Relation of Increasing QRS Duration Over Time and Cardiovascular Events in Outpatients With Heart Failure

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An increase in the duration of the QRS complex over time has been shown to be associated with poor clinical outcomes in specific subgroups of heart failure (HF) patients. There is a paucity of data on the clinical impact of increasing QRS duration on outcomes in HF with narrow QRS duration. This was a retrospective study of consecutive adult referrals to a tertiary outpatient HF clinic over a 2-year period. All patients with a narrow QRS, (<130 ms) were included. The primary outcome was mortality. Secondary outcomes were HF hospitalization and a composite of HF hospitalization, implantation of cardiac resynchronization therapy or left ventricular assist device and cardiac transplant. A total of 253 patients with 2 or more QRS measurments were included. Death occurred in 41 patients (16%), 258 HF hospitalizations occurred in 116 patients (46%) and the composite occurred in 127 patients (50%). Multivariable analyses found that a rate of QRS duration change of ≥1 ms/month was independently associated with increased mortality (odds ratio [OR] 2.26, 95% confidence interval [CI] 1.04 to 4.91), HF hospitalization (relative risk [RR] 2.01, 95% CI 1.37 to 2.94), and the composite (OR 2.40, 95%CI 1.44 to 4.02). A new QRS >130 ms was also independently associated with mortality (OR 3.27, 95%CI 1.29-8.32), HF hospitalization (RR 2.75, 95% CI 1.72 to 4.4) and the composite (OR 2.52, 95%CI 1.27 to 4.99). In conclusion, in patients with HF and a narrow baseline QRS, an increase in QRS duration of ≥1 ms per month is associated with increased mortality and HF hospitalization. HF patients may benefit from serial monitoring of QRS duration. **(Am J Cardiol 2019;124:1907−1911)**

In patients with heart failure (HF), a prolonged duration of the QRS complex, defined as >120 ms, is indicative of intraventricular conduction delay and is associated with worse left ventricular (LV) systolic function, LV dilation, mitral regurgitation, and clinical outcomes.[1−5] In patients with HF, the prevalence of QRS duration >120 ms ranges from 25% to 50%.[1,6,7] In previous studies, an increase in QRS duration ranging from 1 to 9 ms per year has been shown to be an independent predictor for adverse events. However, these studies have been conducted in specific populations, including patients with wide QRS durations at baseline, atrial fibrillation, dilated cardiomyopathy, reduced ejection fractions, and the very elderly.[8−11] This investigation examined a population of HF patients with baseline QRS duration <130 ms to determine whether an increase in QRS duration of ≥1 ms/month was associated with increased mortality and other cardiovascular outcomes.

Methods

This was a retrospective cohort study. The University of Manitoba Research Ethics Board approved the study protocol. Consecutive patients attending their initial Heart Failure Clinic assessment at a tertiary academic center between January 1st, 2012 and December 31st, 2013 were screened and included. Inclusion criteria were ≥18 years of age, a diagnosis of HF and a QRS duration of <130 ms as measured on an electrocardiogram (ECG) performed within 6 months of the clinic visit. A QRS of <130 ms was chosen as the cutoff for inclusion as patients with longer durations are most likely to benefit from cardiac resynchronization therapy (CRT).[12] We excluded patients with left bundle branch block and those with a permanent pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy device at the time of enrollment.

The diagnosis of HF at the initial clinic visit was determined by a cardiologist specializing in HF and was based on the Canadian Cardiovascular Society consensus conference recommendations.[13] We included patients diagnosed with HF with preserved ejection fraction or HF with reduced ejection fraction. Baseline and follow-up data including QRS duration, clinical variables, echocardiographic parameters, and cardiovascular events were collected. The HF clinic's electronic database provided the majority of clinical information. A provincial electronic medical record that provides laboratory and radiology results, hospitalizations, prescriptions data, and vital status provided supplemental data. The QRS duration, in milliseconds, was obtained from an automated algorithm (MUSE system, GE Healthcare, Milwaukee, Wisconsin).

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The primary end point of this study was all-cause mortality. Secondary end points were HF hospitalization and a composite of HF hospitalization, implantation of CRT or left ventricular assist device (LVAD), or cardiac transplant.

We hypothesized that an increase in QRS duration of ≥1 ms/month (or 12 ms/year) would be associated with increased rates of adverse events. This number was chosen *a priori* based on the thresholds observed in the existing literature and the practicality of recognizing differences using an automated system.[8–11,14] A convenience sample of 2 years and 300 patients was chosen. Based on baseline demographics, we estimated the rate of the primary outcome would be 20%.[15] This provided power to test up to 6 variables in a multivariable model.[16]

We compared baseline characteristics between patients with and without an increase in QRS duration of ≥1 ms/month using a Mann-Whitney Test for continuous variables, and a Chi-Square or Fisher's Exact Test (when appropriate) for categorical variables. We compared crude rates of outcomes according to QRS duration using a Chi-Square Test for 2 and 3 group comparisons. We used univariable and multivariable logistic regression to assess factors associated with mortality and the composite outcome. The final multivariable logistic regression models were developed using a stepwise selection process with a cutoff of $p < 0.05$ for entry and $p > 0.05$ for removal from the model. One model included those who had at least 2 measurements of QRS duration and a second model assessed the maximum QRS duration in the entire patient population as a sensitivity analysis. Factors associated with the total number of HF hospitalizations were assessed using univariable and multivariable negative binomial regression. The final multivariable model was generated by minimizing the Akaike Information Criteria after including only variables $p < 0.05$ in the univariable analysis.

Results

There were 450 new referrals to the HF clinic over the study period. A total of 298 patients with a median follow up of 1.8 years (interquartile range, [IQR] 0.6 to 2.8 years) and a median of 3 QRS measurements (IQR 2 to 4) met the inclusion criteria. Baseline charactristics of patients with 2 or more QRS measurements are described in Table 1.

Of the 253 patients who had more than one ECG performed, the median QRS duration measured at the second clinic visit was 102 ms (IQR 92 to 114 ms) followed by 106 ms (IQR 96 to 118 ms) at the third visit. A total of 141 patients (56%) had a QRS duration increase ≥1 ms/month. In these patients, the median maximum QRS duration was 118 ms, as compared with 100 ms in patients in whom QRS duration increased by <1 ms/month (p value <0.01). The left ventricular ejection fraction in patients with QRS duration increase ≥1 ms/month at last follow up was 30% (IQR 20% to 45%), compared with 37% (IQR 26% to 51%) in patients with QRS duration increase <1 ms/month.

The overall mortality rate was 16% (41 patients). When compared with patients with QRS duration change of <1 ms/month, patients with QRS duration changes ≥1 ms/month had an increased rate of mortality (Figure 1). There was a significant trend of an increase in the crude rate of mortality with increasing maximum QRS duration (Figure 2). In multivariable analysis, QRS duration increase ≥1 ms/month and max QRS duration ≥130 ms were associated with increased mortality (Table 2, Univariable odds ratio in Table A1).

A total of 258 HF hospitalizations occurred in 116 patients (46%). When compared with patients with QRS duration change of <1 ms/month, patients with QRS duration changes ≥1 ms/month had an increased rate of hospitalization (Figure 1). There was a significant trend of an increase in the crude rate of hospitalization with increasing maximum QRS duration (Figure 2). In multivariable analysis QRS duration increase ≥1 ms/month and QRS duration >130 ms were associated with HF hospitalization (Table 3, Univariable relative risk (RR) in Table A1).

The secondary composite outcome (HF hospitalization, implantation of CRT or LVAD or cardiac transplant) occurred in 127 patients (50%). This included 7 (3%) patients with HF

Table 1
Comparison between patients with QRS duration rate of change ≥1 ms/month vs <1 ms/month

Variable*	Overall population n = 253	Rate of QRS change <1 ms/month (n = 112)	Rate of QRS change ≥1 ms/month (n = 141)	p Value
Age (years)	66 (57-76)	67 (56-76)	66 (58-77)	0.65
Women	86 (34%)	42 (38%)	44 (31%)	0.29
Baseline QRS duration (ms)	98 (90-110)	98 (90-106)	100 (90-114)	0.13
Medical history				
Diabetes mellitus	102 (40%)	48 (43%)	54 (38%)	0.46
Hypertension	171 (68%)	74 (66%)	97 (69%)	0.65
Ischemic heart disease	149 (59%)	59 (53%)	90 (64%)	0.07
Chronic kidney disease	93 (37%)	32 (29%)	61 (43%)	0.02
Atrial fibrillation	99 (39%)	37 (33%)	62 (44%)	0.08
Ischemic cardiomyopathy	136 (54%)	54 (48%)	82 (59%)	0.10
Ejection fraction (%)	30 (20-40)	30 (20-45)	29 (20-39)	0.33
Medications				
Beta blocker	214 (85%)	97 (87%)	117 (83%)	0.43
Angiotensin converting enzyme inhibitor	153 (60%)	61 (54%)	92 (65%)	0.08
Angiotensin receptor blocker	25 (10%)	13 (12%)	12 (9%)	0.41
Mineralocorticoid receptor antagonist	59 (23%)	28 (25%)	31 (22%)	0.57

* Variables are expressed as n (%) and median (quartile 1 to quartile 3).

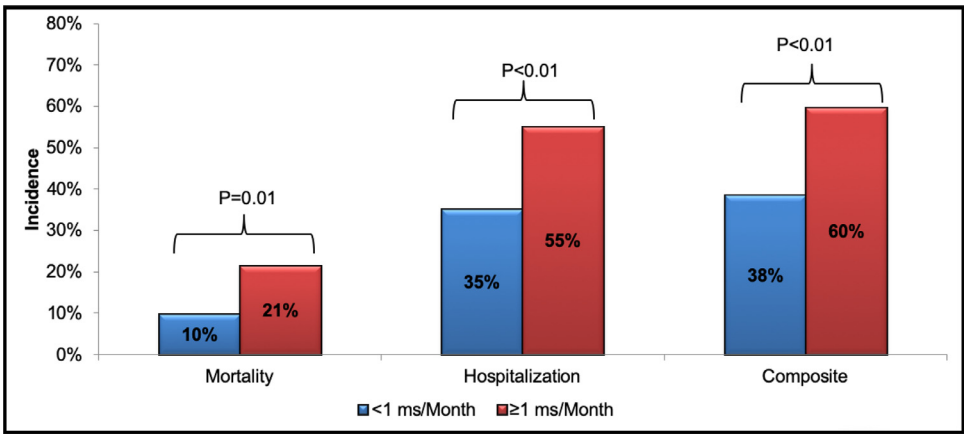

Figure 1. Relationship between rate of QRS duration change over time (<1 ms/month vs ≥1 ms/month) and incidence of mortality, heart failure hospitalization and composite outcome. Composite outcome: heart failure hospitalization, implantation of CRT or LVAD or cardiac transplant.

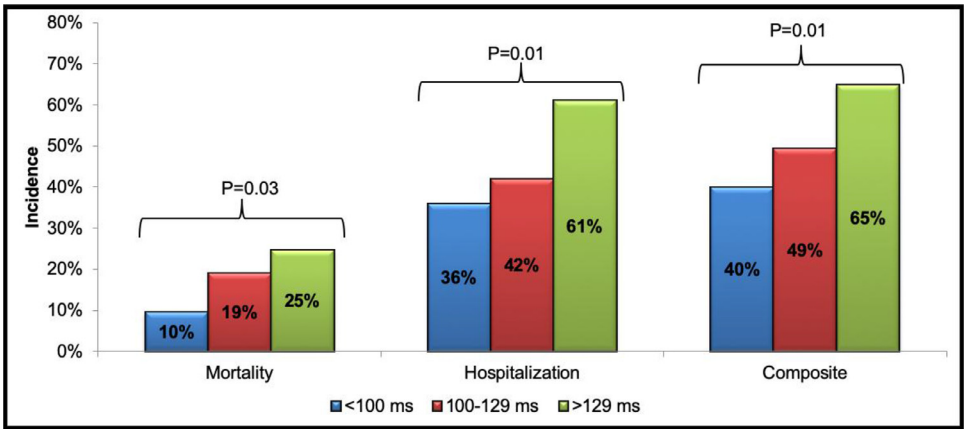

Figure 2. Relationship between maximum QRS duration and incidence of mortality, heart failure hospitalization and composite outcome. Composite outcome: heart failure hospitalization, implantation of CRT or LVAD or cardiac transplant.

Table 2
Multivariable predictors of outcomes – mortality*

Two or more QRS measurements (n = 253)			
Characteristic	Odds ratio	95% Confidence interval	p Value*
Hydralazine use (Baseline)	6.10	1.46–25.50	p = 0.013
Chronic kidney disease	2.18	1.06–4.46	p = 0.034
QRS rate of change ≥1 ms/month	2.26	1.04–4.91	p = 0.040
All study participants (n = 298)			
Characteristic	Odds ratio	95% Confidence interval	p Value*
Hydralazine use (Baseline)	4.21	1.10–16.09	P = 0.036
Chronic kidney disease	2.22	1.16–4.25	P = 0.016
Max QRS 100-129 vs QRS <100	2.13	0.93–4.87	P = 0.073
Max QRS ≥130 vs QRS <100	3.27	1.29–8.32	P = 0.013

* Multivariable logistic regression models developed using stepwise selection process with a cutoff of p <0.05 for entry and p >0.05 for removal form the model.

with reduced ejection fraction who developed left bundle branch block and received a CRT. When compared with patients with QRS duration change of <1 ms/month, patients with QRS duration changes ≥1 ms/month had an increased rate of the composite outcome (Figure 1). There was a significant trend of an increase in the crude rate of the composite outcome with increasing maximum QRS duration (Figure 2). In multivariable analysis, QRS duration increase ≥1 ms/month and QRS duration >130 ms were associated with the composite outcome (Table 4, Univariable odds ratio in Table A1).

Discussion

HF patients with a narrow QRS duration are considered a lower risk population when compared with patients with a wide QRS duration.[6,7] The prognostic value of QRS

Table 3
Multivariable predictors of outcomes − total heart failure hospitalizations*

Two or more QRS measurements (n = 253)			
Characteristic	Risk ratio	95% Confidence interval	p Value*
Beta blocker use (Baseline)	2.37	1.31−4.29	P = 0.004
QRS rate of change ≥1 ms/,onth	2.01	1.37−2.94	p <0.001
All study participants (n = 298)			
Characteristic	Risk Ratio	95% Confidence interval	p Value*
Beta-blocker use (Baseline)	1.77	1.04−3.00	p = 0.034
Max QRS 100-129 vs QRS <100	1.42	0.94−2.15	p = 0.093
Max QRS 130+ vs QRS <100	2.75	1.72−4.40	p <0.001

* Multivariable model selected by minimizing AIC criteria after including only including variables statistically significant in univariable analysis.

Table 4
Multivariable predictors of outcomes − composite (heart failure hospitalization, implantation of CRT or LVAD or cardiac transplant)

Two or more QRS measurements (n = 253)			
Characteristic	Odds ratio	95% Confidence interval	p Value*
Furosemide use (Baseline)	1.82	1.02−3.27	p = 0.044
QRS rate of change ≥1 ms/month	2.40	1.44−4.02	p <0.001
All study participants (n = 298)			
Characteristic	Odds ratio	95% Confidence interval	p Value
Chronic kidney disease	2.01	1.22−3.32	p = 0.006
Pulmonary hypertension	2.67	1.03−6.92	p = 0.044
Max QRS 100-129 vs QRS <100	1.34	0.79−2.27	p = 0.281
Max QRS 130+ vs QRS <100	2.52	1.27−4.99	p = 0.008

* Multivariable logistic regression models developed using stepwise selection process with a cutoff of p <0.05 for entry and p >0.05 for removal form the model. **Composite outcome definition:** heart failure hospitalization, implantation of CRT or LVAD or cardiac transplant.

Table A1
Univariable predictors of outcomes

	Mortality	Heart failure hospitalization	Composite outcome
	OR (95% CI) p	RR (95% CI) p	OR (95% CI) p
Age	1.01 (0.99-1.04) 0.2	1.00 (0.99-1.01) 0.98	1.01 (0.99-1.02) 0.52
Female sex	0.91 (0.48-1.70) 0.75	0.70 (0.48-1.02) 0.06	0.74 (0.46-1.18) 0.2
Diabetes	0.88 (0.47-1.65) 0.68	0.74 (0.51-1.08) 0.01	0.78 (0.49-1.25) 0.3
Hypertension	0.77 (0.41-1.46) 0.42	0.75 (0.51-1.10) 0.14	1.10 (0.68-1.80) 0.7
Ischemic heart disease	1.22 (0.65-2.27) 0.54	0.98 (0.68-1.42) 0.93	0.96 (0.61-1.52) 0.9
Chronic kidney disease	2.61 (1.41-4.84) 0.002	1.61 (1.12-2.33) 0.01	2.06 (1.27-3.34) 0.003
Ischemic cardiomyopathy	1.61 (0.86-2.99) 0.14	1.05 (0.73-1.51) 0.8	1.12 (0.71-1.77) 0.6
Baseline ejection fraction (per 1%)	1.01 (0.98-1.03) 0.67	1.01 (1.00-1.02) 0.15	1.01 (0.99-1.02) 0.3
QRS baseline	1.02 (1.00-1.05) 0.046	1.01 (1.00-1.03) 0.038	1.01 (0.99-1.02) 0.45
Last QRSd	1.02 (1.00-1.03) 0.006	1.01 (1.01-1.02) <0.0001	1.02 (1.01-1.03) 0.003
Max QRSd	1.02 (1.00-1.03) 0.009	1.01 (1.01-1.02) <0.0001	1.02 (1.01-1.03) 0.002
Max QRSd 100-129 ms vs max QRSd <100 ms	2.25 (1.03-4.90) 0.04	1.40 (0.92-2.11) 0.12	1.46 (0.87-2.44) 0.15
Max QRSd ≥130 ms vs max QRS <100 ms	3.09 (1.27-7.52) 0.013	2.84 (1.77-4.56) <0.0001	2.78 (1.42-5.42) 0.003
Rate of QRSd Change ≥1 ms/month	2.48 (1.18-5.21) 0.01	1.92 (1.30-2.81) 0.0009	2.36 (1.42-3.93) 0.0008

Composite outcome definition: heart failure hospitalization, implantation of CRT or LVAD or cardiac transplant.
Odds ratios/risk ratios and corresponding confidence intervals were calculated based on non-missing data for given covariate.

duration progression over time in patients with a narrow QRS duration is not well established. This study explores the effect of QRS duration progression in patients with a QRS duration of <130 ms and the relation of QRS duration to several clinical outcomes. To the best of our knowledge, this is the first study to examine the impacts of prolonging QRS duration in a general HF population with a baseline QRS duration <130 ms.

Similar to exisitng literature, we found a narrow QRS duration is relatively common in HF patients, representing the majority of new referrals to HF clinic. However, the majority of patients also experienced QRS prolongation of greater than

>1 ms/month. This rate of QRS prolongation was independently associated with mortality, HF hospitalization and a composite outcome of HF hospitalization, CRT, LVAD, or cardiac transplant. Our study included patients from a general outpatient HF population irrespective of age, etiology, systolic function, or co-morbidities. The relation between QRS prolongation of ≥1 ms/month and worse clinical outcomes was irrespective of the presence of co-morbidities, apart from patients with CKD who had a higher mortality.

Our results suggest that regular, repeated ECGs should be considered in the outpatient HF population. Progression of QRS duration may identify high-risk patients who may benefit from closer follow-up or changes in management, including consideration of CRT in eligible patients.

This study has several limitations including its single-center, retrospective observational design, and small sample size. QRS duration measurement was based on automated ECG interpretations for consistency but may have affected accuracy.[14] The decision to obtain an ECG was based on clinical judgment with no prespecified algorithm. Time since initial diagnosis was not recorded and might be different between patients. Also, given that this is a tertiary HF clinic, the findings may not be generalizable to all patients.

In conclusion, in HF patients with a narrow QRS, it is common for QRS duration to increase over time and this increase is associated with worse outcomes. HF patients may benefit from longitudinal ECG surveillance.

Disclosures

The authors have no conflicts of interest to disclose.

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