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# Relation of QRS Width in Healthy Persons to Risk of Future Permanent Pacemaker Implantation

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## Abstract

In the setting of acute myocardial infarction, prolongation of the QRS interval on an electrocardiogram identifies patients at risk of needing permanent pacemaker implantation. However, the implications of a prolonged QRS in healthy individuals are unclear, especially since the QRS prolongation encountered in this setting is typically mild. We studied the relation between QRS duration and incident pacemaker implantation in a community-based cohort of 8,311 individuals (mean age 54 years, 55% women) who attended 17,731 routine examinations with resting 12-lead electrocardiography. QRS duration was analyzed as both a continuous and categorical variable (<100 milliseconds [ms]; 100 to <120 ms; ≥120 ms). During up to 35 years of follow up, 157 participants (56 women) developed need for a permanent pacemaker. In multivariable Cox regression models adjusting for cardiovascular risk factors and prior or incident myocardial infarction or heart failure, mild QRS prolongation was associated with a 3-fold risk of pacemaker implantation (adjusted hazards ratio [HR] 2.90; 95% confidence interval [CI] 1.81–4.66; P<0.0001), and bundle-branch block was associated with a 4-fold risk of pacemaker implantation (HR 4.43; 95% CI 2.94–6.68; P<0.0001). Each standard deviation increment in QRS duration (11 ms) was associated with an adjusted hazards ratio of 1.14 (95% CI 1.11–1.18; P<0.0001) for pacemaker placement. This association remained significant after excluding

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individuals with QRS ≥120 ms. In conclusion, individuals with a prolonged QRS duration, even without bundle-branch block, are at increased risk for future pacemaker implantation. Such individuals may warrant monitoring for progressive conduction disease.

**Keywords**

epidemiology; risk factors; pacemaker; conduction disease

## INTRODUCTION

In the ambulatory setting, the most common cause of sinus[1] and atrioventricular[2–4] node dysfunction is thought to be progressive fibrosis and sclerosis of the conduction system. This process may also involve the infranodal conduction system and manifest as marked QRS prolongation (bundle-branch block) on a routine electrocardiogram.[5,6] Although marked QRS prolongation often predicts the likelihood of needing a pacemaker in the setting of acute myocardial ischemia or infarction[7] or following cardiac valve surgery,[8] the relation of QRS prolongation with future need for a pacemaker in ambulatory individuals has not been studied. Furthermore, QRS prolongation in the ambulatory setting is frequently mild (<120 milliseconds [ms]), and the clinical significance of mild QRS prolongation is unclear. Thus, we prospectively investigated the association between QRS interval duration and incident pacemaker implantation in a large, well-characterized community-based cohort.

## METHODS

The design and selection criteria of the original and offspring cohorts of the Framingham Heart Study (FHS) have been described previously.[9,10] In this study, we used pooled epochs from repeated examinations. Original cohort participants were eligible if they attended examination 11 (1968–1971, n=2955), examination 17 (1981–1984, n=2179), or examination 23 (1993–1995, n=1026). Offspring cohort participants were eligible if they attended examination 1 (1971–1975, n=5124), examination 3 (1984–1987, n=3873), or examination 6 (1995–1998, n=3532). Participants were excluded if they had a prior history of pacemaker placement (n=9), an inadequate electrocardiogram for measurement of the QRS interval duration (n=99), were aged <20 years at examination (n=246), were taking antiarrhythmic agents (n=134), or were missing covariates (n=470). After these exclusions, 17,731 observations for 8,311 participants were available for analysis. All participants gave written informed consent and the study protocol was approved by the Institutional Review Board at Boston University Medical Center.

At each FHS examination, all attendees underwent a routine physical examination, anthropometry, laboratory assessment of cardiovascular disease risk factors, and standard 12-lead electrocardiography at a paper speed of 25 mm/second. Physician investigators interpreted all 12-lead electrocardiograms. The QRS interval duration was defined as the interval from the onset of the Q or R wave (junction between the P–R isoelectric line and the beginning of the Q or R deflection) to the end of the R or S wave (junction with the ST segment). The maximum QRS duration was measured and recorded to the nearest 10 ms, based on an assessment of all 12 of the leads. During Original cohort cycle 23 and Offspring cohort cycle 6, when both physician-measured and computer-derived QRS duration was available on the same ECGs, the correlation between techniques was high ($r=0.81$, $p<0.001$). The presence of QRS duration 100 to <120 ms was considered to be mild QRS prolongation. The presence of QRS duration ≥120 ms was considered to be bundle-branch block, and criteria advocated by a World Health Organization working group were used to categorize the type of bundle-branch block.[11] Left bundle-branch block (LBBB) was defined as

presence of QRS ≥120 ms; absence of Q waves and presence of wide-notched R waves in $V_5$ and $V_6$; presence of monophasic QS in $V_1$ and $V_2$; and, absence of secondary R waves in $V_1$. Right bundle-branch block (RBBB) was defined as presence of QRS duration ≥120 ms; presence of broad, notched R waves (rsr', rsR', or rSR' patterns) in $V_1$ and $V_2$; and, presence of wide, deep, and notched S waves in $V_5$ and $V_6$. Cases with QRS duration ≥120 ms that did not meet criteria for LBBB or RBBB were categorized as "indeterminate".[11]

All FHS participants are under surveillance for cardiovascular events and procedures. Pacemaker implantation events were ascertained from a review of medical histories, physical examinations at the FHS, and hospitalization and personal physician records, including electrocardiograms. All participants are additionally under surveillance for death and cardiovascular events, including myocardial infarction, coronary insufficiency, stroke, and heart failure.[12] A panel of 3 experienced investigators reviewed pertinent medical records for all suspected new events. The indication for each pacemaker implantation was reviewed by a physician investigator (SC) based on the available medical records.

We used the method of pooling repeated observations to assess the relation of QRS duration with the incidence of pacemaker events over consecutive 12-year intervals. Participants became eligible to re-enter the analyses if they remained free of events and met the exclusion criteria at each index visit. Original and offspring cohort participants attended a total of 17,731 person-examinations over the course of up to 35 years of follow-up.

Multivariable proportional-hazard Cox models were constructed for each 12-year follow-up interval, a period over which the hazards of pacemaker placement were proportional. We analyzed the QRS duration as a continuous and as a categorical variable, using the following 3 categories:[11] <100 ms (referent), 100 to <120 ms (mild QRS prolongation), and ≥120 ms (bundle-branch block). Multivariable models adjusted for age, sex, body mass index, hypertension, smoking, diabetes, and history of myocardial infarction or heart failure.

In secondary analyses, we adjusted all analyses for interim myocardial infarction or heart failure as time-dependent covariates; we also repeated all analyses after excluding individuals with a history of myocardial infarction or heart failure. Additionally, we adjusted analyses for baseline PR interval duration, heart rate, and electrocardiographic left ventricular hypertrophy.13 Given the previously reported association of PR prolongation and pacemaker implantation,[14] we also analyzed the relation of QRS duration to pacemaker implantation among individuals with PR ≤200 ms and >200 ms separately. Because nodal blocking medications (e.g. beta-blockers, calcium-channel blockers, and cardiac glycosides) and certain antidepressants can potentially affect conduction times, we performed analyses with and without participants taking these medications. We also investigated whether incident pacemaker placement varied according to type of baseline bundle-branch block in multivariable Cox models (adjusting for the same covariates listed above) that compared individuals with left, right, and indeterminate bundle-branch block (as defined above) with the referent group (QRS <100 ms). Lastly, continuous QRS analyses were repeated after excluding participants with QRS duration ≥120 ms.

All statistical analyses were performed using SAS 9.3.1 (SAS Institute, Cary, NC), and a 2-sided P value <0.05 was considered statistically significant.

## RESULTS

The study cohort (17,731 examinations) was aged 20 to 98 years and more than half were women, as shown in Table 1. Across all examinations, 40% of individuals had hypertension and only 4% had a previous history of myocardial infarction or heart failure. The mean

(±standard deviation) QRS duration was 79 ± 14 ms; 93% had a QRS duration <100 ms, 4% had mild QRS prolongation 100 to <120 ms, and 3% had a QRS ≥120 ms.

During follow up, 157 participants (56 women) had a permanent pacemaker implanted. Pacemakers were implanted predominantly for sinus node dysfunction (57%) and atrioventricular block (34%); only 2 implantations occurred in conjunction with indications for internal cardiac defibrillator placement, and none with indications for bi-ventricular pacing. After adjusting for mortality as a competing risk factor, participants with a baseline QRS ≥100 ms had an incidence of permanent pacemaker implantation per 1000 person years of 7.1 over 10 years, 25.7 over 20 years, and 45.5 over 30 years. In contrast, participants with a baseline QRS <100 ms had an incidence of pacemaker placement per 1000 person years of 1.2 over 10 years, 8.9 over 20 years, and 26.6 over 20 years.

In pooled Cox proportional hazards models (Table 2) adjusting for multiple variables, significant predictors of incident pacemaker placement included older age, male sex, and QRS duration. Each standard deviation increment in QRS duration (11 ms) was associated with an adjusted hazards ratio of 1.14 (P<0.0001) for pacemaker implantation. This effect remained unchanged in analyses adjusting for interim myocardial infarction or heart failure as time-dependent covariates. Results were also unchanged when analyses excluded individuals on nodal-blocking medications or prior myocardial infarction or heart failure. Analyses were repeated using clinical categories for QRS. The adjusted hazards ratios were 2.90 (P<0.0001) and 4.43 (P<0.0001) for pacemaker placement in participants with mild QRS prolongation and bundle-branch block, respectively (Table 3). Among participants not taking nodal-blocking medications, these associations remained highly significant.

Among individuals with bundle-branch block at baseline, the crude incidence rates of pacemaker placement per 1000 person-years were 10.9 (95% confidence interval, 7.4–15.8) among those with RBBB (27 events per 307 person examinations), 4.8 (95% confidence interval, 1.8–12.7) among those with LBBB (4 events per 105 person examinations), and 7.0 (95% confidence interval, 2.3–21.8) among those with indeterminate bundle-branch block (3 events per 53 person examinations). In multivariable analyses, individuals with RBBB had an almost 5-fold increased risk of pacemaker placement (adjusted hazards ratio 4.86, 95% confidence interval 3.13–7.53, P<0.0001) compared to those with a QRS <100 ms.

In continuous QRS analyses, there was no significant effect modification by age (<65 versus ≥65 years), sex, or cohort (original versus offspring). In analyses that excluded individuals with bundle-branch block (QRS ≥120 ms), prolongation of the QRS interval by each standard deviation increment (10 ms) was associated with an adjusted hazards ratio of 1.45 (95% confidence interval 1.15–1.83, P=0.002) for incident pacemaker placement. As well, the relation of QRS duration with pacemaker implantation remained significant after adjusting for interval development of myocardial infarction or heart failure (adjusted hazards ratio 1.45, P=0.002) and after excluding individuals with a history of myocardial infarction or heart failure (adjusted hazards ratio 1.13, P<0.0001). Longer QRS duration also remained associated with pacemaker implantation after adjusting for additional electrocardiographic features, including PR interval duration, heart rate, and LVH (adjusted hazards ratio 1.15, P<0.0001), after excluding individuals taking nodal-blocking agents (adjusted hazards ratio 1.58, P=0.003), and after excluding individuals taking antidepressants (adjusted hazards ratio 1.14, P<0.0001). The multivariable-adjusted relation of QRS duration with pacemaker implantation was significant among both those with PR ≤200 ms (adjusted hazards ratio 1.14, 95% confidence interval 1.09–1.19, P<0.001) and those with PR >200 ms (adjusted hazards ratio 1.47, 95% confidence interval 1.19–1.81, P<0.001).

Among participants with mild QRS prolongation at the initial examinations (offspring cohort examination 1 and original cohort examination 11), 16% went on to have bundle-branch block detected by electrocardiography at 2 or more serial follow-up examinations over the subsequent 8 years. Among participants with normal QRS duration (<100 ms) at the initial examinations, only 1% went on to have bundle-branch block detected at 2 or more follow-up examinations over this same time period.

## DISCUSSION

Our results suggest that individuals in the community with even a mildly prolonged QRS interval are at substantially increased risk for developing a cardiac rhythm disturbance severe enough to require pacemaker implantation. Mild QRS prolongation and bundle-branch block were associated with 3- and 4-fold risks of incident pacemaker implantation, respectively. Furthermore, we observed a graded increase in the risk for pacemaker events across increasing QRS values, even after excluding those with frank bundle-branch block (QRS ≥120 ms). The validity of these findings is supported by the large, community-based sample, the routine surveillance of all participants for incident pacemaker events, the long period of follow-up, and the consistency of the finding in multiple subgroups.

Prior studies have investigated the determinants of permanent pacemaker placement in acute settings, most notably following cardiac surgery[8,15] or acute myocardial infarction.[7] However, the vast majority of pacemakers are not implanted in these situations but, rather, for conditions such as sinoatrial and atrioventricular nodal dysfunction that tend to develop over time – often among apparently healthy individuals.[4,16] To our knowledge, there have been no prior studies of the risk factors associated with the eventual likelihood of permanent pacemaker implantation in the population at large.

QRS duration had the strongest association with future need for a pacemaker after older age, male sex, and history of cardiovascular disease. Although progressive lengthening of QRS duration has been previously correlated with poorer outcomes following myocardial infarction[17,18] and heart failure,[17,19] a large proportion of these events may not be specifically related to conduction disease. Among patients with recent myocardial infarction, incremental QRS prolongation has been associated with higher rates of near-term re-infarction and all-cause death.[18] In patients with heart failure, QRS prolongation is related to worsening systolic function, recurrent heart failure, and cardiovascular death.[17,19] Therefore, increased QRS prolongation in the acute setting may reflect, in part, the severity of the underlying cardiac illness.[17] Accordingly, severe myopathic as well as ischemic cardiac conditions are known to predispose to QRS lengthening.

In the absence of acute illness, there are several potential explanations for the observed association of longer QRS duration with risk for pacemaker implantation. The same progressive fibrosis and sclerosis of the cardiac skeleton that often leads to sinoatrial and atrioventricular nodal dysfunction[1–4] can also prolong conduction below the bundle of His and, thus, predispose to bundle-branch block.[2–4,6] Experimental studies also suggest that aging is associated with diffuse interstitial fibrosis and decreased gap junction connexin expression in the myocardium, manifesting as delayed ventricular activation and a prolonged QRS duration.[20] Therefore, prolonged QRS duration may be a marker of degenerative processes affecting the conduction system below as well as above and including the bundle of His.

Although it is possible that the association between QRS duration and incident pacemaker events is due in part to underlying coronary artery disease, with lesions that may directly or indirectly compromise blood supply to the sinoatrial or atrioventricular nodes,[21] our findings

remained robust even after accounting for incident as well as prior myocardial infarction. Furthermore, individuals with prevalent myocardial infarction or heart failure comprised only 4% of our generally healthy, ambulatory cohort.

Individuals with frank bundle-branch block had the highest risk of pacemaker events. In our sample, RBBB appeared more strongly associated with events than LBBB, a pattern that has previously been observed among individuals following valve surgery[8] and myocardial infarction.[7] This trend could be attributed to the fact that RBBB is frequently accompanied by left fascicular block and, thus, poses a higher risk of complete atrioventricular block upon further injury to the left-sided conduction system.[22] The overall frequency of bundle-branch block was low in our sample, however. Thus, the possibility of this being a chance observation cannot be excluded and further studies are needed to validate the comparison of RBBB and LBBB and to explore possible mechanisms.

Overall, the absolute difference with respect to incidence of pacemaker events between individuals with a QRS ≥100 ms compared to those with a QRS <100 ms was on the order of 6 per 1000 person-years over a 10-year period, but the relative difference was nearly 6-fold. Taken together, these data indicate that, although the long-term incidence of pacemaker implantation in the community is relatively low, QRS prolongation is a strong predictor and may serve as an easily accessible clinical marker for distinguishing between individuals with high versus low risk of developing severe conduction disease.

Several limitations of this study merit consideration. Our analyses were based on the physician-measured QRS duration, which approximates what is done in clinical practice. Reduced measurement precision would likely bias the association of QRS duration with pacemaker placement toward the null. Although QRS prolongation may have variable effects on the risk of severe sinoatrial versus atrioventricular nodal dysfunction, we did not have adequate power to examine these indications separately. Although it is possible that a prolonged QRS influenced the clinical decision to pursue pacemaker placement, the presence of bundle-branch block alone, even in the presence of other electrocardiographic abnormalities, does not constitute an indication for pacemaker placement in ambulatory individuals. Furthermore, incident pacemaker placement was also robustly associated with mild QRS prolongation, an electrocardiographic finding that is highly unlikely to trigger consideration for a pacemaker. Since use of antiarrhythmics is rare in our cohort, individuals taking these medications were excluded from our study sample. We did not have data on use of some medications, such as gastric motility agents, that may have a small effect on QRS duration. We expect regular use of such agents to be infrequent in this relatively healthy sample, and such use would be unlikely to be related to pacemaker outcomes. Thus, substantial confounding from undetected use of such medications is unlikely. Lastly, our sample was predominantly white, potentially limiting the applicability of our results to other racial/ethnic groups.

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## Table 1

Sample Characteristics

| Characteristic | Total Sample Examinations = 17,731 |
|---|---|
| **Age (years)** | 54 ± 16 |
| **Women** | 9684 (55%) |
| **Body mass index (kg/m$^2$)** | 26.4 ± 4.7 |
| **Systolic blood pressure (mm Hg)** | 130 ± 20 |
| **Diastolic blood pressure (mm Hg)** | 78 ± 11 |
| **Hypertension** | 7090 (40%) |
| **Antihypertensive treatment** | 3477 (20%) |
| **Diabetes mellitus** | 1496 (8%) |
| **Smoking** | 6999 (39%) |
| **Prior myocardial infarction or heart failure** | 774 (4%) |
| **QRS (ms)** | 79 ± 14 |
| **QRS width (ms)** | |
| **<100** | 16494 (93%) |
| **100 to <120** | 772 (4%) |
| **≥120** | 465 (3%) |
| **Right bundle-branch block** | 307 (2%) |
| **Left bundle-branch block** | 105 (1%) |
| **Indeterminate bundle-branch block** | 53 (0.3%) |
| **Atrioventricular nodal blocking medications** | |
| **Beta-blockers** | 9.3 |
| **Calcium channel blockers** | 3.2 |
| **Cardiac glycosides** | 2.4 |

Values shown are mean ± SD or number (%).

**Table 2**

Multivariable Relations of QRS Duration and Baseline Characteristics with Risk for Pacemaker Implantation

| Risk Factor | No. Events (No. Person Exams) | Age- and Sex-Adjusted | | Multivariable-Adjusted* | |
|---|---|---|---|---|---|
| | | Hazard Ratio (95% CI) | P-value | Hazard Ratio (95% CI) | P-value |
| Age (years) | - | 6.64 (5.20–8.49) | <0.0001 | 6.06 (4.59–7.98) | <0.0001 |
| Male | 101 (8047) | 3.08 (2.21–4.28) | <0.0001 | 2.48 (1.76–3.48) | <0.0001 |
| Body mass index (kg/m$^2$) | - | 1.17 (0.99–1.39) | 0.073 | 1.14 (0.95–1.35) | 0.155 |
| Hypertension | 111 (7090) | 1.46 (1.03–2.08) | 0.035 | 1.27 (0.89–1.82) | 0.195 |
| Smoker | 47 (6999) | 1.18 (0.82–1.69) | 0.381 | 1.19 (0.83–1.72) | 0.349 |
| Diabetes mellitus | 25 (1496) | 1.52 (0.99–2.33) | 0.058 | 1.28 (0.83–1.98) | 0.271 |
| History of myocardial infarction or heart failure | 35 (744) | 3.08 (2.10–4.54) | <0.0001 | 2.82 (1.91–4.17) | <0.0001 |
| QRS duration (ms) | - | 1.14 (1.11–1.18) | <0.0001 | 1.14 (1.11–1.18) | <0.0001 |

*Models are adjusted for age, sex, body mass index, hypertension, smoking, diabetes, history of myocardial infarction of heart failure, and QRS duration. For continuous variables, hazards ratios represent the event risk per standard deviation of the unit listed.

## Table 3

Multivariable Relations of QRS Duration Category with Risk for Pacemaker Implantation

| QRS Duration (ms) | Age- and Sex- Adjusted | | Multivariable-Adjusted* | |
|---|---|---|---|---|
| | Hazard Ratio (95% CI) | P-value | Hazard Ratio (95% CI) | P-value |
| **Model 1: All individuals** | | | | |
| <100 | Referent | | Referent | |
| 100 to <120 | 3.30 (2.07–5.27) | <0.0001 | 2.90 (1.81–4.66) | <0.0001 |
| ≥120 | 5.10 (3.41–7.63) | <0.0001 | 4.43 (2.94–6.68) | <0.0001 |
| **Model 2: All individuals with further adjustment for incident MI or HF** | | | | |
| <100 | Referent | | Referent | |
| 100 to <120 | 2.96 (1.85–4.74) | <0.0001 | 2.92 (1.82–4.68) | <0.0001 |
| ≥120 | 4.52 (3.01–6.80) | <0.0001 | 4.45 (2.95–6.70) | <0.0001 |
| **Model 3: Subgroup not taking nodal blocking agents** | | | | |
| <100 | Referent | | Referent | |
| 100 to <120 | 4.11 (2.28–7.40) | <0.0001 | 3.82 (2.11–6.92) | <0.0001 |
| ≥120 | 5.76 (3.45–9.63) | <0.0001 | 5.44 (3.24–9.16) | <0.0001 |
| **Model 4: Subgroup not taking nodal blocking agents with further adjustment for incident MI or HF** | | | | |
| <100 | Referent | | Referent | |
| 100 to <120 | 3.65 (2.01–6.61) | <0.0001 | 3.67 (2.02–6.64) | <0.0001 |
| ≥120 | 5.33 (3.17–8.96) | <0.0001 | 5.36 (3.18–9.03) | <0.0001 |

In the whole sample, the number of pacemaker events was 101 of 16,494 person-exams among individuals with QRS <100, 22 of 772 person-exams among individuals with QRS 100 to <120, and 34 of 465 person-exams among individuals with QRS ≥120. In the subgroup of participants not taking nodal blocking agents, the number of pacemaker event was 62 of 14,726 person-exams among individuals with QRS<100, 14 of 608 person-exams among individuals with QRS 100 to <120, and 21 of 350 person-exams among individuals with QRS ≥120.

*All models are adjusted for age, sex, body mass index, hypertension, smoking, diabetes, and history of myocardial infarction or heart failure.