Heart rate is associated with mortality in patients undergoing continuous renal replacement therapy

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**Background:** Heart rate (HR) is an essential vital sign based on the finding that HR beyond its normal range is associated with several conditions or diseases, including high mortality in several clinical settings. Nevertheless, the clinical implications of HR remain unresolved in patients undergoing continuous renal replacement therapy (CRRT).

**Methods:** This retrospective cohort study included 828 patients who underwent CRRT due to acute kidney injury between 2010 and 2014. HR and other baseline parameters at the time of CRRT initiation were retrieved. The odds ratio (OR) of 30-day mortality was calculated using a multivariate logistic model.

**Results:** CRRT significantly lowered the HR of patients such that the pre- and post-CRRT HRs (average 6 hours) were 107 beats/min and 103 beats/min, respectively (P < 0.001). When we explored the relationship with 30-day mortality, only HR at the time of CRRT initiation, but not pre- or post-CRRT HR, had a significant relationship with mortality outcome. Based on this result, we divided patients into quartiles of HR at the time of CRRT initiation. Mortality OR in the 4th quartile HR group was 2.6 (1.78–3.92) compared with the 1st quartile HR group. This relationship remained consistent despite adjusting for 28 baseline covariates: OR, 1.7 (1.09–2.76); P = 0.020. However, HR was not associated with the weaning rate from CRRT.

**Conclusion:** High HR at the time of CRRT initiation is subsequently related with high mortality. These results can be a basis for a future predictive model of CRRT-related mortality.

**Keywords:** Acute kidney injury, Continuous renal replacement therapy, Heart rate, Mortality

**Introduction**

Continuous renal replacement therapy (CRRT) controls biochemical imbalance and uremic toxicity in patients with both acute kidney injury (AKI) and hemodynamic instability, which frequently occurs in the intensive care unit. Because of the high incidence of AKI in the intensive care unit, the use of CRRT has increased over the past few years [1]. However, despite the wide use of CRRT, guidelines for the initiation of or weaning from CRRT have not been established. In this respect, certain clinical uses of CRRT might not be restricted even in the risk of overwhelming disadvantages compared with less survival benefit.

Several reports in an intensive care unit have failed to demonstrate the superiority of CRRT compared with conventional intermittent hemodialysis in terms of survival benefit [2,3]. Because the patient subset requiring CRRT already is associated with high mortality risk [4,5], CRRT could not confer visible survival benefit in these studies.
Nevertheless, refraining from obligatory CRRT initiation in all patients with AKI and hemodynamic instability is recommended because of the lack of guidelines and evidence.

CRRT can result in the hemodynamic instability of patients due to intravascular volume depletion and intercompartmental shifts [6]. This disadvantage of CRRT is aggravated by large volume depletion and impaired myocardial function of patients, particularly at the time of connection or early period. The implication of hemodynamic instability represents high patient mortality [4,7,8]. Although this issue has been significantly considered in clinical practice, the optimal values of vital signs for CRRT initiation remain unresolved.

Higher heart rate (HR) is associated with cardiovascular morbidity and mortality across several diseases [9]. This parameter has the advantage of inexpensive and simple measurement, but straightforward concern for HR might be less received in clinical practice compared with blood pressure because certain studies showed a week relationship between HR and mortality [10,11]. Nevertheless, HR is an essential requisite to monitor vital status, and its impact affects the relationship with non-cardiovascular mortality [12]. Herein, we firstly addressed the relationship between HR and overall mortality in a cohort undergoing CRRT due to severe AKI.

Methods

Participants and data collection

Data on patients starting CRRT were obtained retrospectively from a database of a tertiary referral center (Seoul National University Hospital). The inclusion criteria were as follows; adult patients (age, ≥ 18 years) admitted to the intensive care unit and need for CRRT due to severe AKI. Accordingly, 890 patients were enrolled between June 2010 and September 2014. We excluded patients who were previously diagnosed with end-stage renal disease or who were on dialysis before enrollment (n = 61). If the patients underwent CRRT more than once (n = 1), only the first experience was counted as a single case. Consequently, data from 828 patients were analyzed for the present study. The study protocol complied with the Declaration of Helsinki and received full approval from the institutional review board of Seoul National University Hospital (No. H-1610-070-799).

Clinical parameters of patient age; sex; HR; systolic and diastolic blood pressures; weight; cause of AKI; dialysis dose; blood flow rate; dialysate and replacement settings; need for mechanical ventilation; use of vasoactive drugs, anti-coagulants, beta blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; and underlying chronic kidney disease, diabetes mellitus, or atrial fibrillation were recorded at the start of CRRT. The HRs at the time of initiating CRRT, before, and after CRRT (average values during 6 hours) were measured by an automatic monitoring device in the intensive care unit. The mean arterial pressure was calculated as [systolic + (2 x diastolic)]/3. The causes of AKI were divided into sepsis, surgery, nephrotoxins, and others. The Acute Physiology and Chronic Health Evaluation (APACHE) II [13] and Sepsis-related Organ Failure Assessment (SOFA) [14] scores were calculated to quantitatively assess each patient’s status. Blood parameters of hemoglobin, blood urea nitrogen, creatinine, and albumin levels were measured. Volume balance during the first 24 hours of CRRT was recorded as input minus output. The target dose during CRRT initiation was determined based on each patient’s state. No data for any of the variables was missing. All patients were followed up until CRRT was discontinued or December 2016, except for death-censored cases. The primary outcome was all-cause mortality within 30 days. The secondary outcome was weaning from CRRT within 30 days.

Statistical analysis

Data are presented as the mean ± standard deviation for the continuous variables and as the proportion for the categorical variables. The variables with non-normal distributions are expressed as the median (interquartile ranges) based on variable distributions using histograms. The chi-square test was used to compare categorical variables. The comparisons between normally and non-normally distributed continuous variables were performed using the Student’s t-test and Mann-Whitney U test, respectively. Cumulative survival curves were drawn using the Kaplan–Meier method. To compare the curves between the groups, the log-rank test was initially applied. The logistic regression model was used with or without adjustments for all covariates in order to calculate the odds ratios (ORs) of the outcome. A restricted cubic spline analysis was applied to account for the nonlinear
relationship between HR and mortality risk. A value of \(P < 0.05\) was considered significant. All analyses and calculations were performed using the IBM SPSS Statistics software (version 21.0; IBM Co., Armonk, NY, USA) and STATA software (version 12.0; Stata Co. LP, College Station, TX, USA).

**Results**

**Baseline characteristics**

The baseline characteristics of the patients are shown in Table 1. Of the patients, 36.7% and 35.1% had sepsis and underlying chronic kidney disease, respectively. When

| Characteristic | Total (n = 828) | 30-day mortality |  |
|---------------|----------------|------------------|---|
|               | No death (n = 419) | Death (n = 409) | P value |
| Age (yr)      | 63.1 ± 15.1 | 62.6 ± 15.8 | 63.7 ± 14.4 | 0.280 |
| Male sex (%)  | 60.3 | 57.5 | 63.1 | 0.102 |
| Heart rate (beat/min) | 106.0 ± 25.4 | 101.5 ± 24.6 | 110.5 ± 25.3 | < 0.001 |
| Systolic blood pressure (mmHg) | 111 ± 25 | 114 ± 26 | 109 ± 26 | 0.018 |
| Diastolic blood pressure (mmHg) | 65 ± 15 | 66 ± 16 | 64 ± 16 | 0.083 |
| Mean arterial pressure (mmHg) | 80 ± 18 | 82 ± 17 | 79 ± 18 | 0.028 |
| Body weight (kg) | 63.3 ± 12.5 | 63.3 ± 12.4 | 63.3 ± 12.7 | 0.961 |
| Cause of acute kidney injury (%) | 36.7 | 30.1 | 43.5 | < 0.001 |
| Sepsis         | 9.3 | 16.0 | 2.4 | < 0.001 |
| Surgery        | 8.5 | 8.8 | 8.1 | < 0.001 |
| Nephrotoxin    | 45.5 | 45.1 | 46.0 | < 0.001 |
| Dialysis dose (mL/kg/hr) | 43.3 ± 15.7 | 43.2 ± 15.6 | 43.3 ± 15.7 | 0.948 |
| Blood flow rate (mL/min) | 109 ± 22 | 109 ± 23 | 108 ± 22 | 0.232 |
| Dialysate flow (mL/hr) | 1,511 ± 653 | 1,495 ± 648 | 1,527 ± 658 | 0.481 |
| Replacement flow (mL/hr) | 1,491 ± 657 | 1,476 ± 656 | 1,506 ± 659 | 0.524 |
| Mechanical ventilation (%) | 26.7 | 33.4 | 19.8 | < 0.001 |
| Use of vasoactive drugs (%) | 75.5 | 70.2 | 80.9 | < 0.001 |
| Use of anti-coagulant drugs (%) | 40.9 | 43.9 | 37.9 | 0.078 |
| Use of beta blockers (%) | 4.3 | 4.8 | 3.9 | 0.543 |
| Use of calcium channel blockers (%) | 6.9 | 4.8 | 9.0 | 0.015 |
| Use of ACEi/ARB (%) | 2.3 | 2.6 | 2.0 | 0.520 |
| Chronic kidney disease (%) | 35.1 | 40.3 | 29.8 | 0.002 |
| Diabetes mellitus (%) | 22.5 | 23.6 | 21.3 | 0.417 |
| Atrial fibrillation (%) | 4.2 | 5.0 | 3.4 | 0.256 |

Data are presented as mean ± standard deviation, percent only, or median (interquartile range).

Comparisons were evaluated using the chi-squared test for categorical variables, the Student t-test for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables.

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment.
we compared characteristics between patients who survived or died within 30 days of CRRT, a difference in HR was identified, such that those who died had higher HRs than those who survived. Furthermore, the patients who died had higher APACHE II and SOFA scores than those who survived, which indicated that illness severity was prominent in patients who died.

**Relationship between heart rate and mortality**

CRRT lowered the HRs of patients such that the pre- and post-CRRT HRs (i.e., average values during 6 hours) were 107 beats/min and 103 beats/min, respectively \((P < 0.001)\). Within 30 days of CRRT, 409 patients (49.4%) died. We addressed the independent relationship between HR values and 30-day mortality. When we divided the patients by quartiles of HR, only HR at the time of CRRT initiation, not the average values of pre- and post-CRRT HRs, had a significant relationship with mortality outcome. Therefore, we used the HR values at the time of CRRT in all subsequent analyses. The overall survival curves are shown in Fig. 1. The group with high HRs showed higher mortality rates than the counterpart groups \((P < 0.001\) by the log rank test). When we calculated the OR of 30-day mortality (Table 2), the group with high HRs had a higher OR than the group with low HRs, irrespective of other covariates. As a sensitivity analysis, we additionally adjusted the volume balances 24 hours before the initiation of CRRT and 48 and 72 hours after initiation in the multivariate model (\(n = 596\)). The adjusted OR of the 4th quartile group was 2.22 \((1.246–3.948)\) compared with the 1st quartile group \((P = 0.007)\).

The adjusted OR was 1.01 \((1.002–1.015)\) when HR was included as a continuous variable \((P = 0.012)\). This suggests that an increase in 1 beat/min of HR was associated with a 1% increase in mortality rate. Subsequently, a restricted cubic spline analysis was used to explore the possible non-linear relationship between HR and predictability of 30-day mortality (Fig. 2). As a result, the re-

![Figure 1. Kaplan-Meier survival curves based on heart rate. The patients were divided into quartiles (Q) based on the heart rate. CRRT, continuous renal replacement therapy.](image)

![Figure 2. Exploring the possible nonlinear relationship between heart rate and probability of 30-day mortality. Fitted line and 95% confidence intervals are presented with the solid line and shaded area, respectively.](image)

**Table 2. Odds ratios for 30-day mortality according to the heart rate levels**

| Heart rate group | Range (beat/min) | Model 1 | Model 2 |
|------------------|------------------|---------|---------|
|                  | OR (95% CI)      | \(P\) value | OR (95% CI) | \(P\) value |
| 1st quartile     | 48–86            | 1 (Reference) | 1 (Reference) |
| 2nd quartile     | 87–104           | 1.40 (0.94–2.08) | 0.094 | 1.28 (0.83–1.99) | 0.267 |
| 3rd quartile     | 105–123          | 1.68 (1.13–2.48) | 0.010 | 1.38 (0.88–2.16) | 0.156 |
| 4th quartile     | 124–186          | 2.64 (1.78–3.92) | <0.001 | 1.77 (1.11–2.81) | 0.016 |

Model 1, unadjusted; Model 2, adjusted for all covariates shown in Table 1.
CI, confidence interval; OR, odds ratio.
The relationship between HR and mortality seemed to be linear (not non-linear) in the CRRT subset.

**Relationship with weaning from CRRT**

We analyzed weaning from CRRT as a secondary outcome. No significant relationship between HR and weaning rate was shown in the analysis (Table 3). Subsequently, we analyzed only the patients who were alive at discharge because mortality could affect the weaning protocol of each patient (n = 419). Nevertheless, the following unadjusted and adjusted ORs of weaning in the 4th quartile group were not significant compared with the 1st quartile group: unadjusted OR, 1.43 (0.819–2.512); adjusted OR, 1.20 (0.619–2.326) (all P > 0.05).

**Discussion**

CRRT is a critical option to treat severe AKI cases, but the guidelines for initiating and weaning are insufficient, and no mortality-predicting models exist because of the lack of clinical data. The present study focused on HR, one of the widely used vital signs in cardiovascular and non-cardiovascular patients. As a result, high HR at the time of CRRT initiation was associated with subsequent high mortality. This result has clinical implications because no monitoring strategy before or after initiating CRRT is currently established.

High HR is known to be associated with increased morbidity and mortality, which has been demonstrated in the general population [15] and patients with various diseases, such as heart failure [16], ischemic heart disease [17], atrial fibrillation [18], stroke [19], and chronic obstructive pulmonary disease [20]. The relationship has been also consistent in cases of chronic kidney disease [21]. The overall trend for mortality depending on HR seemed to be linear, similar to previous study results. In this respect, the present results focusing on patients with AKI on CRRT support the current clinical context, that high HR should be considered to increase mortality risk.

The relationship between high HR and mortality can be explained by the following issues. High HR is speculated to increase mortality by increasing the sympathetic activity and promoting atherosclerosis in vessels [22]. In addition, high HR decreases tissue perfusion [23], which eventually results in ischemic damage to vital organs. CRRT aggravates hemodynamic instability, which can also help clarify the observation between HR and mortality outcome despite the cohort with extremely high mortality rate. However, the above issues had not been suggested in the setting of CRRT. Future studies are necessary to explore the underlying mechanisms in the CRRT setting.

Although the present results are informative, the study has some limitations. First, the study design was restricted to observing correlations, and this prevented us from drawing a causal relationship. Second, the overall mortality was significantly high, and this might affect the analysis of weaning such that certain patients died before considering the weaning potential. Third, the single-center design requires that the data be validated in other cohorts, although the sample size was large. Finally, unevenly distributed characteristics of patients (e.g., small proportion of chronic kidney disease in the death group) should be carefully considered in the present analyses.

The predictive model of mortality has not been established in the case of CRRT. This issue makes clinical decisions difficult, especially considering the increasing use of CRRT. In this respect, HR as a mortality-related factor in this subset might be a great concern. The present study did not suggest the proper method to monitor HR after CRRT or the adequacy of measuring HR only once. Nevertheless, the results form a basis for later studies setting up a predictive model for CRRT-related mortality.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

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