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CLINICAL RESEARCH STUDY

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Prognostic Significance of Quantitative QRS Duration

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ABSTRACT

BACKGROUND: Although QRS duration is known to be a predictor of mortality in patients with left ventricular dysfunction, our purpose was to evaluate the prognostic power of computer-measured QRS duration in a general medical population.

METHODS: Analyses were performed on the first electrocardiogram digitally recorded on 46,933 consecutive patients at the Palo Alto Veterans Affairs Medical Center between 1987 and 2000. Patients with electrocardiograms exhibiting Wolff-Parkinson-White were excluded (n = 44), and those with bundle branch block or electronic pacing were considered separately, leaving 44,280 patients for analysis (mean age 56 ± 15 years; 90% were males). There were 3659 (8.3%) cardiovascular deaths (mean follow-up of 6.0 ± 3.8 years).

RESULTS: A survival plot showed significant separation according to a QRS duration score. After adjustment in the Cox model for age, gender, and heart rate, the QRS duration score was a strong independent predictor of cardiovascular mortality. For every 10-ms increase in QRS duration, there was an 18% increase in cardiovascular risk. The results were similar in patients with an abnormal electrocardiogram, a bundle branch block, and a paced rhythm.

CONCLUSION: Quantitative QRS duration was a significant and independent predictor of cardiovascular mortality in a general medical population.

KEYWORDS: Electrocardiography; QRS duration; Cardiovascular mortality

The prognostic value of QRS duration in 2 groups of patients with structural heart disease has been demonstrated: those with prior myocardial infarction (MI) and ventricular dysfunction and those with medically refractory congestive heart failure (HF). The Multicenter Automated Defibrillator Implantation Trial II demonstrated that prophylactic implantation of an internal cardioverter defibrillator in patients with previous MI and left ventricular dysfunction improved survival. Subset analysis revealed that patients with the greatest prolongation of QRS duration had the greatest survival benefit from device therapy.[1] As a result of this finding, previous Medicare guidelines for internal cardioverter defibrillator reimbursement required QRS duration greater than 120 ms.[2] Likewise, the emergence of biventricular pacing therapy for HF relies on the premise that multisite pacing can correct the mechanical dyssynchrony seen in patients with intraventricular conduction delay (IVCD). In fact, it has been demonstrated that patients with longer QRS durations are more likely to improve their functional status.[3]

From March 1987 to December 1999, the Palo Alto Veterans Affairs Medical Center has maintained a database with at least one computerized electrocardiogram (ECG) from 46,933 patients. These ECGs were obtained from inpatients and outpatients and represent findings from a broad sample of patients. This is in contrast with previous studies that targeted select populations with structural heart disease or community epidemiologic cohorts (Framingham). Thus, our sample comes from a setting where the ECG is commonly used as the first assessment tool for possible cardiac disease and is used

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by physicians in the decision process to determine the need for further testing.

METHODS

Study Design

The study design is a retrospective analysis of all ECGs obtained at the Palo Alto Veterans Affairs Medical Center from March 1987 to 2000. They were digitally recorded and stored in the General Electric cardiology database system (MUSE, General Electric Medical Systems, Milwaukee, Wis). ECGs obtained in an inpatient or emergency department setting were flagged. When a patient had more than one ECG in the database, only the first one was considered. Standardized, computerized ECG criteria as described by a 12-lead ECG analysis program were used (see *MUSE/12 Lead ECG Physician Program Manual* at www.gemedicalsystems.com). Because digital sampling can lead to underrecognition of pacing spikes, all ECGs with QRS durations greater than 135 ms without appropriate diagnostic classifications (ie, bundle branch block [BBB], n = 506) were visually inspected by 3 separate investigators (A.D.D., T.Y., A.K.) and correctly classified.

Computer-measured ECG waveforms and parameters and several computerized ECG interpretations were extracted. Patients were classified according to a QRS duration score: QRS duration less than 110 ms = score of 1; 111 to 120 ms = score of 2; 121 to 130 ms = score of 3, and greater than 130 ms = score of 4. Criteria for left bundle branch block (LBBB) include that the T-wave vector be 180 degrees from the QRS vector, loss of anterior forces, and an RsR prime in lateral leads.

The institutional review board of the Palo Alto Veterans Affairs Medical Center approved the study.

Patients

Analysis was performed on 2 groups of patients: all those without BBB or electronic pacing and patients with BBB or electronic pacing. The reason for this separation was to determine whether QRS duration alone had prognostic value independent of BBB or pacing. ECGs exhibiting Wolff-Parkinson-White pattern (ventricular pre-excitation, N = 44) were excluded. Further analysis was performed on 2 subsets in those without BBB or electronic pacing: normal and abnormal ECGs. An abnormal ECG was defined as having one of the following: right ventricular hypertrophy or left ventricular hypertrophy (LVH), right or left axis deviation, abnormal Q waves, abnormal T-wave inversion, abnormal ST segment depression, atrial fibrillation, or corrected QT interval greater than 450 ms. Abnormal ST depression was defined as ST depression greater than or equal to 0.5 mm in any one of leads II, V2, or V5. Left axis deviation was defined as an R-wave axis that was more negative than 45 degrees. LVH with strain was defined LVH voltage criteria with abnormal ST depression, and the points for the Romhilt-Estes classification for LVH were calculated (>4 points = LVH).[4]

CLINICAL SIGNIFICANCE

- QRS prolongation measured by computer is a significant predictor of cardiovascular mortality in a general medical population.
- Every 10 millisecond increase in QRS duration was associated with an 18% increase in risk of cardiovascular death.
- Our findings support the use of standard electrocardiography for stratifying patients for interventions that can improve survival.

Outcome Variables

The primary outcome variable was mortality from a cardiovascular (CV) cause. The California Health Department Service and Social Security Death Index were used to ascertain the vital status of each patient as of December 31, 2000. The majority of deaths were the result of CV disease (36.5% of total deaths).

Statistical Analysis

The database was imported into Number Cruncher Statistical System (Kaysville, Utah) for analysis. Descriptive statistics were used to find mean values for continuous variables. Bivariate associations between the two groups were tested by using chi-square tests for dichotomous variables and *t* tests for continuous variables (2-tailed, unpaired). All variables were first tested for normality of distribution. A *P* value less than .05 was considered statistically significant. Kaplan-Meier curves were generated for individual variables to display impact on survival. Cox proportional hazard testing was performed to assess independent predictors of mortality, and hazard ratios were calculated after the assumptions of the model were confirmed. The variables were tested for independence and normal distributions. The significant variables were chosen by auto-selection with a Z value of 2 and 20 iterations.

RESULTS

Thirty-five percent of the ECGs with QRS greater than 135 ms were not recognized as paced rhythms by the computer program and were subsequently reclassified after visual inspection and placed in the correct groups. There were 44,280 patients without BBB or paced rhythms and 18,403 patients in the abnormal ECG subset. The breakdown of patients with BBB and paced rhythms was as follows: 625 with LBBB, 1675 with right bundle branch block (RBBB), and 309 with paced rhythms.

Table 1 Baseline Characteristics of Group 1 (Electrocardiograms without Bundle Branch Block or Paced Rhythms) and Associated Survival Stratified by QRS Duration Score

		QRS Duration (ms)*				
Characteristic	Total	<110	111-120	121-130	≥130	*P* Value†
Number	44,280	41,154	2325	441	360	
Age (y)	56.2 ± 14.6	55.9 ± 14.5	58.9 ± 14.4‡	63.8 ± 13.6‡	66.3 ± 11.3‡	<.001
Males	39,800 (89.9%)	36,749 (89.3%)	2262 (97.3%)‡	435 (98.6%)‡	354 (98.3%)‡	<.001
Outpatient status	32,140 (72.6%)	30,035 (73.0%)	1607 (69.1%)‡	284 (64.4%)‡	214 (59.4%)‡	<.001
QRS duration (ms)	92.7 ± 12.0	90.6 ± 9.3	114.8 ± 3.0‡	125.2 ± 2.3‡	142.7 ± 16.4‡	<.001
Abnormal electrocardiogram‖	18,403 (41.6%)	16,165 (39.3%)	1523 (65.5%)‡	371 (84.1%)‡	344 (95.6%)‡	<.001
Atrial fibrillation	1195 (2.7%)	1069 (2.6%)	81 (3.5%)§	20 (4.5%)§	25 (6.9%)‡	<.001
Premature ventricular contraction	1652 (3.7%)	1393 (3.4%)	175 (7.5%)‡	41 (9.3%)‡	43 (11.9%)‡	<.001
Left ventricular hypertrophy	1955 (4.4%)	1519 (3.7%)	287 (12.3%)‡	87 (19.7%)‡	62 (17.2%)‡	<.001
Corrected QT >450 (ms)	5219 (11.8%)	4354 (10.6%)	514 (22.1%)‡	147 (33.3%)‡	204 (56.7%)‡	<.001
Q waves present	5337 (12.1%)	4527 (11.0%)	560 (24.1%)‡	141 (32.0%)‡	109 (30.3%)‡	<.001
Single Q-wave distribution						
Anterior	769 (16.1%)	656 (16.0%)	79 (16.7%)	18 (16.2%)	16 (19.5%)	<.001
Lateral	115 (2.4%)	91 (2.2%)	7 (1.5%)	5 (4.5%)	12 (14.6%)‡	<.001
Inferior	3217 (67.2%)	2751 (66.9%)	344 (72.9%)‡	75 (67.6%)	47 (57.3%)	<.001
T-wave inversion	4763 (10.8%)	3920 (9.5%)	528 (22.7%)‡	147 (33.3%)‡	168 (46.7%)‡	<.001
ST depression	6838 (15.4%)	5962 (14.5%)	540 (23.2%)‡	160 (36.3%)‡	176 (48.9%)‡	<.001
Cardiovascular death	3659 (8.2%)	3008 (7.3%)	401 (17.2%)‡	114 (25.9%)‡	136 (37.8%)‡	<.001

*QRS duration in milliseconds.

†*P* value for comparison of 4 groups based on QRS duration.

‡$P < .01$ versus QRS duration less than 110 milliseconds.

‖Includes electrocardiograms with atrial fibrillation, premature ventricular contraction, left axis deviation/right axis deviation left ventricular hypertrophy/right ventricular hypertrophy, abnormal Q waves, abnormal ST depression, abnormal T wave inversion, corrected QT interval >450 milliseconds.

§$P < .05$ versus QRS duration less than 110 milliseconds.

Baseline Demographics and Clinical Characteristics

The mean height of our population was 1.75 ± 0.1 m, the weight was 83 ± 18 kg, and the body mass index was 27.2 ± 5.5, with no clinically meaningful differences noted. Table 1 shows the characteristics of patients without BBB or paced rhythms classified by ranges of the QRS duration. Age, CV mortality, inpatient status, and prevalence of ECG abnormalities all increased with increasing QRS duration. Patients with QRS duration greater than 130 ms were the oldest, had the highest prevalence of other ECG abnormalities (95%), and had the highest CV mortality.

Table 2 is comparison of the subsets of normal and abnormal ECGs and LBBB, RBBB, and paced rhythms. The BBB and paced rhythm subsets tended to be older with prolonged QRS durations. The mean QRS duration for the normal and abnormal ECG subsets was relatively normal.

Mortality

In patients without BBB or paced rhythms, there were 3659 CV deaths (36.5% total deaths [N = 10,016]) during a mean follow-up of 6.0 ± 3.8 years. The differences in demographics and clinical characteristics between those who died of CV causes and those who survived were statistically significant (Table 3).

When patients without BBB or paced rhythms and patients with BBB and paced rhythms were compared, the following was noted: Annual mortality was highest in the paced group, followed by those with LBBB and RBBB (Table 2). Those with an abnormal ECG without BBB or paced rhythm had a lower annual mortality, and those with a normal ECG had the lowest annual mortality.

Kaplan-Meier Survival Curves

In patients without BBB or paced rhythms, a survival plot showed significant separation according to the QRS duration score (Figure 1). The annual mortality for a QRS greater than 130 ms (score of 4) was 6.6%. For those with LBBB, RBBB, and paced rhythms, a cut-point was used for QRS duration rather than the score (Figures 2 and 3), and similar associations between QRS duration and CV mortality were seen.

Univariate Survival Analysis

After adjustment in the Cox model for age, gender, and heart rate, the QRS score was a strong independent predictor of CV mortality in patients without BBB or paced rhythms (Table 4). For each score point increase, the risk of CV death increased 60%. Thus, an increase in QRS duration score from 1 to 4 (or a QRS duration ≤ 110 ms to >130 ms) was associated with a 180% increase in the risk of CV death

Table 2 Baseline Characteristics of the Electrocardiogram Subsets and Associated Mortality

Characteristic	Normal Electrocardiogram	Abnormal Electrocardiogram*	Left Bundle Branch Block	Right Bundle Branch Block	Paced	*P* Value†
N	25,877	18,403	625	1675	309	
Age (y)	52.6 ± 14.3	61.2 ± 13.5‡	69.2 ± 10.6‡	68.6 ± 11.2‡	72.2 ± 10.5‡	<.001
Males	23,068 (89.1%)	16,762 (91.1%)‡	565 (90.4%)	1615 (96.4%)‡	294 (95.1%)‡	<.001
Outpatient status	14,910 (57.6%)	12,457 (67.7%)‡	433 (69.3%)‡	1175 (70.1%)‡	201 (65.0%)‡	<.001
QRS duration (ms)‖	90.9 ± 10.0	95.1 ± 14.0‡	152.0 ± 17.7‡	141.4 ± 14.5‡	175.4 ± 28.8‡	<.001
> 120 (ms)	183 (0.7%)	988 (5.4%)‡	623 (99.7%)‡	1621 (96.8%)‡	294 (95.1%)‡	<.001
< 150 (ms)	25,877	18,328 (99.6%)‡	306 (49.0%)‡	1268 (75.7%)‡	39 (12.6%)‡	<.001
150-180 (ms)	(-)	67	271 (43.4%)	374 (22.3%)	112 (36.2%)	<.001
> 180 (ms)	(-)	8	48 (7.7%)	33 (2.0%)	158 (51.1%)	<.001
Cardiovascular Death	1042 (4.0%)	2617 (14.2%)‡	162 (25.9%)‡	307 (18.3%)‡	99 (32.0%)‡	<.001
Annual mortality	0.5%	2.3%	5.3%	3.6%	7.1%	<.001

*Includes electrocardiograms with atrial fibrillation, premature ventricular contraction, left axis deviation/right axis deviation, left ventricular hypertrophy/right ventricular hypertrophy, abnormal Q waves, abnormal ST depression, abnormal T wave inversion, corrected QT interval >450 ms.

†*P* value for comparison of each group based on QRS duration.

‡$P < .001$ versus normal electrocardiogram group.

‖QRS duration categorized into 4 groups.

(1.8 times increased risk). Similarly, for each 10-ms increase in QRS duration, the risk of CV death increased 21%. Furthermore, the results were unaffected by the inpatient/outpatient status.

The results were similar in the patients with LBBB, RBBB, and paced rhythm. Although the paced rhythm subset did not have a statistically significant difference in hazard ratio between patients with QRS durations greater than 180 ms versus those with QRS durations less than 180 ms, there was a trend toward higher mortality in patients with longer QRS durations. When QRS duration was compared with other ECG criteria including LVH, Q waves, and damage scores,[5,6] it had a powerful predictive value being chosen second in the Cox-Hazard model after the Cardiac Infarction Injury Score.

DISCUSSION

This study of a large cohort of general medical patients demonstrates that an increase in QRS duration is associated

Table 3 Survival of Primary Study Group Related to Baseline Characteristics

Characteristic	Total (N = 44,280)	Cardiovascular Deaths (n = 3659)	Survivors (n = 34,264)	*P* Value*
Age (y)	56.2 ± 14.6	67.5 ± 11.3	53.6 ± 14.1	<.0001
Males	39,800 (89.9%)	3475 (95.0%)	30,301 (88.4%)	<.0001
Body mass index (kg/m^2)	27.2 ± 5.5	26.7 ± 5.2	27.6 ± 5.5	<.0001
Outpatient status	32,140 (72.6%)	2130 (58.2%)	26,456 (77.2%)	<.0001
Electrocardiogram features				
QRS duration (ms)	92.7 ± 12.0	97.6 ± 15.8	92.3 ± 11.1	<.0001
Abnormal electrocardiograms†	18,403 (41.6%)	2617 (71.5%)	12,341 (36.0%)	<.0001
Atrial fibrillation	1195 (2.7%)	307 (8.4%)	634 (1.9%)	<.0001
Left ventricular hypertrophy	1955 (4.4%)	435 (11.9%)	1205 (3.5%)	<.0001
Premature ventricular contraction	1652 (3.7%)	321 (8.8%)	1024 (3.0%)	<.0001
Corrected QT interval >450 (ms)	5219 (11.8%)	915 (25.0%)	3015 (8.8%)	<.0001
Q waves present	5337 (12.1%)	927 (25.3%)	3494 (10.2%)	<.0001
Distribution of single Q-wave areas				
Anterior	769 (16.1%)	144 (18.5%)	464 (14.5%)	.006
Inferior	3217 (67.2%)	503 (64.5%)	2214 (69.5%)	.007
T-wave inversion	4763 (10.8%)	1034 (28.3%)	2893 (8.4%)	<.0001
ST depression	6838 (15.4%)	1154 (31.5%)	4338 (12.7%)	<.0001

*P value is based on comparison between cardiovascular deaths and survivors.

†Includes electrocardiograms with atrial fibrillation, premature ventricular contraction, left axis deviation/right axis deviation, left ventricular hypertrophy/right ventricular hypertrophy, abnormal Q waves, abnormal ST depression, abnormal T-wave inversion, and corrected QT interval >450 ms.

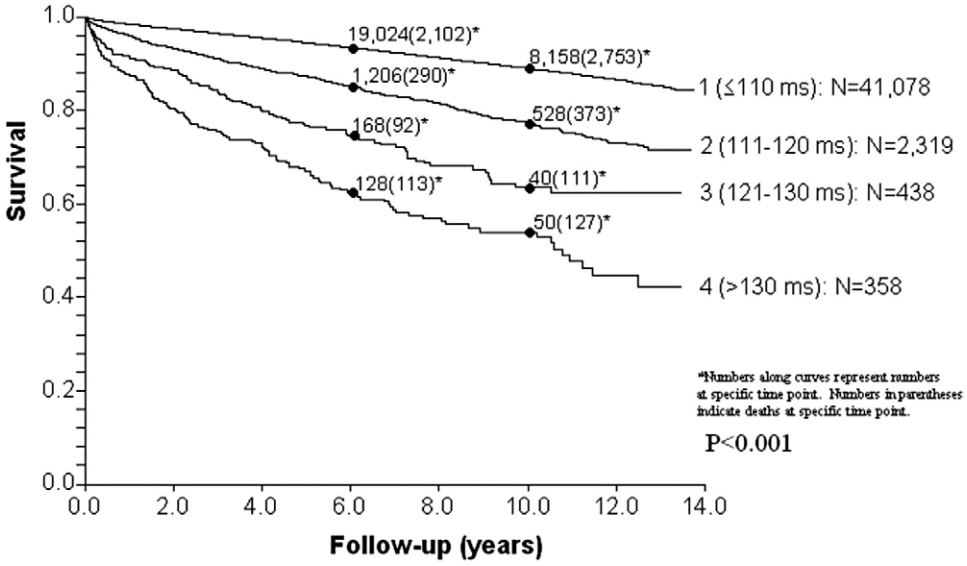

Figure 1 Kaplan-Meier survival plot of primary group according to QRS duration score. Four subject groups are displayed representing different QRS duration ranges. N = total number of subjects in each group. Numbers above each survival curve refer to subjects evaluated at each time point. Numbers in parentheses are cumulative numbers of subject deaths at each point.

with an increase in the risk of CV death. Patients were separated into two main groups: those with BBB and paced rhythms and those without these findings. In patients with BBB and paced rhythms, a markedly prolonged QRS duration (>150 ms for BBB and >180 ms for paced rhythms) was found to be associated with a higher CV mortality risk. More important, in patients without BBB or paced rhythms, an increase in QRS duration from less than or equal to 110 ms to greater than 130 ms was associated with a 180% increased risk of CV death. Few studies have examined the prognostic value of QRS duration independent of BBB, but they have been limited by small numbers or conflicting results.[7-10]

General Medical Populations

Schneider et al.,[11] as part of the Framingham Heart Study, determined CV risk in 70 patients with RBBB who were followed for up to 18 years. CV mortality was three times greater in patients with RBBB than an age-matched sample of the population at large. ECGs with QRS duration greater than 130 ms were most likely to have associated CV abnormalities such as HF. These same investigators studied 55 patients who developed LBBB and found that the QRS duration did not correlate with the prevalence of associated CV abnormalities.[12] A higher mortality rate from CV disease was seen in men with LBBB versus RBBB. This rate was higher than in women with either conduction abnor-

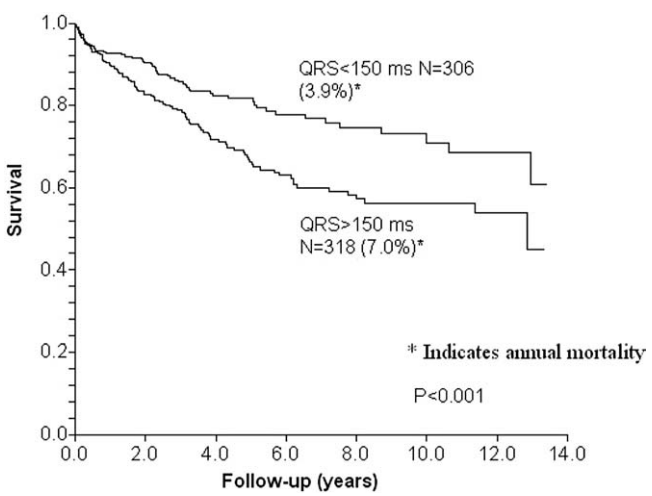

Figure 2 Kaplan-Meier survival plot of left bundle branch block (LBBB) group. Two groups are displayed: QRS < 150 ms and QRS > 150 ms. *Annual mortality for each group.

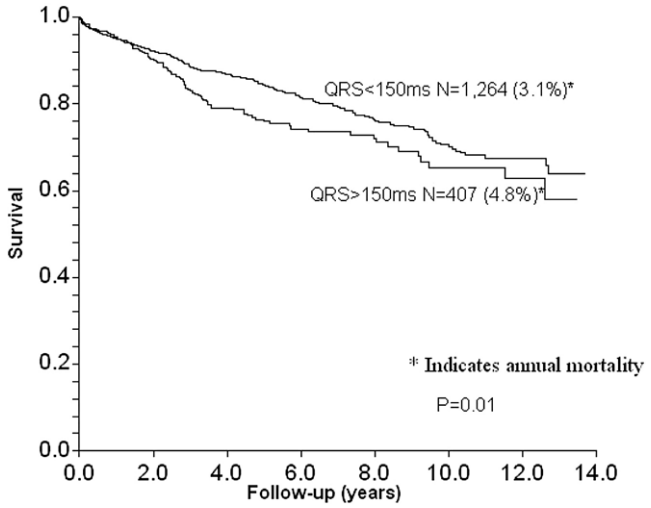

Figure 3 Kaplan-Meier survival plot of right bundle branch block (RBBB) group. Two groups are displayed: QRS < 150 ms and QRS > 150 ms. *Annual mortality for each group.

Table 4 Univariate Analysis of QRS Duration Adjusted for Age, Heart Rate, and Sex

Study Group	Variable	Hazard Ratio	95% CI	*P* Value
Group 1: All subsets	QRS duration score (1-4)	1.59	1.53-1.67	<.001
Group 1: All subsets	QRS duration (10 ms* increments)	1.21	1.19-1.22	<.001
Group 2: Left bundle branch block	QRS > 150 ms	1.75	1.26-2.41	<.001
Group 2: Right bundle branch block	QRS > 150 ms	1.44	1.12-1.84	<.005
Group 2: Paced	QRS > 180 ms	1.48	0.99-2.22	.07

CI = confidence interval.
*Milliseconds.

mality.[13] Kreger et al.[14] found the age-adjusted incidence of MI, angina pectoris, and coronary death to be unrelated to baseline QRS prolongation.

Select Samples

Acute Myocardial Infarction. Brilakis et al.[15] found that increased QRS duration in the absence of BBB was independently associated with higher in-hospital and overall mortality in patients with non-ST elevation MI versus ST elevation MI. A Global Utilization of Strategies to Open Occluded Coronary Arteries substudy of patients with ST elevation MI found that QRS duration was a strong predictor of mortality.[16]

Postmyocardial Infarction. Greco et al.[17] studied the 10-year survival rate of 321 patients post-MI by analyzing the impact of an IVCD on mortality. Mortality was 74% in the presence of an IVCD versus 39% without an IVCD. Analyzed by QRS duration, survival was 55% with QRS less than 120 ms, 23.8% with QRS from 120 to 140 ms, and 4% with QRS greater than 140 ms.[17]

Heart Failure. Brophy et al.[18] reported that IVCD was associated with worsened survival in patients with HF. Shenkman et al.[19] found a linear relationship between increased QRS duration and decreased ejection fraction. A prolonged QRS duration of 120 to 149 ms demonstrated increased mortality. Shamim et al.[20] found that QRS prolongation over time predicted mortality and that a greater than 20% increase in duration was associated with the worst prognosis. Iuliano et al.[21] found that LBBB was associated with a worse survival than RBBB or IVCD and that among a given ejection fraction class, QRS duration still stratified risk. Bruch et al.[22] prospectively enrolled 193 patients with HF and an ejection fraction less than 45%. They found that in subjects with HF and systolic dysfunction, transmitral flow patterns added incremental value to QRS duration in determining the prognosis.

Sick Sinus. Baseline QRS duration from 12-lead ECGs before pacemaker implantation was analyzed in the Mode Selection Trial, a 6-year, 2010-patient, randomized trial of dual-chamber versus ventricular pacing in sinus node dysfunction.[23] Baseline QRS duration was greater than or equal to 120 ms in 23% of patients and was associated with older age, lower EF, cardiomyopathy, and prior HF. QRS duration greater than or equal to 120 ms was a predictor of death.

Hypertensives. The Losartan Intervention For Endpoint Reduction in Hypertension study investigators measured the QRS duration and QT intervals from hypertensive patients with ECG-LVH randomized to two treatments to decrease blood pressure.[24] Only QRS duration and maximum rate-adjusted QT interval were significant independent predictors of CV mortality.

Several unique characteristics of this study should be considered. The study includes one of the largest sample sizes compared with those published, involves analysis of computer-measured ECG parameters rather than manual assessments, and specifically examines the prognostic power of QRS duration in a general medical population rather than a specialized target group. Furthermore, our findings have a sound theoretical basis. Abnormal and impaired electrical activation of the ventricle(s) can worsen heart function, signify impairment of infra-His conduction as a precursor to advanced heart block, and set the stage for ventricular arrhythmogenesis.[25]

CONCLUSION

QRS duration provides a simple method to stratify patients as to their risk of CV death. In a general medical sample without BBB or paced rhythms, those with a QRS duration greater than 130 ms experience nearly twice the risk of CV death compared with those with a QRS duration of 110 ms or less. Similarly in patients with LBBB and RBBB, a QRS duration greater than 150 ms is associated with greater risk of CV death.

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