Aspects of Left Ventricular Morphology Outperform Left Ventricular Mass for Prediction of QRS Duration

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Background: The knowledge of the case-specific normal QRS duration in each individual is needed when determining the onset, severity and progression of the heart disease. However, large interindividual variability even of the normal QRS duration exists. The aims of the study were to develop a model for prediction of normal QRS complex duration and to test it on healthy individuals.

Methods: The study population of healthy adult volunteers was divided into a sample for development of a prediction model ($n = 63$) and a testing sample ($n = 30$). Magnetic resonance imaging data were used to assess anatomical characteristics of the left ventricle: the angle between papillary muscles (PM_A), the length of the left ventricle (LV_L) and left ventricular mass (LV_M). Twelve-lead electrocardiogram (ECG) was used for measurement of the QRS duration. Multiple linear regression analysis was used to develop a prediction model to estimate the QRS duration. The accuracy of the prediction model was assessed by comparing predicted with measured QRS duration in the test set.

Results: The angle between PM_A and the length of the LV_L were statistically significant predictors of QRS duration. Correlation between QRS duration and PM_A and LV_L was $r = 0.57$, $P = 0.0001$ and $r = 0.45$, $P = 0.0002$, respectively. The final model for prediction of the QRS was: $QRS_{\text{Predicted}} = 97 + (0.35 \times LV_L) - (0.45 \times PM_A)$. The predicted and real QRS duration differed with median 1 ms.

Conclusions: The model for prediction of QRS duration opens the ability to predict case-specific normal QRS duration. This knowledge can have clinical importance, when determining the normality on case-specific basis.

Ann Noninvasive Electrocardiol 2010;15(2):124–129

QRS duration; prediction; papillary muscles

QRS duration serves as a key prognostic and diagnostic determinant of several cardiac conditions.¹ Prolonged QRS duration is a marker of long-term mortality in different patient categories.^{2,3} Large interindividual variability of the QRS duration exists, however, not only in different patient categories, but also in healthy subjects.^{4–8} Normal values of the QRS duration can overlap with abnormal values suggesting heart disease. Distinguishing between abnormal QRS duration and normal variants can be difficult. For example, QRS duration over 120 ms is

a diagnostic criterion of systolic heart failure and a standard selection criterion for cardiac resynchronization therapy.⁹ However, in a recent study, 23% of the study population with systolic heart failure had lower QRS duration and these patients were therefore misdiagnosed by this criterion.¹⁰

The aim to improve the diagnostic accuracy of electrocardiogram (ECG) criteria has been of interest for decades, with variable success.¹⁰ The case-specific normal QRS duration has, however, not been taken in account. The knowledge of the

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Financial support: Grant of Lund University and Region of Skåna.

normal QRS duration in each individual is needed when determining the onset, severity and progression of the heart disease. It becomes more and more evident, that when making conclusions regarding normality or abnormality of the electrophysiologic status, considering anatomic characteristics is important and vice versa. Development of an algorithm for prediction of normal QRS duration on patient specific basis, accounting for anatomic factors responsible for variation of QRS duration between individuals, is essential.

Several factors influence the QRS duration. Studies that were undertaken on patient populations suggest that mass and anatomic characteristics, such as length of the left ventricle influence the QRS duration.^{11,12} In normal subjects, the main factor responsible for the QRS duration seems to be the extent of the myocardial area that is directly activated by the anterior, middle and posterior fascicles of the left bundle.^{13,14} It was suggested that the borders of this area supplied by fascicles can be indirectly estimated by the locations of the respective mitral papillary muscles (PMs) toward which left and right bundle branch fascicles course.^{15,16}

The aim of this study was to develop a model that considers major predictors of QRS complex characteristics for prediction of QRS complex duration in healthy subjects.

METHODS

The study was approved by an institutional review committee and the protocol complies with the Declaration of Helsinki.

Study Population

The study population consists of 93 healthy adult volunteers recruited by advertising at the Lund University Hospital between 2005 and 2008. All subjects provided written informed consent to use their clinical and demographic information for research purposes.

The study population had the following inclusion criteria: Feeling healthy, nonsmokers. Subjects were excluded if they had medical history of cardiac disease or lung disease, ECG and/or magnetic resonance imaging (MRI) abnormality suggesting myocardial infarction, right bundle branch block or left bundle branch (LBB) block, electrical axis deviation beyond the normal limits (less than -10° or more than 90° in the frontal plane).¹⁷

The study population was randomly divided into two samples. The first sample ($n = 63$) was used for development of the prediction model of the QRS duration. The second sample ($n = 30$) was used as testing sample.

Data Collection

Demographic data (gender, age, weight, height, and medical history) were obtained by one of the coinvestigators (K.S.).

MRI Data

MRI data were obtained on a 1.5-T cardiac MRI scanner (Philips Healthcare Best, The Netherlands). Sequential 8-mm-thick short-axis images of the heart were acquired with breath hold according to the standard institutional protocol. All MRI images were analyzed by using the freely available image analysis program Segment (Segment 1.8; <http://segment.heiberg.se>).

Left ventricular (LV) mass was determined by manual delineation of endo- and epicardial borders of the left ventricle for each short axis view in both end-systole and end-diastole. PMs were included in the overall LV mass. The length of the LV was determined from the four-chamber long axis view of the heart as the distance between the apex and mitral annulus at the lateral side of the left ventricle in end-diastole.

The angle between PMs was determined as previously described.¹⁸ In short, the location of the septal side of the PM was determined at the short axis level at which the PM inserts in the LV wall. The angle between PMs was used to indirectly estimate the extent of the area supplied by the LBB fascicles (Fig. 1).

ECG Data

Electrocardiographic leads were placed according to the standard manner. All ECGs were recorded with Megacart electrocardiographs (Siemens, Solna, Sweden) and stored in a Megacare ECG management system (VF 2.1, Dräger, Germany). QRS duration was analyzed by software algorithm (Uni-G, Glasgow, UK)¹⁹ and by the visual inspection of two independent observers. In two cases the QRS duration measured by the software was affected by artifacts and therefore adjusted manually.

Figure 1. Determination of the angle between papillary muscles. RV = Right ventricle, LV = Left ventricle, PM angle = angle between papillary muscles, A-PM = septal side of the anterior papillary muscle, P-PM = septal side of the posterior papillary muscle.

Data Analysis

Development of a Prediction Model

Independent variables that are known to be associated with QRS duration in normal subjects (gender, age, BMI, position of PMs, LV mass, and LV length) were first evaluated by simple linear regression to predict the value of the QRS duration (QRS_P) from a single independent variable (X) given by $QRS_P = b_0 + b_1X$, where b_0 is the intercept, and b_1 the coefficient associated with the variable X. Multiple linear regression was used to develop a prediction model to estimate the QRS duration. "Forward stepwise selection" was used to identify those independent variables that best predicted QRS duration. The Pearson r correlation coefficient was used to measure the degree of association between two variables, and the R^2 statistic was used to assess the overall fit of the model.

Testing the Model

The accuracy of the prediction model was assessed by comparing predicted with measured QRS duration in the test set. The difference between predicted and observed values was calculated. SPSS statistical software 12.0.1 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. Data are presented as mean $\pm$ standard deviation or median and range. All tests were 2-tailed and P-values of <0.05 were assumed to be statistically significant.

Statement of the Responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Model Development

Study Population: Sample for Development of Model

Sixty-three healthy adults, of whom 26 were females, were designated as the model development set. The mean age of study population was 32.6 ± 12.2 years, mean weight was 73.8 ± 12.0 kg, mean body mass index (BMI) was 24.1 ± 3.1 . The mean mass and length of the LV were 115.7 ± 24.0 g, and 99.1 ± 7.4 mm, respectively. The mean QRS duration of the sample was 89.8 ± 7.5 ms.

QRS Duration and Predictive Variables

Figure 2A shows correlation between QRS duration and mass, and Figure 2B shows correlation between QRS duration and length of the LV. The correlation coefficients between the QRS duration and mass and length of the LV were $r = 0.44$; $P = 0.0003$ and $r = 0.45$, $P = 0.0002$, respectively.

The correlation between the free wall angle of PMs in the short-axis view and QRS duration is shown in the Figure 2C. A significant correlation was found between free wall angle of PMs and QRS duration ($r = 0.57$, $P = 0.0001$). Age, gender, and BMI were not associated with QRS duration.

Multiple stepwise linear regression identified the position of PMs and length of the left ventricle as statistically significant predictors of QRS duration (Table 1). The mass of the left ventricle was not a statistically significant factor. The final model for prediction of the QRS was:

$$QRS_P = 97 + (0.35 \times LVL) - (0.45 \times PMA),$$

where QRS_P is predicted QRS duration in milliseconds, LVL is length of the left ventricle in centimeters, and PMA is angle between the PMs in degrees.

Model Testing

Study Population: Sample for Testing of Model

The developed model was tested on 30 healthy subjects (9 females, 21 males). The mean age of the

Figure 2. (A) Correlation between the mass of the left ventricle (LV) and QRS duration. (B) Correlation between the length of the left ventricle (LV) and QRS duration. (C) Correlation between the free wall angle between papillary muscles (PMs) and QRS duration.

Table 1. Data from Multivariable Analysis of Regression Model for Prediction of QRS Duration by Independent Variables

Independent Variables	Coefficient	Std. Error	t	P
Constant	96.9024			
LV _L ^a	0.3596	0.09919	3.626	0.0006
PM _A ^b	-0.4469	0.08699	-5.137	<0.0001
LV _M ^c				NS

^aLV_L = length of the left ventricle; ^bPM_A = angle between the papillary muscles; ^cLV_M = left ventricular mass.

testing sample was 33.3 ± 11.3 years, mean weight was 70.5 ± 10.2 kg, mean BMI was 24.1 ± 1.5 . The mean mass and length of the LV were 104.0 ± 32.3 g and 100.2 ± 16.0 mm, respectively. The mean QRS duration of the sample was 88.7 ± 6.7 ms.

Results of Testing

In the test set the model explained 77% of the variation in QRS duration. The correlation between predicted and real QRS duration was: $r = 0.88$, $P < 0.0001$ (Fig. 3A). The predicted and real QRS duration differed with median 0.9 ms (range 0–7 ms). Twenty-three out of 30 subjects (77%) were within the range –3 to +3 ms of difference between predicted and real QRS duration. As shown at the Bland-Altman plot (Fig. 3B), underestimation of the QRS duration with difference of –6 and –7 ms was present in two patients, and overestimation of +6 ms was present in 1 subject.

DISCUSSION

In this study, a model for prediction of the QRS duration in healthy subjects was developed and subsequently tested on healthy individuals. The results show that the model can predict the individual normal QRS duration within 3 ms difference between predicted and real QRS duration value in the majority of healthy subjects.

The ability to predict individual's normal QRS duration is essential when distinguishing between heart disease and variant of normal. In the heart disease, the active and passive properties of myocardium are changed and the major determinant that influence the QRS axis duration is the area activated by the branch fascicles. Substantial changes of electrophysiological properties of myocardium

Figure 3. (A) Correlation between predicted and measured QRS duration in testing population. Dashed line represents line of agreement, bold line represents regression line. (B) Bland–Altman plot of difference between measured and predicted QRS duration in each tested subject plotted according to its measured QRS duration. SD = Standard deviation.

are documented under pathological conditions.^{20,21} Understanding the variables that influence QRS duration in normal conditions is necessary to distinguish normal and abnormal.

Among the studied variables, the extent of the LBB fascicles indirectly measured as the angle between PMs, provides the most significant predictive information of the QRS duration in healthy subjects. This result is in agreement with previous studies, where the distance between PMs correlated with both real and simulated duration of the QRS complex.^{15,16}

The influence of the left ventricular mass on the QRS duration does not seem to have dominant role. Some studies have however shown that the mass is weak predictor of the QRS duration,²² even though the correlation of QRS duration and left ventricu-

lar mass is positive.^{12,23} In the present study, the length of the left ventricle was found to be a better predictor of QRS duration than the mass. Prolonged QRS duration, even within the normal range, was shown to be associated with larger ventricular volumes in patients.²⁴ Greater contribution of dimensions rather than the mass of the left ventricle to the QRS duration can be suggested also in healthy subjects.

Although MRI was used in our setting, ECHO provided excellent intermodality agreement in comparison with MRI with regards to assessment of PM position and may be therefore used in clinical setting as less expensive and more available modality.¹⁸

Testing the models used in clinical practice is essential before application.^{10,25} The developed model was therefore tested on healthy subjects with promising results to be able to predict QRS duration within 3 ms difference from real QRS duration in the majority of subjects.

Using ECG for prediction of anatomic changes might be possible, when both electrophysiologic and anatomic modalities are used together. The main message and perspective of the article is that both electrophysiologic and anatomic characteristics need to be considered together when making conclusions about normality or abnormality.

Conclusions and Future Outlook

A model for the prediction of the normal QRS duration by considering anatomic characteristics for each individual was developed and tested in the presented study. Considering both electrophysiologic and anatomic characteristics is important when making conclusions regarding "normality" and "abnormality" of the heart. Future directions may lead to testing the model for differentiating between variants of normal and abnormal changes of the QRS duration on a patient specific basis. This would have important clinical applications in providing patient specific diagnosis, clinical decision making and in the planning of patient-specific treatment.

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