Prolonged QRS duration in patients with heart failure: relation to exercise tolerance, diastolic function and aetiology

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Abstract

Background: In patients with chronic heart failure (CHF) QRS prolongation is a frequent finding and is related to increased morbidity and mortality. It is not clear if prolonged QRS in CHF of ischaemic origin (CAD) represents the same severity of the syndrome as in non-ischaemic (non-CAD) cardiomyopathy.

Aim: To assess the relationship between QRS duration and BNP levels, diastolic function and peak VO2 in patients with CAD CHF and non-CAD CHF.

Methods: In 70 patients with left ventricular ejection fraction (LVEF) <45% [35 with left bundle branch block (LBBB)] echocardiography, cardiopulmonary exercise test and standard ECG were performed as well as BNP level was measured.

Results: Peak VO2 was significantly lower, BNP level higher in patients with LBBB than those without LBBB. In the non-CAD CHF peak VO2 was significantly lower, whereas BNP levels and restrictive filling pattern prevalence higher in the group with LBBB than without LBBB, which was not seen in the CAD CHF group. A significant correlation between peak VO2 and BNP levels (r=–0.31; p=0.02), QRS duration (r=–0.27; p=0.02), and diastolic function parameter - DTE (r=0.28; p=0.02) was found. Peak VO2 was significantly lower in the CAD CHF than in non-CAD CHF. In multivariate regression analysis, LVEF (r=–0.32; p=0.012) and LVEDD (r=0.30; p=0.015) were independently associated with QRS duration.

Conclusion: In patients with CHF, QRS duration is independently related to LVEF and LVEDD. It seems that prolonged QRS may be a better predictor of more advanced CHF in patients with non-ischaemic rather than ischaemic cardiomyopathy.

Key words: heart failure, prolonged QRS, peak VO2, BNP, diastolic function
acute infection, chronic inflammatory disease, cancer, coronary event or revascularisation in the previous 3 months. Only patients with sinus rhythm were included in the present study, and there were 70 such patients (mean age 51.9±10.1 years, LVEF 26.8±7.9 % and NYHA class 2.5±0.8). Ischaemic heart disease was diagnosed in 35 (50%) patients (>50% stenosis of at least 1 major epicardial branch at angiography) and non-CAD CHF in 35 patients. All patients were in stable clinical condition. They were on optimal stable pharmacological therapy for at least 2 weeks before investigation (Table I).

The study protocol was approved by the local Ethics Committee of the University of Medical Sciences and informed consent was obtained from each patient.

**Echocardiography**

All patients underwent 2D and Doppler echocardiography (ECHO) with a Hewlett-Packard Sonos 5500 device and 2.5 MHz transducer. LVEF was calculated from the 4-chamber view using modified Simpson’s algorithm. Doppler recordings from the mitral inflow were obtained from the apical 4-chamber view to assess LV filling pattern. We evaluated peak early (E wave) and late (A wave) transmitral velocities, E/A ratio, and deceleration time of E wave (DTE). Left ventricular RFP was defined as E/A ratio ≥2 or between 1 and 2 with DTE ≤130 ms.

**Cardiopulmonary exercise treadmill test**

All patients underwent maximal cardiopulmonary exercise treadmill test according to the Bruce protocol modified by the addition of a stage 0 with 1.7 km/h and 5% gradient. The peak oxygen consumption (peak VO\textsubscript{2}), carbon dioxide production (VCO\textsubscript{2}), and minute ventilation (VE) were measured using the breath-by-breath technique (Sensor Medicis, model V max29). The system was calibrated with a standard gas mixture of known concentration before each test. A standard 12-lead ECG was continuously recorded. All tests were terminated because of fatigue and/or dyspnoea. No test was terminated because of angina pectoris or arrhythmia. Peak VO\textsubscript{2} was calculated as an average value during the last 20 s of exercise.

**Resting ECG**

A 12-lead ECG was performed in every patient in resting supine position for measurement of QRS duration, which was computer read with the Marquette Mac System.

**Biochemical analysis**

Fasting venous blood was drawn in the morning after at least 30 minutes of rest (supine position). BNP level was measured using the RIA method (SHIONORIA-BNP, CIS Bio International) and was available in 31 patients in the QRS >=120 ms group and 25 in the QRS <120 ms group.

**Statistical analysis**

The values are given as a mean ± SD. The Mann-Whitney and Chi-square analyses were used to evaluate significance of differences between the groups. Correlations between variables were assessed using

**Table I. Clinical characteristics of the whole group and patients with QRS <120 vs. ≥120 ms**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>QRS &lt;120 ms (n=35)</th>
<th>QRS ≥120 ms (n=35)</th>
<th>p</th>
<th>QRS &lt;120 vs. ≥120 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years, mean ± SD]</td>
<td>51.9±10.1</td>
<td>48±10</td>
<td>55±9</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>NYHA [class, mean ± SD]</td>
<td>2.5±0.8</td>
<td>2.2±0.9</td>
<td>2.7±0.7</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>CAD (%)</td>
<td>35 (50)</td>
<td>37</td>
<td>63</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>QRS [ms, mean ± SD]</td>
<td>125.6±31.4</td>
<td>100.7±10</td>
<td>150.4±205</td>
<td>&lt;0.0000</td>
<td></td>
</tr>
<tr>
<td>LVEF [%]</td>
<td>26.9±7.9</td>
<td>31.2±6.7</td>
<td>22.5±6.6</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LVEDD [mm, mean ± SD]</td>
<td>70.2±8.8</td>
<td>66.7±7.3</td>
<td>73.7±8.8</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>BNP [pg/ml, mean ± SD]</td>
<td>69.0±65.8</td>
<td>44 ±38</td>
<td>89±76</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Peak VO\textsubscript{2} [ml/Kg/min, mean ± SD]</td>
<td>16.5±4.7</td>
<td>18.1±4.4</td>
<td>15.0±4.5</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>RFP (%)</td>
<td>30 (42.9)</td>
<td>12 (34)</td>
<td>18 (51)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>ACEI (%)</td>
<td>66 (94)</td>
<td>33 (94)</td>
<td>33 (94)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>53 (76)</td>
<td>27 (77)</td>
<td>26 (74)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>34 (49)</td>
<td>20 (57)</td>
<td>14 (40)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Furosemide (%)</td>
<td>56 (76)</td>
<td>25 (71)</td>
<td>31 (89)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Statins (%)</td>
<td>32 (46)</td>
<td>13 (37)</td>
<td>19 (54)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid (%)</td>
<td>40 (57)</td>
<td>19 (54)</td>
<td>21 (60)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic drugs (%)</td>
<td>24 (34)</td>
<td>8 (23)</td>
<td>16 (46)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations**: CAD – coronary artery disease, LVEF – left ventricular ejection fraction, LVEDD – left ventricular end-diastolic diameter, BNP – B-type natriuretic peptide, RFP – restrictive filling pattern, ACEI – angiotensin converting enzyme inhibitors
Spearman rank test. Multivariate regression analysis was used to assess which of the statistically significant correlations between variables were independently correlated with QRS width. A p value of <0.05 was considered as statistically significant. All analyses were performed using the Statistica 7.0 package.

Results

Patient’s characteristics and comparison between groups with and without QRS prolongation are summarised in Table I. There were 35 patients with QRS <120 ms (group I) and 35 with QRS ≥120 ms (group II). In all patients with prolonged QRS, the LBBB morphology was present. There was a significant difference in age between the two groups with slightly older patients in group II. Group I patients had significantly higher LVEF and peak VO$_2$ and significantly lower NYHA class and BNP levels compared to group II. There was no significant difference in the percentage of patients with RFP. There was no significant difference in the treatment between the two groups with only a trend for higher prevalence of furosemide and antiarrhythmic treatment in the LBBB group.

In patients with CAD CHF 13 had normal QRS and 22 had LBBB (Table II). In patients with non-CAD CHF, 22 had normal QRS and 13 had LBBB (Figure 1). In patients with CAD CHF there were no significant differences between groups with or without LBBB in peak VO$_2$, BNP levels and severe diastolic dysfunction prevalence (Table II). In contrast, in patients with non-CAD CHF (Table III) there were significant differences between groups with or without LBBB in peak VO$_2$, BNP levels and severe diastolic dysfunction prevalence.

In the whole group there was a significant inverse correlation between QRS duration and peak VO$_2$ and LVEF, a significant positive correlation between QRS and LV end-diastolic diameter (LVEDD) (Figure 2), a weak but significant correlation between QRS and age (r=0.24; p=0.04), and a non-significant trend for QRS and BNP levels (r=0.26; p=0.052). In non-CAD CHF correlations between QRS and LVEF, BNP, peak VO$_2$, and LVEDD were significant, but there was no correlation between QRS and age (data not presented). In the CAD CHF group only correlations between QRS and age and LVEDD remained significant.

Table II. Characteristics of patients with CAD in relation to QRS width

<table>
<thead>
<tr>
<th></th>
<th>Total (n=35)</th>
<th>QRS &lt;120 ms (n=22)</th>
<th>QRS ≥120 ms (n=13)</th>
<th>P QRS&lt;120 vs. ≥120 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS [ms, mean ± SD]</td>
<td>100.6±7.6</td>
<td>143±23.9</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age [years, mean ± SD]</td>
<td>54.9±7.5</td>
<td>52.8±9.1</td>
<td>65.2±6.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF [%], mean ± SD</td>
<td>26.1±7.2</td>
<td>30.6±5.3</td>
<td>23.4±6.8</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEDD [mm, mean ± SD]</td>
<td>70.5±8.9</td>
<td>65.3±6.5</td>
<td>73.6±8.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Peak VO$_2$ [ml/kg/min, mean ± SD]</td>
<td>14.7±4.8</td>
<td>15.4±4.8</td>
<td>14.3±4.9</td>
<td>NS</td>
</tr>
<tr>
<td>BNP [pg/ml, mean ± SD]</td>
<td>80.5±67.8</td>
<td>61.9±48</td>
<td>90.3±75.5</td>
<td>NS</td>
</tr>
<tr>
<td>RFP (%)</td>
<td>16 (60)</td>
<td>6 (46)</td>
<td>10 (45)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Abbreviations:** as in Table I

Table III. Characteristics of patients with non-CAD CHF in relation to QRS width

<table>
<thead>
<tr>
<th></th>
<th>Total (n=35)</th>
<th>QRS &lt;120 ms (n=22)</th>
<th>QRS ≥120 ms (n=13)</th>
<th>P QRS&lt;120 vs. ≥120 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS [ms, mean ± SD]</td>
<td>100.7±10.7</td>
<td>162±23</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Age [years, mean ± SD]</td>
<td>49.0±11.6</td>
<td>45.8±10.1</td>
<td>54.4±12.3</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF [%], mean ± SD</td>
<td>27.6±8.6</td>
<td>31.5±7.4</td>
<td>20.8±6.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>LVEDD [mm, mean ± SD]</td>
<td>69.9±8.7</td>
<td>67.5±7.7</td>
<td>74.0±9.1</td>
<td>0.056</td>
</tr>
<tr>
<td>Peak VO$_2$ [ml/kg/min, mean ± SD]</td>
<td>18.4±3.8</td>
<td>19.6±3.4</td>
<td>16.3±3.6</td>
<td>0.009</td>
</tr>
<tr>
<td>BNP [pg/ml, mean ± SD]</td>
<td>56.8±62.4</td>
<td>32.4±27.2</td>
<td>87.3±80.3</td>
<td>0.02</td>
</tr>
<tr>
<td>RFP (%)</td>
<td>14 (40)</td>
<td>6 (27)</td>
<td>8 (62)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

**Abbreviations:** as in Table I
of RFP, aetiology and peak VO₂) LVEF (β = –0.32; p = 0.012) and LVEDD (β = 0.30; p = 0.015) were independently associated with QRS duration. The same analysis for the non-CAD CHF patients showed an independent association with LVEF, whereas for the CAD CHF group there was not such a correlation.

Discussion

We showed that in patients with CHF, QRS width was independently related to LVEF and LVEDD. Interestingly, we also showed that prolonged QRS may be a better predictor of more advanced CHF in patients with non-CAD rather than CAD-CHF.

Our patients with prolonged QRS duration had lower peak VO₂ together with LVEF and LVEDD (which are similar findings to those of Kalra et al. [3]) and BNP levels were higher in comparison to patients with normal QRS duration. All these parameters are important prognostic indicators in CHF [7, 16]. Many studies have shown that biventricular pacing improves LVEF, LVEDD, peak VO₂ and prognosis in patients with CHF and prolonged QRS [17, 18]. Peak VO₂ is an established measure of exercise capacity in patients with CHF and it is an important prognostic marker when considering transplantation and prognosis [19]. In severe CHF, patients with ischaemic heart disease have worse prognosis than those with dilated non-ischaemic cardiomyopathy [20]. It has been suggested that aetiology of heart failure may influence functional capacity [11, 12, 21]. Our results are in agreement with these observations. Patients with ischaemic aetiology had significantly lower peak VO₂ than patients with non-ischaemic CHF. As in the study of De Feo et al. [11], patients with CAD were older. Ischaemic aetiology was also an independent predictor of exercise tolerance in patients with CHF in the study of Duncan et al. [22], besides total isovolumetric time, which is determined by LBBB. In CAD CHF exercise may be associated with worse adaptation to excessive wall stress than in non-ischaemic cardiomyopathy due to the presence of akinetic or dyskinetic cardiac function.
QRS duration in patients with CHF

segments and variable degree of mitral regurgitation [23]. Moreover, CAD might be associated with more widespread peripheral vascular disease.

A common finding in patients with systolic CHF is LV diastolic dysfunction. It has been shown in different studies that among other things, severe diastolic dysfunction, which is defined as RFP, is a predictor of lower survival rate and reduced exercise capacity in patients with CHF [24]. Surprisingly, we found that prevalence of severe diastolic dysfunction in patients with CAD was independent of QRS duration, but in patients with non-CAD CHF it was significantly more frequently found in the group with prolonged QRS than in patients with normal QRS.

Up to 50% of patients with CHF have a prolonged QRS complex, mostly presenting as LBBB, which has been identified as an indicator of adverse prognosis, and intraventricular conduction delays, which result in abnormal depolarisation of the heart and mechanical asynchrony of ventricles. These QRS abnormalities have been suggested to be responsible for increased morbidity and mortality [25-27]. Prolonged QRS duration is also associated with worse NYHA class, peak VO2, and LVEF, which is in line with our observations [3]. Bruch et al [4] found that in patients with CHF and comparable systolic LV function, LBBB was associated with more severe diastolic dysfunction and higher NT-proBNP levels. The prevalence of RFP in their group was significantly higher in patients with rather than without LBBB. They concluded that these findings may contribute to increased morbidity and mortality in patients with CHF and LBBB. It was shown in another study that in patients with systolic CHF, the RFP indeed adds incremental value to QRS duration in determining prognosis [28]. These investigators did not analyse prevalence of RFP in relation to the aetiology of CHF and QRS duration.

In our study the prevalence of RFP was similar in patients with CAD and LBBB and those without LBBB, but was significantly higher in patients with rather than without LBBB and non-CAD CHF. Furthermore, LBBB in non-CAD CHF was associated with significantly lower peak VO2 and higher BNP levels in comparison to the no-LBBB group, which was not observed in the CAD group. These findings may suggest that prolonged QRS may be a better predictor of more severe CHF in patients with non-ischaemic CHF than with ischaemic heart disease. This may be an explanation why patients with prolonged QRS with non-ischaemic cardiomyopathy may have worse prognosis [13]. Interestingly, improvements in patients treated with resynchronisation therapy were greater in patients with non-ischaemic than rather ischaemic cause of CHF [29]. To confirm these suggestions further studies with a higher number of patients are needed.

Conclusions

In patients with CHF, QRS duration is independently related to LVEF and LVEDD. It seems that prolonged QRS may be a better predictor of more advanced CHF in patients with non-ischaemic than with ischaemic cardiomyopathy.

References

Wydłużenie zespołu QRS u chorych z niewydolnością serca – związek z tolerancją wysiłku, czynności rozkurczową i etiologią zespołu

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I Klinika i Katedra Kardiologii, Uniwersytet Medyczny w Poznaniu

Streszczenie

Wstęp: U chorych z niewydolnością serca często spotyka się wydłużenie QRS, najczęściej o morfologii bloku lewej odnogi pęczka Hisa (LBBB). Jest ono uznawanym czynnikiem ryzyka nagłego zgonu. Ponadto LBBB związane jest z bardziej zaawansowaną niewydolnością serca i wyższymi stężeniami NT-proBNP. Trwa dyskusja, czy wydłużenie QRS reprezentuje ten sam stopień zaawansowania choroby w niewydolności serca o podłożu choroby niedokrwiennej (CAD) i nieniedokrwiennej (non-CAD).

Cel: Zbadanie zależności pomiędzy obecnością wydłużonego QRS a stężeniem peptydu natriuretycznego typu B (BNP), czynnością rozkurczową lewej komory i tolerancją wysiłku u chorych ze stabilną klinicznie skurczową niewydolnością serca w zależności od etiologii niedokrwiennej i nieniedokrwiennej.

Metoda: Grupę badaną stanowiło 70 chorych z niewydolnością serca (wiek 51,9±10,1 roku) i obniżoną frakcją wyrzucania lewej komory (LVEF <45%, 26,8±7,9%), z rytmem zatokowym. U wszystkich wykonano standardowe badanie echokardiograficzne i maksymalny test spiroergometryczny na bieżni ruchomej. Restrykcyjny profil napływu mitralnego (RFP) rozpoznawano, gdy E/A >2 lub pomiędzy 1 i 2 z czasem deceleracji fali E (DTE) <130 ms. Tolerancję wysiłku oceniano jako peak VO2. Czas trwania QRS mierzono automatycznie za pomocą systemu Marquette Mac System. Stężenia BNP mierzono metodą radioimmunologiczną.

Wyniki: W badanej grupie u 35 chorych (50%) stwierdzono wydłużenie QRS ≥120 ms o morfologii LBBB. Chorzy w grupie z QRS <120 ms byli istotnie młodszy niż chorzy w grupie z QRS ≥120 ms, charakteryzowali się istotnie większą LVEF, peak VO2 oraz istotnie niższą klasą wg NYHA oraz stężeniami BNP. Chorzy z QRS ≥120 ms miało niższy peak VO2 oraz istotnie niższą klasę wg NYHA oraz stężeniami BNP. Spośród chorych z CAD u 13 stwierdzono QRS <120 ms (100,6±7,6 ms), u 22 – QRS ≥120 ms (143±23,9 ms). Spośród chorych z kardiomiopatią nieniedokrwiennej 22 miało QRS <120 ms (100,7±10,7 ms), a 13 – QRS ≥120 ms (162±23 ms, p=0,015 w porównaniu z grupą CAD). W grupie chorych z CAD nie stwierdzono istotnych różnic między grupami z LBBB i bez LBBB w odniesieniu do peak VO2, stężeń BNP i częstości występowania RFP. Przeciwnie w grupie osób z kardiomiopatią nieniedokrwiennej – chorych z LBBB mieli istotnie mniejsze peak VO2, większe stężenia BNP i częściej RFP niż chorzy bez LBBB. W całej badanej grupie istotne były korelacje pomiędzy czasem trwania QRS a peak VO2, LVEF, wymiarem końcoworozkurczowym lewej komory serca (LVEDD) i wiekiem oraz tendencja ze stężeniami BNP. W analizie regresji z uwzględnieniem LVEF, LVEDD, wieku, obecności RFP, etiologii CHF i peak VO2 wykazano, że niezależnie związane z czasem trwania QRS są LVEF i LVEDD.

Wnioski: U chorych z niewydolnością serca niezależnymi wskaźnikami szerokości QRS są LVEF i LVEDD. Wydłużenie QRS w standardowym EKG może wskazywać na bardziej zaawansowaną niewydolność serca u chorych z kardiomiopatią nieniedokrwiennej. Nie stwierdzono takiej zależności w grupie z CAD.

Słowa kluczowe: niewydolność serca, wydłużony QRS, peak VO2, BNP, czynność rozkurczowa

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