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Cardiac resynchronization therapy-induced acute shortening of QRS duration predicts long-term mortality only in patients with left bundle branch block

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Aims QRS narrowing with initiation of biventricular pacing might be an acute electrocardiographic indicator of correction of left bundle branch block (LBBB)-induced depolarization delay and asynchrony. However, its impact on prognosis remains controversial, especially in non-LBBB patients. Our goal was to evaluate the impact of QRS narrowing on long-term mortality and morbidity in a large cohort of patients undergoing cardiac resynchronization therapy (CRT) with different pre-implantation QRS types: LBBB, non-LBBB, and permanent right ventricular pacing.

Methods and results This study included consecutive patients who underwent CRT device implantation. Study endpoints: death from any cause or urgent heart transplantation and death from any cause/urgent heart transplantation or hospital admission for heart failure. All pre- and post-implantation electrocardiograms were analysed using digital callipers, high-amplitude augmentation, 100 mm/s paper speed, and global QRS duration measurement method. A total of 552 CRT patients entered the survival analysis. During the 9 years observation period, 232 (42.0%) and 292 (52.9%) patients met primary and secondary endpoints, respectively. QRS narrowing predicted survival in the Kaplan–Meier analysis only in patients with LBBB. Multivariate Cox regression model showed that QRS narrowing was the major determinant of both study endpoints, with hazard ratios of 0.46 and 0.43, respectively. There was a strong relationship between mortality risk and shortening/widening of the QRS, albeit only in the LBBB group. Patients with non-LBBB morphologies had unfavourable prognosis similar to that in LBBB patients without QRS narrowing.

Conclusion Acute QRS narrowing in patients with LBBB might be a desirable endpoint of CRT device implantation.

Keywords Cardiac resynchronization therapy • Left bundle branch block • QRS duration • QRS narrowing • Mortality

Introduction

There are no good acute endpoints of successful cardiac resynchronization therapy (CRT) device implantation that would be similar to the acute endpoints of classic pacemaker implantation. Cardiac resynchronization therapy's paradigm is to correct the delayed depolarization of the left ventricular (LV) free wall induced by left bundle branch block (LBBB). Therefore, technically correct biventricular (BiV) capture seems insufficient to define a successful CRT device implantation procedure. Abatement or disappearance of LBBB features might offer a desirable electrocardiographic endpoint of acute procedural success. Several studies have assessed the impact of shortening QRS duration with BiV pacing on long-term outcomes of CRT patients. However, most of these studies assessed only short-term

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What's new?

- This longest retrospective mortality study reinforces importance of QRS shortening with initiation of cardiac resynchronization therapy.
- The present study is the first to demonstrate that shortening of QRS duration predicts favourable prognosis only in patients with left bundle branch block (LBBB).
- We show that patients with non-LBBB morphologies do not benefit from QRS narrowing and have unfavourable prognosis similar to that seen in LBBB patients without QRS narrowing.

echocardiographic response, peak oxygen consumption rate change, functional status, or other 'soft' endpoints,[1–10] and only four studies investigated long-term mortality.[11–14] These four mortality studies provided partially divergent results, and all were limited methodologically with regard to the attention to pre-implantation QRS morphology type and QRS duration measurement methodology.[11–14] QRS narrowing in patients with LBBB might not mean the same as QRS narrowing in patients with right bundle branch block (RBBB), nonspecific intraventricular conduction delay (NIVCD), or right ventricular (RV) pacing. Consequently, QRS narrowing's role in predicting mortality in patients with LBBB is uncertain, and in patients with non-LBBB QRS morphologies it is unknown. Current CRT guidelines either do not mention QRS narrowing[15] or are ambiguous.[16]

The aim of this study was to evaluate the impact of acute shortening of QRS duration with initiation of BiV pacing on long-term mortality and morbidity in a large cohort of patients with CRT including all different pre-implantation QRS morphologies.

Methods

Study population

A longitudinal cohort study including all consecutive patients who had undergone CRT device implantation in our institution between 2006 and 2014 were retrospectively analysed. In all patients, CRT device was implanted in standard fashion with due attention to position the LV lead on the LV free wall in the mid-ventricular segments, when possible. Supplementary methods to optimize LV lead position (inter-lead distance, inter-lead electrical delay, acute QRS narrowing, paced QRS morphology, etc.), were used at the physician discretion. Follow-up was completed by June 2016. Information concerning deaths and hospitalizations were obtained through our out-patient department (where the vast majority of our CRT patients undergo regular device follow-up) and via analysis of all available medical documentation (mainly hospital discharge notes), telephone contact with patients and their families, and, in case of no contact with a patient/family, the death/life status was determined via the national PESEL registry. Outcome was categorized according to two endpoints: all-cause mortality and all-cause mortality or heart failure (HF) hospitalization. Urgent heart transplantation was classified as death. Left bundle branch block was diagnosed when conventional criteria of QRS duration of ≥120 ms, QS/rS morphology in V1 and R/Rs morphology in V6 with intrinsicoid deflection time > 60 ms in V6 were present. Right bundle branch block was diagnosed when there was a predominantly positive QRS in V1 with QRS duration of ≥120 ms and NIVCD when neither LBBB nor RBBB could be diagnosed but QRS duration was ≥120 ms. Heart failure aetiology was categorized as ischaemic (when either a history of myocardial infarction was present or coronary angiography showed significant stenotic lesions) or non-ischaemic.

Study was approved by institutional review board (Bioethics Committee).

Assessment of QRS duration/narrowing

In all patients, 12-lead electrocardiograms (ECGs) were continuously digitally registered during the whole CRT device implantation procedure including pre-implantation and post-implantation ECGs (BiV-paced ECG). These ECGs were archived on the polygraph (Bard Labsystem/Boston Scientific Corp., Marlborough, MA, USA) for all consecutive CRT cases and were available for offline analysis and assessment with the use of high paper speed, high augmentation, and digital callipers. QRS duration was assessed according to the global QRS method (*Figure 1*) (i.e. from the earliest onset of the QRS in any of the 12 simultaneously recorded standard ECG leads [or from pacing spike] to the latest QRS end in any of the 12 simultaneously recorded leads), as recommended by the American Heart Association and the World Health Organization for patients with interventricular conduction disturbances and recently, according to De Pooter *et al.*,[17] for CRT patients. Four or more QRS duration measurements were made and averaged for both pre-implantation and post-implantation QRS duration value. Pacemaker interventricular timing was set at zero. The pacemakers/defibrillators were programmed to DDD or VVI pacing mode as appropriate; atrioventricular delay was mostly left at the default values of the implanted device (usually 100–120 ms for atrial-sensed events and 130–150 ms for atrial-paced events); this eliminated or minimized fusion.

QRS narrowing was calculated by subtracting global BiV QRS duration from the pre-implantation global QRS duration.

Intraobserver variability was assessed by comparison of 100 QRS duration measurements with repeated measurements made in 50 randomly selected patients by the same observer (M.J.). Interobserver variability was assessed by comparing the same 100 initial QRS measurements with repeated measurements made by a different observer (T.S.).

Statistical methods

The Kaplan–Meier method was used to estimate the survival functions for each endpoint. Univariate and multivariate Cox proportional hazard (CPH) models were used to describe the effect of predictors on survival. All variables believed to be clinically important were prespecified and entered into multivariate CPH models. More in-depth univariate Cox analysis was performed for continuous ΔQRS. Spline functions were fitted to investigate the presence of the non-linear effect of ΔQRS on survival. Results of Cox models were presented as hazard ratios (HRs) along with tests of significance and 95% confidence intervals (CIs). There were no significant violations of the proportionality assumption that underlies the CPH method. To descriptively quantify the agreement between two repeated continuous measurements, the mean and standard deviation of absolute differences were calculated. To measure the agreement between binary measurements, the kappa statistic was calculated. Statistical analysis was performed in R 3.2. *P*-values <0.05 were considered statistically significant.

Results

Population studied and implant results

We have identified 590 patients who have undergone a CRT device implantation during the analysed period (*Table 1*); of these, 30 cases were excluded due to unsuccessful LV lead implantation (success

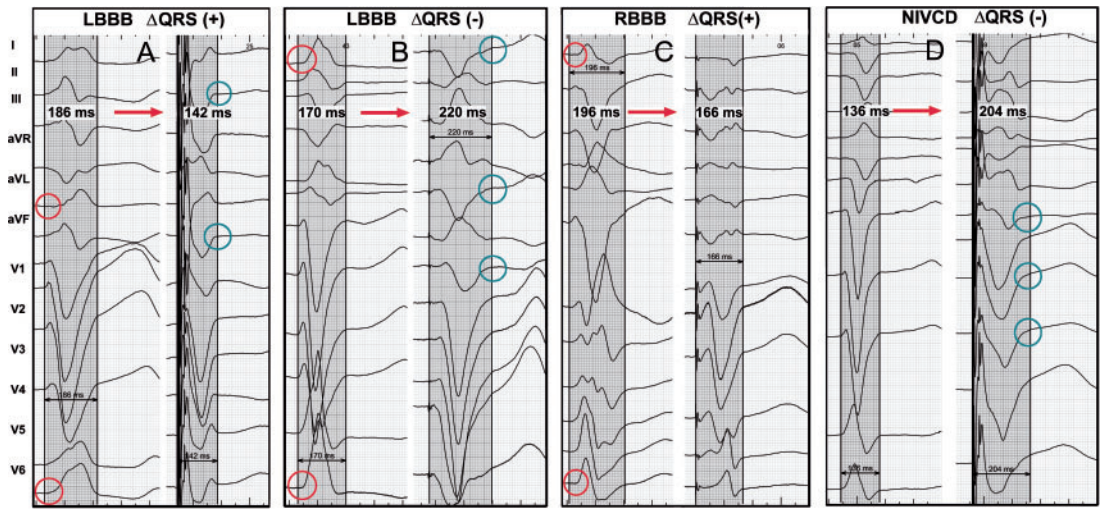

Figure 1 Examples of positive and negative ΔQRS in different native QRS categories and illustration of the global QRS measurement method with electrophysiological system. (*A*) LBBB QRS narrows from 186 to 142 ms, (*B*) LBBB QRS widens from 170 to 220 ms, (*C*) RBBB QRS of 196 ms narrows to 166 ms, (*D*) IVCD QRS of 136 ms widens to 204 ms. QRS duration measurements were done with paper speed of 100 mm/s, amplitude augmentation of 16 times, and digital callipers on Bard/Boston Scientific electrophysiology LAB system. Please note that measuring QRS duration in a single lead might have resulted in QRS duration underestimation as QRS is initially isoelectric in several leads (circles); at the same time, QRS end is difficult to ascertain in many leads (circles). Global QRS measurement method with simultaneous recording of 12 leads and digital callipers overcomes these difficulties. IVCD, intraventricular conduction delay; LBBB, left bundle branch block; NIVCD, non-specific intraventricular conduction delay; RBBB, right bundle branch block; ΔQRS (−), no QRS shortening; ΔQRS (+), QRS shortening.

Table 1 Patient pre-implantation clinical and procedure-related characteristics with regard to QRS morphology

	All ($n = 552$)	LBBB ($n = 350$)	Non-LBBB ($n = 104$)	RV paced ($n = 98$)
Age (years)	67.8 ± 10.4	66.4 ± 10.6	68.6 ± 8.9	71.9 ± 10.1
Male sex	451 (81.7%)	275 (78.6%)	90 (86.5%)	86 (87.8%)
Non-ischaemic aetiology	203 (36.8%)	143 (40.9%)	30 (28.8%)	30 (30.6%)
NYHA functional class				
Class II	47 (8.5%)	31 (8.9%)	5 (4.8%)	11 (11.2%)
Class III	434 (78.6%)	277 (79.1%)	82 (78.8%)	75 (76.5%)
Class IV	71 (12.9%)	42 (12.0%)	17 (16.3%)	12 (12.2%)
Permanent atrial fibrillation	156 (28.3%)	77 (22.0%)	47 (45.6%)	32 (32.7%)
Diabetes mellitus	243 (44.0%)	147 (42.0%)	52 (50.0%)	44 (44.9%)
Creatinine (μmol/L)	107.7 ± 44.3	106.1 ± 45.4	108.0 ± 45.8	113.0 ± 38.0
LV ejection fraction (%)	24.5 ± 7.6	23.5 ± 7.1	25.8 ± 8.7	26.8 ± 7.4
LV end-diastolic dimension (mm)	69.4 ± 9.4	70.8 ± 9.6	67.7 ± 8.3	66.4 ± 8.7
QRS duration (ms)	172.7 ± 33.1	171.8 ± 26.5	144.6 ± 33.3	205.6 ± 24.3
Pharmacologic therapy				
ACEI/ARB	479 (86.6%)	297 (84.9%)	94 (90.4%)	87 (88.8%
β-Blocker	524 (92.6%)	332 (94.9%)	101 (97.1%)	91 (92.9%)
Aldosterone antagonist	362 (65.6%)	237 (67.7%)	64 (61.5%)	61 (62.2%)
Loop diuretic	511 (92.6%)	322 (92.0%)	97 (93.3%)	92 (93.9%)
Procedure-related data				
LV lead apical or non-lateral	61 (11.1%)	39 (11.2%)	15 (15.1%)	14 (14.6%)
LV lead lateral[a]	468 (96.1%)	295 (96.1%)	87 (95.6%)	86 (96.6%)
CRT-P device	247 (44.7%)	145 (41.4%)	39 (37.5%)	63 (64.3%)
LV pacing threshold (mV)	1.2 ± 0.9	1.1 ± 0.9	1.3 ± 0.9	1.3 ± 0.9

ACEI/ARB, angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker; CRT, cardiac resynchronization therapy; EF, ejection fraction; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricle.
[a]Including antero-lateral and postero-lateral.

rate of 97.5%), late LV lead repositioning, loss of CRT or a non-standard resynchronization type, and eight cases were excluded due to incomplete baseline medical records.

QRS narrowing and study endpoints

The 9-year observation period resulted in an average follow-up time of 46 ± 28 months. The primary endpoint (death from any cause or urgent heart transplantation) was met in 232 (42.1%) patients, including 228 deaths and 4 urgent heart transplantations. There were 101 deaths due to worsening of HF and 23 sudden deaths. Eighteen deaths were classified as other cardiac and 44 as non-cardiac. The cause of death could not be determined in the remaining 42 patients. The survival rates at the end of years 1–7 were 89.7%, 80.7%, 70.6%, 63.6%, 57.2%, 52.7%, and 46.9%, respectively. Death status was available in 100% of cases.

During the same time period, 128 patients were hospitalized for unplanned HF-related reasons and 239 were hospitalized for other reasons. Of the 128 patients hospitalized for unplanned HF-related reasons, 68 patients eventually died. Thus, 292 patients met the combined endpoint of all-cause mortality or hospitalization for HF.

QRS narrowing was observed in 394 (71.9%) patients; average QRS narrowing was 16.7 ± 32 ms. LBBB was present in 350 patients (63.4%), NIVCD in 52 (9.4%), RBBB in 31 (5.6%), narrow QRS in 21 (3.8%), and RV-paced QRS in 98 (17.7%). Examples of QRS response to initiation of BiV pacing are presented on *Figure 1*.

Kaplan–Meier estimates of all-cause mortality and combined endpoint of all-cause mortality or HF hospitalization, with regard to QRS narrowing, in the whole group and in different pre-implantation QRS categories are shown in *Figure 2* and Supplementary material online, *Figure S1*. Patients with QRS narrowing were found to have a significantly better prognosis. Statistical significance was observed for QRS narrowing in the whole group and in the LBBB subgroup. In the subgroup with non-LBBB native QRS and in the subgroup with RV-paced QRS neither all-cause mortality nor all-cause mortality or HF admissions differed between patients with QRS narrowing and no QRS narrowing. Benefit of QRS shortening was seen also in patients with advanced HF [New York Heart Association (NYHA) Class IV

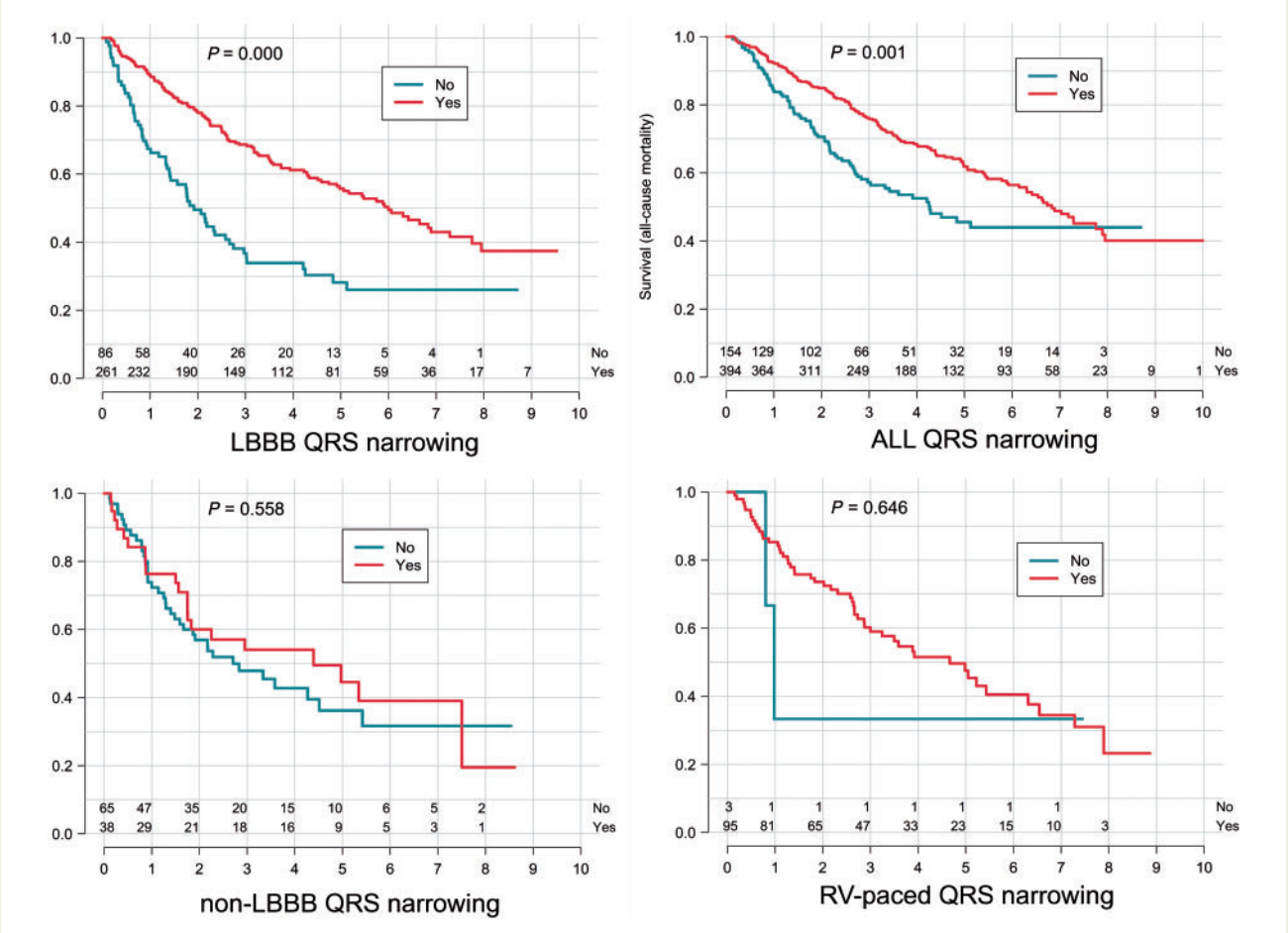

Figure 2 The Kaplan–Meier survival curves for the combined endpoint of all-cause mortality/hospital admission for heart failure in patients with and without QRS narrowing. LBBB QRS denotes patients with left bundle branch block; ALL QRS denotes whole studied cohort; non-LBBB denotes patients with remaining native QRS morphologies; RV-paced denotes patients with permanent right ventricular pacing; Yes/No denotes groups with and without acute QRS narrowing. LBBB, left bundle branch block; RV, right ventricle.

vs. NYHA Class III–II, and EF ≤ 20% vs. EF > 20%)] as evidenced by the Kaplan–Meier analyses in these subgroups (Supplementary material online, *Figure S2*).

The relationship between ΔQRS treated as a continuous variable and the risk of all-cause mortality during follow-up was estimated using Cox model with splines for ΔQRS. Results are presented in *Figure 3*. Briefly, in the LBBB group, a strong and significant relationship between QRS narrowing and mortality risk was found; in the non-LBBB subgroup, only a non-linear relationship was observed with an increase in mortality risk with change in any direction from the baseline QRS duration, and in the RV-paced subgroup neither a linear nor non-linear relationship between ΔQRS and mortality risk was present.

In univariate analysis, QRS shortening HR for all-cause mortality was 0.64 (CI 0.49; 0.85) and for all-cause mortality/HF hospital admission 0.55 (CI 0.43; 0.70). The results of multivariate Cox HRs analysis are presented in *Table 2*. Despite inclusion of other prognostically significant variables (NYHA class, LVEF, LV end-diastolic dimension, permanent AF, QRS duration, age, gender, HF aetiology, creatinine level, and diabetes mellitus), QRS narrowing remained the most significant determinant of both mortality and combined endpoint of mortality and HF hospitalizations.

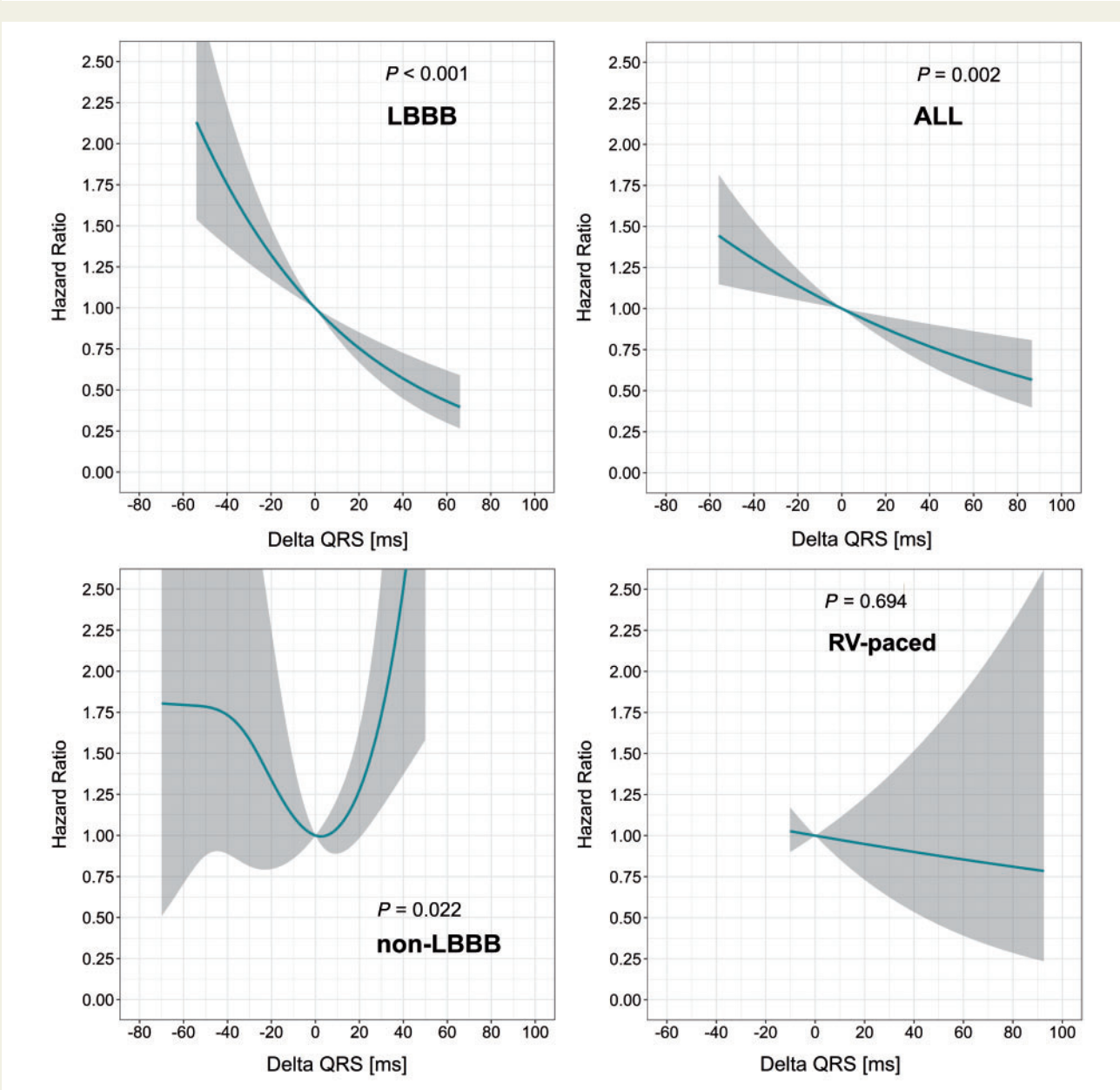

Figure 3 HRs from Cox model for ΔQRS as a continuous predictor of overall mortality in full cohort (ALL) and LBBB/non-LBBB/RV-paced subgroups (shaded regions are 95% CIs, ΔQRS = 0 is a reference level for HRs), *P*-values are for spline effects. LBBB, left bundle branch block; RV, right ventricle.

Table 2 Predictors of all-cause mortality and all-cause mortality or heart failure hospitalization: multivariate Cox proportional hazards analysis

	All-cause mortality		All-cause mortality or HF hospitalization	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
QRS shortening	0.46 (0.31–0.67)	**0.000**	0.43 (0.31–0.61)	**0.000**
QRS duration (>150 ms)	1.46 (0.95–2.24)	0.084	1.32 (0.91–1.91)	0.142
LBBB	0.90 (0.67–1.20)	0.475	0.92 (0.71–1.19)	0.519
Age 60–70 years	0.99 (0.67–1.46)	0.946	0.93 (0.66–1.30)	0.660
Age > 70 years	1.37 (0.94–1.99)	0.100	1.06 (0.76–1.47)	0.732
Gender male	1.05 (0.72–1.54)	0.804	0.96 (0.69–1.33)	0.794
Ischaemic aetiology	1.31 (0.96–1.77)	0.086	1.13 (0.86–1.47)	0.385
NYHA III	1.84 (0.90–3.77)	0.094	1.57 (0.89–2.77)	0.118
NYHA IV	4.54 (2.12–9.75)	**0.000**	3.18 (1.70–1.21)	**0.000**
AF permanent	0.76 (0.55–1.04)	0.086	0.92 (0.70–1.21)	0.539
EF 20–30%	0.74 (0.55–1.00)	**0.047**	0.81 (0.62–1.06)	0.130
EF > 30%	0.58 (0.37–0.90)	**0.016**	0.67 (0.46–0.99)	**0.044**
LVEDD 60–70 mm	0.70 (0.47–1.04)	0.078	0.77 (0.55–1.10)	0.152
LVEDD > 70 mm	0.74 (0.50–1.11)	0.147	0.79 (0.55–1.14)	0.209
Diabetes mellitus	1.18 (0.90–1.54)	0.229	1.25 (0.99–1.59)	0.063
Creatinine 80–100 μmol/L	1.05 (0.70–1.57)	0.829	1.02 (0.71–1.45)	0.933
Creatinine 100–120 μmol/L	1.01 (0.65–1.55)	0.971	0.96 (0.66–1.41)	0.837
Creatinine >120 μmol/L	1.30 (0.87–1.96)	0.201	1.34 (0.94–1.93)	0.109

AF, atrial fibrillation; CI, confidence interval; EF, ejection fraction; HF, heart failure; HR, hazard ratio; LBBB, left bundle branch block; LVEDD, left ventricle end diastolic diameter; NYHA, New York Heart Association.
P-values indicating statistical significance ($P < 0.05$) are shown in bold.

The mean (±standard deviation) of absolute differences between the initial measurements and the measurements repeated by the same observer for pre-implantation QRS/QRS BiV/ΔQRS in were 4.9 ± 3.5 ms, 4.6 ± 3.9 ms, and 6.4 ± 4.7 ms, respectively. The mean (±standard deviation) of absolute differences between the initial measurements and the measurements repeated by the second observer for pre-implantation QRS/QRS BiV/ΔQRS in were 7.3 ± 5.1 ms, 6.8 ± 6.2 ms, and 9.4 ± 7.6 ms, respectively. The Kappa statistics for the interobserver and intraobserver agreement were 86% and 82%, respectively, indicating very good agreement.

Discussion

The present study is the first to show that QRS narrowing after CRT implantation is prognostically important only in patients with LBBB, associated with over two times lower mortality rate, while other patients receiving CRT do not show mortality/morbidity benefit from QRS narrowing. Another major and novel finding of the current study is that the degree of change in QRS duration in LBBB patients matters, with a strong relationship between risk of death and both QRS narrowing and QRS widening.

Study population

The patient cohort evaluated in the present study, despite single-centre recruitment, was comparable to cohorts in other large studies assessing CRTs benefits.[18] The short-term results of CRT device implantation, including success rate, LV lead position, and acute LV threshold, were good, and the long-term outcomes were within expected ranges. The death rate among our patients was higher than in patients with mild HF who participated in some CRT trials (e.g. MADIT-CRT),[19] but it was almost identical to the death rate observed in trials with sicker patients (e.g. COMPANION) and other large, 'real life' patient cohorts (MEDICARE database).[18] The proportion of various pre-implantation QRS morphologies was also comparable to that in other studied cohorts.[4,13,18,19]

QRS narrowing and prognosis

QRS duration narrowing immediately after BiV pacing was seen in approximately two-thirds of patients, which is consistently reported by various authors.[8,11,13,14] In this study, QRS narrowing was seen in 75.2% of patients with LBBB, 36.9% of patients with non-LBBB morphologies, and in 96.9% of patients with RV-paced QRS. The current study showed that acute QRS narrowing in LBBB patients affected both short-term and long-term prognosis: 1- and 5-year absolute difference in all-cause mortality rates between patients with and without QRS narrowing was 13% and 23%, respectively. Similarly, 1- and 5-year difference in mortality/HF hospitalizations between LBBB patients with and without QRS narrowing was 22% and 28%, respectively. Multivariable analysis confirmed independent impact of QRS narrowing on CRT outcome in patients with LBBB: HR for any degree of QRS narrowing was 0.46. Moreover, benefit of QRS shortening was present in both more and less advanced stages of HF as determined by analysis with regard to NYHA class and LVEF (Supplementary material online, *Figure S2*). The relationship between ΔQRS treated as a continuous variable and the risk of all-cause

Table 3 Comparison of studies that assessed mortality in cardiac resynchronization therapy patients with regard to acute QRS narrowing/widening

Study	*n*	LBBB	ΔQRS +	Follow-up (months)	Deaths/ HTX (*n*)	QRS measurement method	QRS shortening/widening as predictor of mortality?	Missing ECG data	Other
Iler *et al.*[11]	337	45%	64%	27 ± 15	84/7 (27%)	Standard 25 mm/s ECG; QRS measured manually from lead II only	Only in K–M survival analysis; not significant in multivariable analysis (HR 1.3)—for widening	39%	ΔQRS assessed in mixed QRS type cohort; NYHA II in 40% of patients
Kronborg *et al.*[13]	634	80%	72%	30 (14–48)	215/25 (56%)	100 mm/s and 25 mm/s paper speed; widest QRS complex on a standard 12-lead ECG	Both in uni- (HR 0.6) and multivariable analysis (HR 0.6)—for narrowing	7%	ΔQRS assessed in mixed QRS type cohort; NYHA I-II in 17% of patients
Jastrzebski *et al.*[12]	362	69%	75.3%	24.7 ± 16.9	79/0 (21.8%)	Simultaneous 12-lead ECG; 100 mm/s, 8 × amplitude, digital callipers on EP system; global QRS duration	Both in uni- (HR 0.69) and multivariable (HR 0.53) analysis—for narrowing	0.6%	ΔQRS assessed in mixed QRS type cohort; NYHA II in 24% of patients
Menet *et al.*[14]	237	77%	79%	24	39/x (16.5%)	Standard 25 mm/s ECG, QRS measured manually on millimetre paper; no data on method	Both in uni- (HR 1.37) and multivariable (HR 3.63) analysis—for widening	–	ΔQRS assessed in mixed QRS type cohort; NYHA I-II in 49% of patients
Current study	552	63%	72%	46 ± 28	228/4(42%)	Simultaneous 12-lead ECG;100 mm/s, 16 × amplitude, digital callipers on EP system; global QRS duration	Both in uni- (HR 0.64) and multivariable (HR 0.46) analysis—for narrowing	2.1%	ΔQRS assessed separately in different QRS types; NYHA II in 8.5% of patients

ECG, electrocardiogram; EP, electrophysiology; HR, hazard ratio; NYHA, New York Heart Association.

mortality during follow-up was estimated using Cox model with splines for ΔQRS. In the LBBB group, there was a strong, almost linear relationship between ΔQRS and mortality risk (decrease of mortality risk with QRS narrowing and increase in mortality risk with QRS widening)—*Figure 3*. In contrast, no such association was observed in other subgroups. Interestingly, in the non-LBBB subgroup, a non-linear relationship was observed with an increase in mortality risk, with both more narrowing and more widening of the QRS. It is clear from this analysis that the relationship between QRS shortening and mortality seen in the whole cohort was driven by LBBB patients. Four prior papers that reported impact of QRS narrowing on mortality analysed patient cohorts consisting on all types of pre-implantation QRS types together, without any sub-analyses. It seems possible that benefit of QRS narrowing seen in these studies was also driven by mortality reduction in LBBB patients. The only study of these four that failed to show independent association between ΔQRS and mortality in multivariable analysis was the study with highest proportion of non-LBBB patients.[11]

Comparison of the current study and the four prior mortality studies is summarized in *Table 3*. Our study paid attention to the pre-implantation QRS category, had the highest absolute number of observed deaths, longest follow-up, and most reliable QRS duration measurement methodology. Both manual and automatic QRS duration measurements might be unreliable,[17] with potential superiority pointing to the global QRS method used in this study. Moreover, our results point to very good inter- and intraobserver agreement of QRS duration assessment using electrophysiologic systems, with differences between repeated measurements at the level of a few milliseconds, which might change ΔQRS categorization only in borderline cases.

Clinical translation

Pathophysiologic and clinical grounds for the observed relationship between QRS narrowing with initiation of BiV pacing and better long-term prognosis are mostly speculative. However, it is reasonable to consider QRS narrowing as an electrocardiographic hallmark of correction of LBBB-induced delay in depolarization of the LV free wall. If so, then it is also sound to consider QRS narrowing as a biomarker of reduction or elimination of asynchronous contraction and the negative consequences that LBBB produces. Several studies convincingly showed that QRS narrowing was a strong predictor of reverse LV electrical remodelling.[2,3,8,10] As such, QRS narrowing seems to be a promising acute electrocardiographic indicator that the CRT device implantation's initial goal was achieved. Potentially, aiming to achieve this endpoint of CRT device implantation procedure might increase LV electrical remodelling odds and reduce the percentage of CRT non-responders. Intraprocedural BiV QRS measurements/QRS narrowing assessment can be used as a tool for choosing optimal coronary sinus branch and both LV lead and RV lead positions, similarly to using maximal electric separation.[20] During follow-up, response in BiV QRS duration can guide AV delay optimization (to limit fusion or to allow greater fusion with native conduction via the right bundle) and VV delay interval optimization (to compensate for latency during LV pacing, if present). It was recently shown that such strategy, i.e. programming deliberately aimed at QRS narrowing can influence outcomes.[21,22] When QRS narrowing is unachievable with BiV pacing, perhaps it should be an indication that a different approach should be used to correct LBBB, such as direct His-bundle pacing or endocardial LV pacing. In cases of post-procedural QRS widening, careful clinical and echocardiographic monitoring might be warranted to exclude deterioration of cardiac function with BiV pacing (i.e. a desynchronization rather than a resynchronization effect). Worsening of prognosis with both QRS narrowing and widening in the non-LBBB patients (*Figure 3*) might indicate that a desynchronization effect is present in these patients as well. Perhaps LV epicardial pacing cannot improve native conduction when this proceeds via functioning left bundle branch.

Limitations

Retrospective nature of the study may have introduced bias. Impact of echocardiographic optimization was not analysed, however, in our centre this was generally only performed for clinical non-responders. Changes in VV and AV interval during follow-up might have influenced the QRS duration and impact on the relationship between the initial delta QRS and outcome. Neither acute QRS narrowing at implant nor programming aimed at QRS narrowing during follow-up were deliberately and systematically pursued while it was recently reported that this might affect outcomes.

Conclusions

This study showed that immediate shortening of QRS duration with initiation of CRT in patients with LBBB strongly predicts favourable prognosis. Perhaps this reflects correction of LBBB by LV pacing and should be considered a desirable acute electrocardiographic endpoint of CRT device implantation procedure. In contrast, patients with non-LBBB morphologies do not benefit from QRS narrowing and have unfavourable prognosis similar to that seen in LBBB patients without QRS narrowing. This might reflect the fact that in both these patient categories LV pacing corrects nothing. These results prompt questions: if there is QRS widening with commencement of CRT, should BiV pacing be continued? How QRS narrowing can be achieved, and what determines it? We believe that a randomized trial assessing benefits of CRT in patients without acute QRS narrowing and further research aimed at defining operator modifiable factors influencing acute QRS narrowing is necessary.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: none declared.

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