which corresponds to 'wasted' time within the cardiac cycle (i.e. when the ventricle is neither filling nor ejecting), offers a quick, reliable, reproducible, and easily accessible measure of global ventricular asynchrony. It is prolonged in patients with uncorrected coronary artery disease (CAD), and is consistently reduced by surgical revascularisation [8]. Moreover, prolongation of t-IVT in patients with left bundle branch block (LBBB) can be shortened with biventricular pacing [9–11]. Indeed, there is a close relationship between increased peak VO_2 and reduction in t-IVT following atrio-biventricular pacing, a correlation not found with conventional markers of cardiac function including left ventricular ejection fraction (LVEF) [12,13]. While native t-IVT is a prognostic marker in heart failure patients with predominate medical management [14], little is known

Abbreviations: BNP, B type natriuretic peptide; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NYHA, New York Heart Association; T-IVT, total isovolumic time.

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about the long-term clinical effect of any reduction of t-IVT following CRT. We therefore hypothesised that when CRT reduces prolonged t-IVT, this reduction translates into an improved clinical outcome.

2. Methods

2.1. Patient population

A series of patients were identified from the specialist heart failure pacing clinic within the Royal Brompton Hospital, London. All patients fulfilled current ESC criteria for CRT implantation (LVEF <35%, QRS duration >120 ms, NYHA II-IV heart failure on optimal tolerated medical therapy) [1]. A full physical examination and baseline clinical and laboratory data were recorded before CRT implantation. A baseline transthoracic echocardiogram was performed within 2 months before CRT implantation. All patients were followed up clinically after CRT implantation, with a transthoracic echocardiogram between 1 and 24 months following CRT. Only data belonging to patients in sinus rhythm and with >95% biventricular pacing were identified for data analysis. The study end point was a composite of unplanned heart failure hospitalisation (requiring the usage of intravenous diuretic therapy) and all-cause mortality.

2.2. Measurement of t-IVT

Stored echocardiographic studies were reviewed by two investigators who were unaware of the clinical outcomes of each patient. Sub aortic flow velocity was obtained by pulsed wave Doppler from the apical five chamber view, with the sample volume placed in the LV outflow tract, 1 cm below the aortic cusps. LV ejection time (ET), was measured from the onset of forward aortic flow to aortic valve closure artifact. Transmitral flow velocities were recorded from the apical four-chamber view using pulsed-wave Doppler. LV filling time (FT) was measured from the onset of E wave to the end of the A wave. When the end of A wave was unclear (for example in patients with a restrictive filling pattern), the duration of LV filling between 2 consecutive functional mitral regurgitation traces was used. The corresponding RR interval for each ET and FT was also measured. Total LVET was then calculated as the product of ET∗60/RR (in s/min), total filling time (LVFT) was then calculated as the product of FT∗60/RR (in s/min), t-IVT was derived as [60 − (total ET + total FT)] [15]. Upper limit of normal for t-IVT is 15 s/min [16]. LV end systolic volume (LVESV) and LVEF were measured using Simpson's biplane method. Measurements were made by the same investigators using the same methods and again blinded to the baseline measurements.

2.3. Statistical analysis

All analysis was performed using the SPSS v 16.0 for Windows (Chicago, IL, USA). Continuous variables were reported as mean and standard deviation or median and interquartile range in case of non-normal distribution and dichotomous variables as numbers and percentages. Differences between 2 groups were sought by Student's t test or the Mann–Whitney U test for normally or non-normally distributed variables respectively. Differences between pre and post implantation variables were explored by the paired t-test or the Wilcoxon–Sign rank test accordingly. Linear regression analysis was used to explore correlation between continuous variables. The event-free survival of patients was evaluated by the Kaplan–Meier analysis. The effect of various baseline and follow up variables on event-free survival was investigated by the Cox regression analysis. Variables with a p value ≤0.10 in the univariate analysis were entered in a stepwise multivariate Cox proportional hazard model. For all analysis a p value<0.05 was considered statistically significant. Inter and intra observer agreements were assessed by previously established methods [17].

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Baseline demographics

Seventy three patients, mean age 66 ± 13 years with mean LVEF 25 ± 8%, were studied. Patients' baseline characteristics are presented in Table 1. Mean NYHA class at implantation was 2.9 ± 0.6 and 51% had CAD (>70% stenosis in at least 1 major epicardial coronary artery). Baseline QRS duration was 160 ± 26 ms, LVESV was 181 ± 85 ml and mean t-IVT was 14.9 ± 5.0 s/min. There was, however, considerable scatter in t-IVT values: in 30 patients, t-IVT values were longer than the upper 95% limit of normal (of 15 s/min).[16] There was no correlation between baseline values of t-IVT and QRS duration (p = 0.334), LVESV (p = 0.141) or LVEF (p = 0.174).

Table 1
Whole patient group patient characteristics and effect of CRT.

	All patients n = 73		
	Pre CRT	With CRT	p value
Age, years	66 ± 13		
Male gender, n (%)	57 (78)		
NYHA class	2.9 ± 0.6	1.9 ± 0.5	<0.001
Ischaemic, n (%)	35 (51)		
Hypertension, n (%)	17 (23)		
Diabetes mellitus, n (%)	18 (25)		
β-blockers n (%)	41 (62)		
ACEi or ARBs n (%)	61 (92)		
QRS duration (ms)	160 ± 26		
LVEF (%)	25 ± 8	31 ± 11	0.002
LVESV (ml)	181 ± 85	153 ± 88	<0.001
t-IVT (s/min)	14.9 ± 5.0	12.9 ± 4.3	<0.001

ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CRT: cardiac resynchronisation therapy; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association; t-IVT: total isovolumic time.

3.2. Effect of CRT on t-IVT

Echocardiography was performed after a median of 79 days (IQR 247) after CRT implantation. In the whole patient group, mean t-IVT shortened by 2 s/min (from 14.9 ± 5.0 s/min to 12.9 ± 4.3 s/min, p<0.001, Table 1). However, the change in t-IVT with CRT showed considerable variation (Table 2): in 50 patients, t-IVT shortened with pacing (group A), while in 23 patients, t-IVT lengthened with pacing (group B). There was no difference in gender, NYHA class, ischaemic aetiology, hypertension, diabetes mellitus, LVEF, or medical therapy between group A and group B (Table 2), though patients in group A were slightly younger (64 ± 12 years vs. 70 ± 13 years, p = 0.037). The magnitude of change in t-IVT with CRT was unrelated to QRS duration (r = 0.059, p = 0.630), correlated weakly with the change in LVESV (r = 0.251, p = 0.035), and was strongly and negatively correlated with baseline t-IVT (r = −0.619, p<0.001), (Fig. 1A). Thus baseline t-IVT (significantly longer before CRT in group A compared with group B: 16.2 ± 4.8 s/min vs. 11.7 ± 4.2 s/min, p<0.001) reversed after CRT, so

Table 2
Characteristics of patients group A (when t-IVT shortened with CRT) versus group B (when t-IVT lengthened with CRT).

	Group A n = 50	Group B n = 23	p value
A: baseline			
Age, years	64 ± 12	70 ± 13	0.037
Male gender	76%	83%	0.526
NYHA class	2.8 ± 0.5	2.9 ± 0.6	0.468
Ischaemic, n (%)	23 (46%)	12 (52%)	0.778
Hypertension, n (%)	12 (24%)	5 (22%)	0.813
Diabetes mellitus, n (%)	12 (24%)	6 (26%)	0.674
eGFR (ml/1.73 cm^2)	60 ± 21	54 ± 22	0.243
β-blockers, n (%)	30 (60%)	16 (68%)	0.751
ACEi or ARB, n (%)	47 (94%)	20 (89%)	0.624
QRS duration (ms)	157 ± 23	167 ± 30	0.081
LVEF (%)	25 ± 9	25 ± 5	0.145
LVESV (ml)	186 ± 83	183 ± 88	0.896
t-IVT (s/min)	16.2 ± 4.8	11.7 ± 4.2	≤0.001
B: change with CRT			
t-IVT c CRT, s/min	11.7 ± 3.7	14.5 ± 4.3	0.005
LVESV c CRT, ml	143 ± 82	160 ± 95	0.449
Death or hospitalisation, n (%)	16 (32%)	13 (56%)	0.047
Death, n (%)	8 (16%)	5 (22%)	0.552

CRT: cardiac resynchronisation therapy; t-IVT: total isovolumic time; NYHA: New York Heart Association; eGFR: estimate glomerular filtration rate; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume.