Prognostic Value of QRS Duration among Patients with Cardiogenic Shock Complicating Acute Heart Failure: Data from the Korean Acute Heart Failure (KorAHF) Registry

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ABSTRACT

Background and Objectives: Prolonged QRS duration is associated with poor outcomes in patients with chronic heart failure (HF). However, the prognostic value of QRS duration in patients with cardiogenic shock complicating acute HF remains unknown. We evaluated the hypothesis that prolonged QRS duration may be associated with short-term mortality among acute HF patients with cardiogenic shock (CS).

Methods: From March 2011 through December 2013, a total of 5,625 acute HF patients were consecutively enrolled in ten tertiary university hospitals. Among them, we analyzed patients who presented with CS. Patients were divided into three groups by QRS duration cutoff values of 130 and 150 ms. The primary endpoint was 30-day in-hospital mortality.

Results: Two hundred eleven patients presented with CS at admission and those with available electrocardiograms were included in this analysis. There were 35 patients with QRS durations of 150 ms or above, 30 patients with QRS durations between 130 ms and 150 ms, and 146 patients with QRS durations below 130 ms. The 30-day all cause in-hospital mortality rates were 43.7%, 33.1%, and 24.9%, respectively. After multivariate adjustment, severe prolonged QRS duration was a significant prognostic factor for 30-day in-hospital mortality (hazard ratio, 1.909; 95% confidence interval, 1.024–3.558; p=0.042).

Conclusions: Prolonged QRS duration was associated with a higher risk of 30-day in-hospital mortality among patients with acute HF who presented with CS.
INTRODUCTION

Cardiogenic shock (CS) is generally defined as a systolic blood pressure (SBP) <90 mmHg and clinical or laboratory signs of tissue hypoperfusion despite adequate volume status.\(^1\) CS has many causes, including acute coronary syndrome (ACS), heart failure (HF), and valvular heart disease, and it is one of the most serious complications of these conditions. Previous studies have shown that in-hospital mortality increases to 40–50% when CS develops in HF patients.\(^4\) In this regard, early identification of risk factors associated with CS in HF may prove particularly helpful when considering therapeutic options.

Prolonged QRS duration means electrical and mechanical dyssynchrony in the diseased heart.\(^8\) A wide QRS complex reflecting left-sided intraventricular conduction delay in patients with chronic HF is associated with more advanced myocardial disease, worse left ventricular (LV) function, poorer prognosis, and a higher all-cause mortality rate compared with patients with a narrow QRS complex.\(^9\)

However, the prognostic implications of QRS duration have not been clearly defined in the context of acute HF. The present study aimed to evaluate the prognostic implications of QRS duration and associated factors in a large cohort of acute HF patients with CS. We hypothesized that patients with prolonged QRS duration could represent a high-risk phenotype within the CS spectrum.

METHODS

Study population and data collection

The study population was selected from The Korean Acute Heart Failure (KorAHF) registry, a prospective multicenter cohort study. Patients hospitalized for acute HF from 10 tertiary university hospitals throughout the country were enrolled from March 2011 to February 2014 (NCT01389843). Demographic characteristics, comorbidities, clinical presentation, medical history, laboratory tests, electrocardiographic findings, transthoracic echocardiographic findings, additional treatments, and outcome data were collected at admission and during the follow-up period. Detailed information of the study design and its results have been previously reported.\(^11\) Among the patients enrolled in the KorAHF registry, patients who met the following criteria were included in this analysis: 1) patients who were initially diagnosed with CS and 2) were able to undergo baseline electrocardiography. The study protocol was approved by the Ethics Committee/Institutional Review Board (IRB) at each hospital. Written informed consent was obtained from each patient early on during this study; however, the IRBs of each hospital waived the requirement for informed consent, as this study presented minimal risk for the patients and was initiated and sponsored by the Korean Ministry of Health and Welfare to improve public health.

Study design, variables, and statistical analysis

CS was defined as evidence of tissue hypoperfusion induced by HF after adequate correction of preload and major arrhythmia and characterized by reduced SBP (<90 mmHg or a drop
of mean arterial pressure >30 mmHg) and absent or low urine output (<0.5 mL/kg/h). The study sample was classified into three groups based on QRS duration in the baseline electrocardiogram (ECG): 1) patients with QRS durations ≥150 ms (severe prolonged QRS group), 2) patients with QRS durations ≥130 ms and <150 (intermediate prolonged QRS group), and 3) patients with QRS durations <130 ms (narrow QRS group). ECGs were recorded at a standard paper speed of 25 mm/s and calibration of 10 mm/mV. The QRS duration was measured automatically. Complete left bundle branch block (LBBB) and right bundle branch block (RBBB) were identified by standard criteria. The primary endpoint was 30-day in-hospital mortality.

Continuous variables are presented as means±standard deviations and were analyzed by analysis of variance. Categorical variables are represented as percentages and compared using the chi-square test. Mortality analyses were performed using Kaplan–Meier survival curves and Cox proportional hazard ratios (HR). A total of 28 variables, including demographics, clinical presentation, and laboratory and ECG findings, were included in this analysis (Supplementary Table 1). The variables with p<0.05 on univariate analysis were included in a multivariate Cox proportional hazard model. HRs are shown with 95% confidence intervals (CIs). The statistical analyses were performed using SPSS Statistics, Version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

Among 5,625 consecutive patients enrolled prospectively in the KorAHF registry, 214 patients who presented with cardiogenic shock at admission were identified. An initial ECG was not available for 3 patients; therefore, 211 patients were included in this analysis. Among these 211 patients, 35 had QRS durations ≥150 ms, 30 had QRS durations between 130 and 150 ms, and 146 had QRS durations below 130 ms (Figure 1). The mean age of the 211 patients was 60.6±16.6 years, and 62.6% (n=132) were male. Baseline characteristics were similar between the three groups, except the prevalence of diabetes mellitus (DM). A more prolonged QRS duration was associated with a higher prevalence of DM (Table 1).
Comparison of electrocardiogram and echocardiogram findings among the groups

The overall mean QRS duration was 116.5±33.6 ms. Mean QRS durations differed significantly among the three groups; the values were 175.0±23.0 ms, 138.8±6.5 ms, and 97.8±15.0 ms in the severe, intermediate, and narrow groups, respectively (Table 2). Baseline ECGs revealed ventricular conduction block (VCB) in 28% of the patients (n=55) (Figure 2). LBBB was

Table 1. Baseline characteristics and laboratory findings

| Variables (unit) | Severe prolonged QRS group (n=35) | Intermediate prolonged QRS group (n=30) | Narrow QRS group (n=146) | p value |
|------------------|-----------------------------------|----------------------------------------|--------------------------|---------|
| Age (years)      | 60.2±15.5                         | 62.7±15.1                              | 60.3±16.6                | 0.768   |
| Sex (male)       | 26 (74.3)                         | 18 (60.0)                              | 88 (60.3)                | 0.302   |
| Body mass index  | 24.7±4.1                          | 23.6±3.6                               | 23.0±3.6                 | 0.054   |
| SBP (mmHg)       | 108.6±37.4                        | 96.0±25.6                              | 107.5±31.7               | 0.242   |
| DBP (mmHg)       | 68.4±19.2                         | 63.8±20.5                              | 67.2±20.5                | 0.686   |
| Hypertension     | 18 (51.4)                         | 14 (46.7)                              | 70 (47.9)                | 0.933   |
| Diabetes         | 26 (74.3)                         | 15 (50.0)                              | 65 (44.5)                | 0.007   |
| Insulin          | 24 (68.6)                         | 13 (43.3)                              | 60 (41.1)                | 0.013   |

Etiology
- Ischemic heart disease: 24 (68.6%), 21 (70.0%), 89 (61.0%) (p=0.533)
- Valvular heart disease: 0 (0.0%), 1 (3.3%), 7 (4.8%) (p=0.407)
- Dilated cardiomyopathy: 5 (14.3%), 2 (6.7%), 9 (6.2%) (p=0.259)
- Stress induced cardiomyopathy: 0 (0.0%), 0 (0.0%), 6 (4.1%) (p=0.253)
- Chronic lung disease: 4 (11.4%), 1 (3.3%), 12 (8.2%) (p=0.515)
- Chronic kidney disease: 4 (11.4%), 1 (1.1%), 15 (10.3%) (p=0.478)
- Stroke: 3 (8.6%), 3 (10.0%), 21 (14.4%) (p=0.601)
- Malignancy: 4 (11.4%), 3 (10.0%), 8 (5.5%) (p=0.410)
- De novo HF: 26 (74.3%), 24 (80.0%), 109 (74.7%) (p=0.856)

Medication at admission
- ACEI/ARB: 8 (22.9%), 5 (16.7%), 35 (24.0%) (p=0.685)
- BB: 3 (8.6%), 9 (30.0%), 34 (23.3%) (p=0.084)
- MRA: 4 (11.4%), 4 (13.3%), 18 (12.3%) (p=0.973)

Labs
- Sodium (mmol/L): 136.8±6.6, 137.2±5.9, 137.4±5.7 (p=0.882)
- Hemoglobin (g/dL): 13.3±2.4, 12.9±2.5, 12.7±2.4 (p=0.368)
- Potassium (mmol/L): 4.5±1.1, 4.3±1.1, 4.2±0.8 (p=0.205)
- Creatinine (mg/dL): 2.38±3.54, 1.40±0.71, 1.71±2.17 (p=0.199)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HF = heart failure; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; MRA = mineralocorticoid receptor antagonist.

Table 2. Electrocardiogram and echocardiography findings

| Variables (unit) | Severe prolonged QRS group (n=35) | Intermediate prolonged QRS group (n=30) | Narrow QRS group (n=146) | p value |
|------------------|-----------------------------------|----------------------------------------|--------------------------|---------|
| ECG              |                                   |                                        |                          |         |
| QRS duration     | 175.0±23.0                        | 138.8±6.5                              | 97.8±15.0                | <0.001  |
| QTc duration     | 513.8±52.1                        | 494.1±40.9                             | 458.4±40.0               | <0.001  |
| Heart rate (beat/min) | 96.1±34.9                  | 99.4±12.9                              | 97.8±29.8                | 0.914   |
| RBBB             | 18 (51.4)                         | 11 (36.7)                              | 3 (2.1)                  | <0.001  |
| LBBB             | 3 (8.6)                           | 3 (10.0)                               | 0 (0.0)                  | 0.005   |
| Other IVCD       | 7 (20.0)                          | 10 (33.3)                              | 5 (2.1)                  | <0.001  |

Echocardiography
- LVEF (%): 31.6±14.7, 24.9±11.5, 33.6±14.8 (p=0.019)
- LVEDD (mm): 60.9±14.5, 55.5±12.2, 53.1±9.0 (p=0.002)
- LVESD (mm): 49.2±16.3, 45.8±11.0, 41.3±11.0 (p=0.007)
- LA (mm): 43.2±11.4, 41.5±10.9, 39.9±8.1 (p=0.215)

ECG = electrocardiogram; RBBB = right bundle branch block; LBBB = left bundle branch block; IVCD = intra-ventricular conduction delay; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; LA = left atrial diameter.
found in 6 patients and RBBB in 32 patients (Table 2). In addition, 25 patients had other intraventricular conduction delays (IVCDs). A more prolonged QRS duration was associated with a higher incidence rate of VCB.

**In-hospital course and clinical outcomes**

The study sample had a high rate of in-hospital complications and additional management (Table 3). Among 211 patients, 59 patients died during hospitalization, 52 of which were classified as cardiac deaths. In-hospital mortality was higher among patients who had longer QRS durations. The 30-day all-cause in-hospital mortality rates were 42.7%, 33.1%, and 24.9%, respectively, in descending order of association with QRS durations (p=0.038). Regarding in-hospital management, patients with longer QRS durations were treated with mechanical circulatory support, including extracorporeal membrane oxygenation (ECMO) and invasive mechanical ventilator support more frequently than patients in the narrow QRS group. However, there were no significant differences among the three groups in terms of renal replacement therapy, intravenous (IV) inotrope, or IV diuretic administration.

In the 30-day all-cause in-hospital mortality analysis, QRS duration was associated with increased short-term mortality risk. The severe prolonged QRS group showed the highest cumulative incidence of 30-day in-hospital death at 42.7%, while the narrow QRS group had

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**Table 3. In-hospital course and pharmacological treatment**

| Variables (unit)                  | Severe prolonged QRS group (n=35) | Intermediate prolonged QRS group (n=30) | Narrow QRS group (n=146) | p value |
|-----------------------------------|-----------------------------------|----------------------------------------|--------------------------|---------|
| Death                             | 16 (45.7)                         | 11 (36.7)                              | 32 (21.9)                | 0.009   |
| Cardiac death                     | 16 (45.7)                         | 10 (33.3)                              | 26 (17.8)                | 0.001   |
| Heart transplantation             | 1 (3.8)                           | 3 (13.0)                               | 5 (3.5)                  | 0.425   |
| Hospitalization duration (days)   | 19.9±16.6                         | 26.8±29.5                              | 23.8±26.0                | 0.532   |
| ECMO                              | 18 (51.4)                         | 16 (53.3)                              | 45 (30.8)                | 0.012   |
| Renal replacement therapy         | 13 (37.1)                         | 9 (30.0)                               | 39 (26.7)                | 0.480   |
| Mechanical ventilator support     | 27 (77.1)                         | 24 (80.0)                              | 88 (60.3)                | 0.035   |
| Support duration (days)           | 7.8±5.9                           | 7.5±6.3                                | 10.1±22.3                | 0.737   |
| IV inotrope support*              | 33 (94.3)                         | 29 (96.7)                              | 126 (86.3)               | 0.140   |
| IV diuretics                      | 26 (74.3)                         | 24 (80.0)                              | 107 (73.3)               | 0.784   |

ECMO = extra corporeal membrane oxygenation; IV = intravenous.

*IV inotrope: dobutamine, dopamine, milrinone, norepinephrine.
the lowest rate at 24.9% (Figure 3A). However, no significant difference was observed in terms of 30-day in-hospital mortality according to the type of ventricular conduction blocks on baseline ECG (Figure 3B).

**Clinical factors associated with mortality**

Clinical factors significantly associated with 30-day in-hospital mortality among HF patients with CS included age, history of ECMO support during admission, hyperkalemia, and severe prolonged QRS duration (QRS ≥150 ms) (Table 4 and Supplementary Table 1). In univariate Cox proportional hazard model, the categorized variable of QRS duration which is divided by the cut-off of 130 ms and 150 ms was statistically significant (the overall p value=0.044). The HR in the severe prolonged QRS group to the narrow QRS group was 2.237 (95% CI, 1.176–4.255; p=0.014), while in the intermediate prolonged QRS group was 1.441 (95% CI, 0.623–3.333; p=0.394). Moreover, this variable divided by cut-off of 130 ms and 150 ms was insignificant as overall p value for 0.114 in multivariate analysis. In multivariate analysis, on the other hand, a binary variable of QRS duration which is divided by the cut-off of 150 ms was an independent factor associated with outcome (HR, 1.909; 95% CI, 1.024–3.558; p= 0.042).

**Table 4. Variables associated with 30-day in-hospital mortality**

| Variables                  | Univariate HR (95% CI) | p value | Multivariate HR (95% CI) | p value |
|----------------------------|------------------------|---------|--------------------------|---------|
| Age                        | 1.026 (1.007–1.045)    | 0.007   | 1.040 (1.029–1.060)      | <0.001  |
| Hypertension               | 1.973 (1.118–3.483)    | 0.019   | 1.481 (0.779–2.814)      | 0.231   |
| Diabetes                   | 1.822 (1.026–3.236)    | 0.041   | 1.063 (0.567–1.992)      | 0.850   |
| Mechanical ventilation     | 4.594 (1.823–11.579)   | 0.001   | 2.118 (0.770–5.824)      | 0.146   |
| ECMO                       | 3.929 (2.173–7.105)    | <0.001  | 5.370 (2.915–9.891)      | <0.001  |
| QRS ≥150 ms                | 2.042 (1.104–3.779)    | 0.023   | 1.909 (1.024–3.558)      | 0.042   |
| Potassium ≥5.5 mmol/L      | 3.199 (1.502–6.814)    | 0.003   | 3.273 (1.518–7.059)      | 0.002   |

HR = hazard ratio; CI = confidence interval; ECMO = extracorporeal membrane oxygenation.
DISCUSSION

The main conclusions of the present study can be summarized as follows: 1) among patients with wider QRS durations, 30-day in-hospital mortality incidence was higher, while there was no difference in mortality according to the type of ventricular conduction block; 2) age, hyperkalemia, ECMO support during hospitalization, and severe prolonged QRS duration were closely associated with in-hospital mortality.

The majority data associated with CS are so far derived from registries of patients with ACS or myocardial infarction (MI). Of course, the main cause of CS is ACS presenting as MI, but there are other causes, such as HF or valvular heart disease. It is known that CS occurs in about 5–8% of patients with ACS,14,15 but little is known about CS occurring in the HF setting. A previous EuroHeart Failure Survey II (EHFS II) reported that CS was seen in 3.9% of acute HF cases at presentation.16 This was similar to our result showing a low incidence of CS (n=214, 3.8%) among 5,625 KorAHF registry patients. The EHFS II registry demonstrated that the in-hospital mortality associated with CS was about 40%. However, the in-hospital mortality from our study was about 28%. This difference may be derived from the increased use of mechanical circulatory support devices (30.9% of IABP use in EHFS II versus 37.4% of ECMO use in KorAHF) or the improvement of intensive care management.

We observed that patients with prolonged QRS duration had a significantly poor prognosis than the narrow QRS group. The longer the QRS duration, the higher the 30-day cumulative mortality incidence in the K–M plot. It is well known that QRS duration is an important prognostic factor for patients with chronic HF.9,10 These studies highlighted QRS duration and morphology because the QRS complex reflects pathologic changes in LV components, such as the conduction system, cardiomyopathy, and ventricular fibrosis.17,18 However, little is known about the clinical implications of QRS duration in unstable acute HF patients with CS whose ECGs could change dynamically. The study showed that prognosis is affected by a QRS duration that is longer than a certain threshold for a pathologic insult burden on the myocardium.

On the other hand, it is unclear that mechanical dyssynchrony affected clinical outcomes in CS complicating acute HF. Mechanical dyssynchrony was not evaluated here. However, it may not be associated with a poor prognosis. First, QRS duration is known to be inaccurate as a surrogate marker for mechanical dyssynchrony as a prognostic factor among patients with end-stage HF.17 Second, the VCB pattern did not have a significant effect on mortality according to the K–M plot and univariate Cox proportional hazard model analysis in the current study; therefore, it meant that QRS duration but not mechanical dyssynchrony reflected by QRS morphology was an independent prognostic factor. Finally, it has been reported that mechanical dyssynchrony by echocardiography tends to be altered according to the loading condition; thus, it is difficult to use a prognostic marker in acute clinical settings.18

One study showed that prolonged QRS duration identifies HF in patients with preserved ejection fractions at a higher risk of adverse clinical outcomes independent of QRS morphology.21 The authors insisted that prolonged QRS duration was solely affected by myocardial fibrosis among many biological parameters. However, the markers of fibrosis could not be assessed using the KorAHF registry data. Besides, a long history of HF may reflect the severity of myocardial fibrosis. However, the numbers of de novo HF cases in the three groups with different QRS durations were similar, with high proportions above 70% (Table 1). It is intriguing that myocardial fibrosis may be a prognostic marker in the context of CS associated with acute HF.
One plausible mechanism by which QRS duration is associated with poor prognosis is an increased LV afterload in cardiogenic shock. The use of vasoconstrictors and compensatory vasoconstriction to maintain blood pressure generally increase myocardial afterload in cardiogenic shock. An abrupt increase in myocardial wall stress is known to widen the QRS complex. In other words, prolonged QRS durations may suggest an excessive increase in LV afterload and poor condition of the patient. The present study showed trends toward higher blood pressure and more use of inotropics in the prolonged QRS duration group, which did not meet statistical significance (Tables 1 and 2). Even though this should be further investigated, QRS duration can be used as a prognosticator since it may indicate unstable clinical situation rather than reflect underlying cardiac problem in cardiogenic shock.

Among patients with prolonged QRS durations, the rates of ECMO support and invasive mechanical ventilation support were higher than among patients in the narrow QRS group during hospitalization. These additional supportive interventions reflected the severity of illness. Based on the results of the multivariate Cox proportional hazard model, supporting ECMO during admission was the most significant factor associated with adverse outcomes; mechanical ventilation support was not associated with adverse outcomes. Although ECMO support might indicate the severity of HF itself, it was possible that the complications associated with ECMO itself might have further affected mortality.

First, this was not a randomized controlled trial specifically designed to evaluate the implications of QRS duration as a prognostic factors in acute HF patients with CS. Furthermore, the possibility cannot be ruled out that confounding factors may have influenced the results. However, we believe our analysis is still important as a stimulus for further research. Second, as the study sample was relatively small, the possibility of underestimating the effect of the intermediate prolonged QRS duration and the VCB on 30-day in-hospital mortality could not be excluded.

In conclusion, CS is not an uncommon complication, and it is associated with worse in-hospital short-term mortality. Prolonged QRS duration was associated with a higher risk of 30-day in-hospital mortality among patients with acute HF who presented with CS. Patients with severe prolonged baseline QRS durations should be treated as particularly high-risk patients.

**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1**

Univariate and multivariate predictors of 30-day in-hospital mortality

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