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Delayed prolongation of the QRS interval in patients with left ventricular dysfunction☆

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ABSTRACT

Aims: Patients with left ventricular dysfunction (LVD) and prolonged QRS on surface electrocardiogram are at increased risk for heart failure and death and may benefit from resynchronization therapy. Patients with initial narrow QRS may prolong their QRS during the disease course. The occurrence of delayed QRS prolongation, its predictors and associated risk of heart failure hospitalizations (HFH) or death are currently unknown and the subject of this investigation.

Methods & results: Patients with LVD, QRS < 120 ms and available follow-up ECGs were retrospectively evaluated for persistent unprovoked QRS prolongation >130 ms. Impact on mortality or HFH was assessed using Cox regression with QRS > 130 ms as a time dependent covariate. Following 178 patients for 30 (10;59) median (IQR) months, 28 (16%) patients prolonged their QRS to >130 ms, reaching a QRS duration of 154 ± 29 ms; LBBB pattern was diagnosed among 14 (50%) patients. Patients with delayed QRS prolongation were older (71.9 ± 11.8 vs 64.4 ± 15.1 years $p = 0.014$), had larger left ventricle and left atrial diameters (6.3 ± 0.9 vs 5.7 ± 0.9 cm $p = 0.010$; 4.9 ± 0.6 vs 4.5 ± 0.7 cm $p = 0.006$, respectively) and wider baseline QRS (104.8 ± 12.6 vs 91.4 ± 14.5 ms $p < 0.001$) which was linearly associated with late QRS prolongation (p for trend<0.0001). In a multivariable model, age, baseline QRS width and left atrial diameter were significantly associated with delayed QRS prolongation. QRS prolongation at follow-up was independently associated with risk of death or HFH (HR 7.426, 95% CI3.017−18.280, $p < 0.0001$).

Conclusion: QRS prolongation occurs in a significant proportion of patients with LVD and portends adverse outcome. Advanced age, prolonged QRS and larger left atria are potential predictors. Routine monitoring is justified and physicians may choose to plan ahead for resynchronization therapy in patients at risk for QRS prolongation.

1. Introduction

Among patients with heart failure (HF), ventricular conduction delay manifested by wide QRS interval duration on surface electrocardiogram (ECG) frequently occurs [1,2]]. QRS prolongation is associated with an increased mortality in the general population [3]], and specifically in patients with HF [4]. Wide QRS representing a conduction delay, is usually defined as QRS ≥ 120 milliseconds (ms) [1,5], and is associated with electrical and mechanical dyssynchrony. Left ventricle (LV) dysynchrony adversely affects the pumping function of the ventricle causing elevation in the left atrial pressure together with left ventricular enlargement and valvular dysfunction. Cardiac resynchronization therapy (CRT) delivers synchronized biventricular pacing and was found to improve cardiac function in heart failure patients with wide QRS complexes, resulting in an improved quality of life, decreased hospitalizations due to heart failure exacerbation and improved survival, [1,2,6,7] .

QRS prolongation is a prerequisite for CRT implantation, which is not recommended for QRS < 130 ms [8]]. Patients with a left bundle branch block (LBBB) on ECG benefit more than patients without LBBB [8]]. However, patients presenting with HF

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symptoms may have a narrow QRS initially, and develop a wide QRS later on during the course of their disease. In this sense, patients who are initially ineligible for CRT may become CRT eligible later on. The proportion of patients that present with narrow QRS and develop QRS prolongation during the course of their disease (delayed QRS prolongation) and their characteristics are currently unknown.

This research aims to quantify and characterize patients with LV dysfunction that develop QRS prolongation during routine follow-up.

2. Methods

Medical electronic records of hospitalized and outpatient patients at Shaare Zedek Medical Center between the years 2005–2015 were reviewed. In our hospital, ECGs with computerized analysis (Norav Medical Ltd.) are performed routinely during every outpatient visit, emergency department visits and hospitalizations. The study included patients with echocardiographically determined left ventricular dysfunction (moderate to severe or severe); QRS < 120 ms on surface ECG performed within 90 days of the time of the first echocardiographic evaluation and existence of ≥2 follow-up ECG's done on separate dates >30 days following the initial ECG. The patients were initially identified using computerized queries and were subsequently manually validated and analyzed for QRS duration (AN). Patients with pacing devices were excluded. All consecutive ECGs were evaluated for QRS duration. Patients in which one of the follow-up ECGs revealed a QRS > 130 ms were identified as the group with QRS prolongation. ECGs with QRS prolongation (>130 ms) were manually evaluated by 2 investigators including a senior electrophysiologist (AN, MRA) for QRS duration and pattern and differentiated into left bundle branch block (LBBB), right bundle branch block (RBBB) or nonspecific IVCD (intra ventricular conduction delay). The diagnosis of LBBB and RBBB was made according to the ACC/AHA recommendations for standardization and interpretation of intra ventricular conduction disturbances on ECG [5]. In case of discrepancy between manual and computerized QRS duration, the computerized analysis was used if the discrepancy was <15 ms, otherwise the manual analysis was used. Thereafter, the medical records of these patients were thoroughly reviewed, looking at any potential triggers for QRS prolongation that might have occurred consequent with QRS prolongation; including electrolyte disturbance, cardio-pulmonary resuscitation, acute coronary syndrome, myocardial infarction, or rate dependent-BBB. Patients with any of the above triggers (considered as provoked QRS prolongation) were excluded from this trial. Patients in whom QRS did not persist in a subsequent ECG's were excluded as well. Thus, only patients with persistent unprovoked QRS prolongation were included in this group.

Patient characteristics were retrieved from the electronic medical records. Global echocardiographic assessment of left ventricle and left atrial dimensions were obtained utilizing M-mode from the parasternal position. A global qualitative estimation of left ventricular function was performed with occasional verification using Simpson's technique. Heart failure hospitalization (HFH) was retrieved from the electronic records of our department and defined as hospitalization with documentation of one of the following diagnoses: (1) Heart Failure (2) Congestive Heart Failure (3) CHF (4) Pulmonary congestion as 1st or 2nd diagnosis. Mortality was determined from the Israeli national database.

Statistical analysis: Categorical data are represented as proportions, continuous data as mean ± SD for normally distributed variables or median and interquartile range for non-normal distribution. Comparisons were made using Chi-Square Test, Fisher's exact test, unpaired student t-test and Mann-Whitney test. Linear correlations were assessed using Spearman's method. Multivariable COX proportional hazards model was conducted to identify independent characteristics associated with QRS prolongation. Optimal thresholds for potential predictors were analyzed by receiver operating characteristic (ROC) curves. Cutoff points were determined as the points on ROC curves where the sensitivity and specificity of the variables are equal. Impact on the cumulative endpoint of mortality or HFH was evaluated using stepwise Cox regression with QRS prolongation as a time dependent co-variate. All tests were two sided, p-values < 0.05 were considered statistically significant. Analyses were carried out using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY.

3. Results

Of 315 patients initially considered for the study 137 were excluded mostly due to improper ECGs, inadequate follow-up or transient/provoked QRS prolongation leaving 178 with reduced ejection fraction and narrow QRS on presentation for the primary analysis (Fig. 1). During 30(10;59) median (IQR) months of follow-up, the patients had median (IQR) 11(5;20) electrocardiograms performed. There were 28 (16%) patients with persistent unprovoked QRS prolongation to >130 ms (Fig. 1). Among those, the median time to QRS prolongation was 17[2;38] months and the maximal QRS width during follow up was 153.9 ± 29 ms. Among these patients, 14 (50%) developed LBBB, 9 (32%) had RBBB, and 5 (18%) had an IVCD pattern.

Baseline QRS had a skewed distribution pattern (Supplementary Fig. 1s) with a median (IQR) of 91 (82;106) ms. Baseline QRS was significantly associated with the probability for a delayed QRS prolongation to >130 ms, p for trend <0.0001 (Supplementary Fig. 2s). Table 1 describes the patients' characteristics and comparisons between patients with and without delayed QRS prolongation. Patients with QRS prolongation were significantly older (mean ± SD 71.9 ± 11.8 Vs. 64.4 ± 15.1 years $p = 0.014$), had wider baseline QRS (104.8 ± 12.6 ms vs. 91.4 ± 14.5 ms $p < 0.001$), and

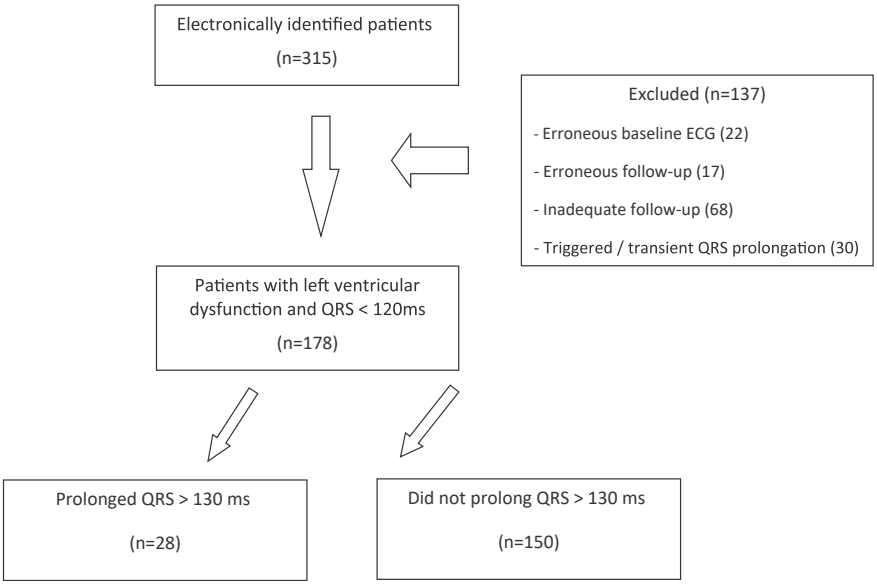

Fig. 1. Potential candidates with significant LV dysfunction and a narrow baseline QRS were identified by computer analysis. Cases with QRS prolongation who had an unprovoked and persistent (≥2 ECG's during follow-up) QRS prolongation>130 ms were validated manually.

Table 1
Patient characteristics.

Variable	All $N = 178$	QRS prolongation $N = 28$	no QRS prolongation $N = 150$	p-value
Demographic and clinical characteristics				
Age (years)	65.6 ± 14.8	71.9 ± 11.8	64.4 ± 15.1	0.014
Male (%)	74.2	75.0	74.0	0.91
Hypertension (%)	60.1	60.9	60.0	0.93
Diabetes Mellitus (%)	34.8	29.2	35.9	0.53
Ischemic heart disease (%)	76.0	87.0	74.0	0.18
Atrial Fibrillation (%)	6.7	7.1	6.6	0.93
Renal Failure (%)	20.8	21.7	20.6	0.90
Echocardiographic measurements				
Mitral Regurgitation ≥Moderate (%)	58	64	57	0.49
Left ventricle end diastolic diameter (cm)	5.8 ± 0.9	6.3 ± 0.9	5.7 ± 0.9	0.010
Left atrial diameter (cm)	4.6 ± 0.7	4.9 ± 0.6	4.5 ± 0.7	0.006
Aortic diameter (cm)	3.3 ± 0.4	3.5 ± 0.6	3.3 ± 0.4	0.14
Tricuspid incompetence gradient (mm Hg)*	38.9 ± 14	37.8 ± 14	39.1 ± 15	0.912
Electrocardiogram				
Baseline QRS (ms)	93.5 ± 15	104.8 ± 13	91.4 ± 15	<0.0001
Maximal QRS (ms)	113.6 ± 26	153.9 ± 29	106.0 ± 18	<0.0001
QRS prolongation from baseline (ms) – "delta QRS increment" (median[IQR])	15 (6;26.5)	41 (26;65.5)	12 (4;20.5)	<0.0001

Available for 176 patients*, values are presented as mean ± SD; median (IQR) or proportions as appropriate.

larger left ventricle and left atrial diameters (6.3 ± 0.9 vs 5.7 ± 0.9 $p = 0.010$; 4.9 ± 0.6 vs 4.5 ± 0.7 $p = 0.006$ cm, respectively). However, there was no significant difference between the groups regarding most other clinical characteristics including atrial fibrillation (AF). Notably, while the patients in the group with delayed QRS prolongation had wider baseline QRS, they also had a significantly larger QRS width increment (delta QRS) during follow up (41 (26;65.5) ms vs. 12 (4;20.5) ms $p < 0.0001$) (Table 1). Nevertheless, on the whole there was no linear correlation between the baseline QRS width and the change in QRS width during follow-up ($R = -0.153$; $p = 0.042$), as illustrated in Supplementary Fig. 3s. Thus, although higher baseline QRS width was associated with the higher probability of QRS prolongation during follow up, it was not associated with a larger increment of QRS prolongation.

In a Multivariable COX model including age, baseline QRS, left atrial and left ventricle end diastolic diameter the former three were significantly associated with delayed QRS prolongation to>130 ms. A separate model including the three parameters which were significantly associated with delayed QRS prolongation, namely age (HR 1.04 (95% CI [1.007–1.076], p 0.017), baseline QRS (HR 1.055 (95%CI [1.025–1.87] $p < 0.0001$), and left atrial diameter (HR 2.115 (95% CI[1.099–4.071] p 0.025) is presented in Supplementary Table 2. Analysis for optimal cutoff values yielded age older than 70 years (AUC 0.6), baseline QRS duration longer than 100 ms (AUC 0.736) and left atrial diameter larger than 4.75 cm (AUC 0.607) as possible predictors for late QRS prolongation (Fig. 2). During 5 years of follow-up, QRS prolongation occurred more frequently and with a constant rate among those with baseline QRS > 100 ms (Supplementary Fig. 4s).

During follow-up 43 (24%) of the patients had a HFH and 71 (39.9%) died. In a multivariable COX model including QRS prolongation to >130 ms (as a time dependent variable) adjusted to age, gender, baseline QRS, left ventricle end diastolic and left atrial diameter, QRS prolongation to > 130 ms was significantly and independently associated with the cumulative adverse outcome (HR 7.426 (95% CI[3.017–18.280] $p < 0.0001$) (Fig. 3).

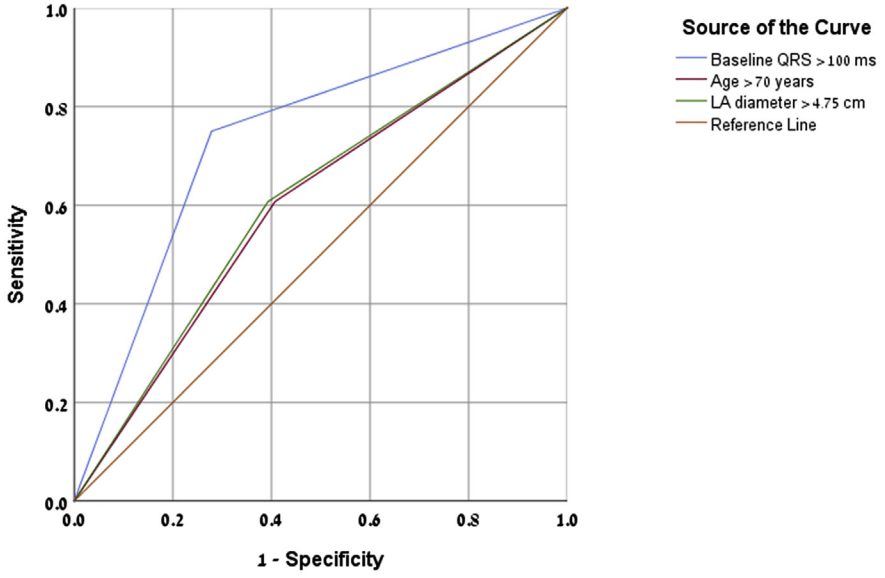

Fig. 2. ROC curves for associated covariates of late QRS prolongation to >130 ms. Baseline QRS > 100 ms is the best predictor (AUC 0.736 $p < 0.0001$).

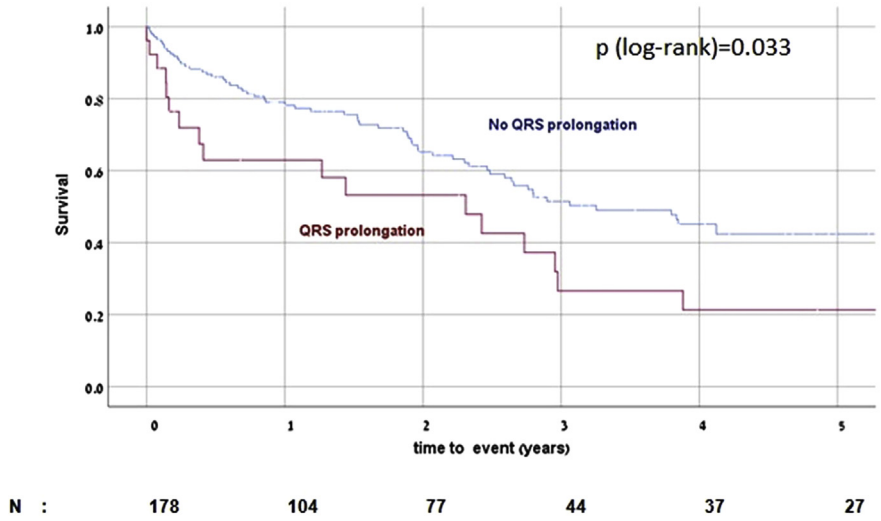

Fig. 3. Occurrence of the cumulative endpoint of death or heart failure hospitalization with QRS prolongation to >130 ms as a time dependent covariate. Patients that prolonged QRS had a significantly worse outcome.

4. Discussion

This study evaluates QRS prolongation over time among patients with LV dysfunction and a narrow QRS. QRS prolongation to >130 ms was identified in 16% of the patients during a median follow-up of 30 months. Half of these patients had LBBB pattern. Increased age, wider baseline QRS, larger left ventricle and atrium were identified as significant possible predictors of future QRS prolongation. Notably, age, baseline QRS width and LA enlargement were found as significant predictors of future QRS prolongation in a multivariable model with baseline QRS > 100 ms as the strongest possible predictor. QRS prolongation over time was significantly and independently associated with an adverse cumulative outcome of mortality or heart failure hospitalizations.

Early studies have described an increase in QRS duration over time in patients with dilated cardiomyopathy [9]. In one of these studies following 58 patients, QRS increased by 5 ± 5 ms/year [10]. Nevertheless, to the best of our knowledge this is the first study to investigate the occurrence and predictors of QRS prolongation in a contemporary cohort of patients with LV dysfunction and initially short QRS duration.

The patients who prolonged their QRS had distinctive baseline features, being older, with a wider baseline QRS and larger atrial and ventricular diameters. While older age is not associated with QRS prolongation in the general population [11], we found increased age to correlate with a delayed QRS prolongation in our population with LV dysfunction. Baseline QRS duration was also associated with the chance of future QRS prolongation. However, there was no linear correlation between baseline QRS duration and the numerical change in QRS (delta QRS). Therefore, delayed QRS prolongation to the range > 130 ms is probably due to a sudden increase in QRS duration that occurs in patients with longer baseline QRS and not due to gradual increase in QRS duration that occur in all patients. Indeed, the significantly larger delta QRS increment among the group with QRS prolongation to a mean QRS duration of 154 ms reinforces this observation. Patients with larger left ventricles may prolong ventricular activation time and QRS duration due to pathology of the specialized conduction system or due to prolonged conduction at the cellular level. Left atrial dilatation may reflect increased left ventricular end diastolic pressures and diastolic dysfunction as well as pathology of atrial electrical conduction.

Wide QRS (>120 ms) is known to be associated with increased mortality among patients with heart failure [4,12]. Indeed the current study validated a significant correlation between wide QRS during follow-up and an increased risk of death or heart failure hospitalization, highlighting the importance of surveillance for QRS prolongation. Therapeutic manipulations directed at the identified risk factors such as left atrial and left ventricle dilatation may prove useful to prevent QRS prolongation and possibly reduce its associated risks.

Importantly, more than half of the patients that widened their QRS developed LBBB pattern. These patients are likely to benefit from biventricular pacing, as was shown in the CARE-HF and MADIT-CRT trials [7,13]. In contrast, biventricular pacing is not recommended and may even be harmful for patients with narrow QRS [2,14]. Heart failure patients with narrow QRS may need a defibrillator implanted for primary or secondary prevention. In the case that electrical desynchrony develops later, the defibrillator may need to be upgraded to a CRT device, a procedure which is associated with potential medical complications and excess cost. Our study provides possible predictors for delayed QRS prolongation. The clinical implication of our study is that patients older than 70 years with CHF, LV dysfunction, QRS width > 100 ms and LA diameter > 4.75 cm in whom our study suggests a significant probability of developing QRS prolongation to QRS width ~150 ms within a median of 17 months, a serious consideration should be taken for implanting a CRT device initially as opposed to the current practice of ICD device in patients with narrow QRS. One might consider implanting a full CRTD system with its LV lead to prevent necessity for another upgrade procedure, associated with a strikingly increased infectious rate, once QRS widens [15,16]. However, this would impose a major financial burden as many patients would be implanted with an expensive CRTD system without widening their QRS. Moreover, many of these patients would be exposed to increased infectious and device malfunction related complications over the years, due to the existence of the “extra” LV lead [15,16], without enjoying the clinical benefit of CRT. Another option would be to implant a “CRTD with plug” in which a CRTD device is implanted without an LV lead and functions as an ICD. This option has the advantage of not exposing patients to increased complication due to excess procedure time and unnecessary endovascular materials (LV lead), and has some financial advantage (as one will save the extra cost of a new CRTD device in case of future upgrade),

but still suffers from the increased risk associated with upgrade procedure (for implanting an LV lead) in those who will prolong their QRS. Whether patients prone to late QRS prolongation would benefit from early CRTD system implantation, or whether a "CRTD with plug" should be implanted at initial presentation in these patients remains to be established.

In conclusion: During portended follow-up, 16% of the patients with left ventricle dysfunction and an initially narrow QRS prolong their QRS to >130 ms, half of these have LBBB pattern. Risk factors for QRS prolongation are advanced age, wide baseline QRS and larger left atrium and left ventricular diastolic diameters. Late occurring QRS prolongation is independently associated with worse outcome.

4.1. Limitations and strengths

The current study has several strengths including the availability of electronic database including repeat EGCs and the manual verification of all baseline and prolonged QRS ECGs. Limitations of the study are its retrospective nature and the limited cohort size as well as the variability in follow-up time between patients that may have caused underestimation of the proportion of patients with QRS prolongation. Heart failure hospitalization events were limited to one center and thus possibly underestimated. Patients with repeat ECGs may be a selected high-risk group; thus, the proportion of QRS prolongation may be over-estimated.

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Declaration of Competing Interest

There was no conflict of interest for any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.024.

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