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Original article

The beneficial prognostic value of hemoconcentration is negatively affected by hyponatremia in acute decompensated heart failure: Data from the Korean Heart Failure (KorHF) Registry☆

Jaewon Oh (MD)[a], Seok-Min Kang (MD, PhD)[a,*], In-Cheol Kim (MD, PhD)[a], Seongwoo Han (MD, PhD)[b], Byung-Su Yoo (MD, PhD)[c], Dong-Ju Choi (MD, PhD)[d], Jae-Joong Kim (MD, PhD)[e], Eun-Seok Jeon (MD, PhD)[f], Myeong-Chan Cho (MD, PhD)[g], Byung-Hee Oh (MD, PhD)[h], Shung Chull Chae (MD, PhD)[i], Myung-Mook Lee (MD, PhD)[j], Kyu-Hyung Ryu (MD, PhD)[b]

[a] Division of Cardiology, Severance Cardiovascular Hospital and Cardiovascular Research Institute, Seoul, Republic of Korea
[b] Division of Cardiology, Hallym University Medical Center, Hwaseong, Republic of Korea
[c] Division of Cardiology, Yonsei University Wonju Severance Christian Hospital, Wonju, Republic of Korea
[d] Division of Cardiology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[e] Division of Cardiology, Ulsan University Asan Medical Center, Seoul, Republic of Korea
[f] Division of Cardiology, Sungkyunkwan University Samsung Medical Center, Seoul, Republic of Korea
[g] Division of Cardiology, Chungbuk National University Hospital, Cheongju, Republic of Korea
[h] Division of Cardiology, Seoul National University Hospital, Seoul, Republic of Korea
[i] Division of Cardiology, Kyungpook National University Hospital, Daegu, Republic of Korea
[j] Division of Cardiology, Dongguk University Ilsan Hospital, Goyang, Republic of Korea

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ABSTRACT

Background: Hemoconcentration (HC) is associated with reduced mortality, whereas hyponatremia (HN) has been associated with an increased risk of adverse outcomes in patients with acute decompensated heart failure (ADHF). We sought to determine if the presence of HN influences the beneficial prognostic value of HC in ADHF patients.

Methods: We analyzed 2046 ADHF patients from the Korean Heart Failure Registry. We defined HC as an increased hemoglobin level from admission to discharge, and HN as sodium <135 mmol/L at admission. Our primary composite endpoint was all-cause mortality and/or HF re-hospitalization.

Results: Overall, HC occurred in 889 (43.5%) patients and HN was observed in 418 patients (20.4%). HC offered higher 2-year event-free survival in patients without HN (73.2% vs. 63.1% for no-HC, log-rank $p < 0.001$), but not in patients with HN (54.2% vs. 58.7% for no-HC, log-rank $p = 0.879$, p for interaction = 0.003). In a multiple Cox proportional hazard analysis, HC without HN conferred a significant event-free survival benefit (hazard ratio: 0.703, 95% confidence interval 0.542–0.912, $p = 0.008$) over no-HC with HN.

Conclusions: Only HC occurring in ADHF without HN was associated with improved clinical outcomes. These results provide further support for the importance of HN as a challenging therapeutic target in ADHF patients.

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* Corresponding author at: Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, 134 Shinchon-dong Seodaemun-gu, Seoul 120-752, Republic of Korea. Fax: +82 2 2227 7732.
E-mail address: smkang@yuhs.ac (S.-M. Kang).

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Introduction

Heart failure (HF) is associated with high morbidity, mortality, and healthcare expenditures in developed countries. In the USA, almost one million hospitalizations for HF occur annually. Fluid overload is a main reason for re-hospitalizations in HF patients [1]. The effective and safe removal of congestion is an important therapeutic goal in hospitalized acute decompensated heart failure (ADHF) patients. Evidence-based data regarding the extent and duration of decongestion in ADHF have been limited. Hemoconcentration (HC), the relative increase in the cellular elements in blood, is a clinical parameter that predicts effective diuresis and is related to aggressive fluid removal. Several recent studies have shown that HC was related to improved clinical outcomes in patients with ADHF [2–6].

Hyponatremia (HN) is the most common electrolyte abnormality and is associated with adverse clinical outcomes in hospitalized patients with ADHF [7–11]. Therefore, it has been a component of the risk factors used in the prediction of prognosis in HF patients [12]. The pathophysiology of HN in ADHF is predominantly hypervolemic, accompanied by an excess of body water, which is a marker of congestion. However, the exaggerated sodium loss by a high dose of diuretics could lead to depletion of sodium, resulting in depletional HN during decongestion therapy, as it were treatment-induced hyponatremia. Therefore, we set out to determine if the presence of HN influences the beneficial prognostic value of HC in ADHF patients using data from a large nationwide registry in Korea. To our knowledge, there have been no studies conducted to evaluate the association between HC with or without HN and subsequent clinical outcomes in ADHF.

Methods

Study sample and design

The primary results of the Korean Heart Failure (KorHF) Registry have been previously reported [5,10,13,14]. Briefly, KorHF Registry was a nationwide, prospective, observational, multicenter, online registry that investigated the etiology, clinical characteristics, treatment modalities, morbidity, mortality, and the prognostic markers of hospitalized ADHF patients. A total of 3200 patients with the diagnosis of ADHF who were admitted within 24 h after symptom onset were enrolled from 24 hospitals in Korea. The ADHF diagnosis was based on specific symptoms in the patient's medical histories and signs on physical examination, according to the Framingham criteria. A confirmed diagnosis of HF was required also at discharge [13]. From the initial recruitment of 3200 patients, 357 patients without available echocardiographic data and 797 patients without other baseline and discharge laboratory data [e.g. hemoglobin (Hb), serum sodium, etc.] were excluded. Thus, the final analysis included 2046 patients. The primary composite endpoint of all-cause mortality and/or re-hospitalization due to HF exacerbation was collected by a review of the medical records and from telephone interviews conducted at the end of the study (1-year follow-up rate: 78.4%, 2-year follow-up rate: 65.5%). Research coordinators guided by documented definitions used standardized report forms to collect the follow-up events. Medical records were reviewed whenever patients required repeat hospitalization. In addition to patient telephone interviews, the referring physicians and institutions were contacted when necessary for additional information.

HC was defined as an increased Hb level from admission to discharge, i.e. Hb change (ΔHb) > 0 [5]. We used the widely accepted definition of HN as a serum sodium level <135 mmol/L at admission and discharge [10]. We calculated the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation: eGFR = $175 \times$ [standardized serum creatinine (mg/dL)] $- 1.154 \times$ age $- 0.203 \times (0.742$ if female) $\times (1.212$ if black) [14].

Statistical analysis

Continuous variables were described using means and standard deviations (or median and interquartile range when it distributes non-normally), and categorical variables were described using numbers or percentages. We compared differences among groups using Student's *t*-test, Chi-square test, and ANOVA if necessary. Kaplan–Meier (K–M) survival analysis was used to estimate event-free survival, and log-rank tests were used to compare clinical outcomes in patients with HC and no-HC. Independent effects of variables and *p*-value for interaction on clinical events were calculated using Cox multivariable proportional hazards regression analysis and incorporating covariates with *p*-values less than 0.1 from unadjusted analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) demonstrated the risk of clinical events. Correlations between various laboratory value changes were examined by Pearson correlation analysis. Values of p less than 0.05 were considered statistically significant and all reported probability values were two-tailed. All analyses were conducted using SPSS version 21.0 software (SPSS/IBM Corp., Chicago, IL, USA).

Results

Baseline characteristics

The baseline characteristics and laboratory findings of ADHF patients (4 groups) are presented in Table 1 according to the presence of HC and HN. Overall, in ADHF patients, the mean Hb level was significantly decreased (12.4 ± 2.3 g/dL vs. 12.1 ± 2.1 g/dL, paired *t*-test $p < 0.001$), but the serum sodium level was not significantly changed (138.1 ± 5.2 mmol/L vs. 138.2 ± 4.6 mmol/L, paired *t*-test $p = 0.660$) from admission to discharge. No significant correlation was observed between Hb and serum sodium level changes between admission and discharge ($r = -0.039$, $p = 0.080$, $n = 1991$). Based on our definition of HC and HN, HC occurred in 889 (43.5%) patients and HN was observed in 418 (20.4%) patients. Patients who developed HC had significantly lower Hb, glucose, total cholesterol levels, and higher eGFR at admission compared to no-HC patients. Patients with HN had significantly lower Hb, total cholesterol, and sodium, while demonstrating higher glucose, blood urea nitrogen (BUN), and creatinine level compared to patients without HN. However, BUN/creatinine ratio, left ventricular ejection fraction, the prevalence of hypertension, diabetes mellitus, HF with reduced ejection fraction, and medication administration history were not significantly different among the four groups.

Associations with clinical outcomes

The primary endpoint of our study was the composite of all-cause mortality and/or re-hospitalization for HF aggravation. During median follow-up of 371 days (interquartile range, 85–872 days), 2-year events as a primary composite endpoint occurred in 34.6% ($n = 708$) of the patients, including in 16.6% ($n = 339$) of deaths. In K–M survival analysis, the HC group had a significantly higher 2-year event-free survival than the no-HC group (73.2% vs. 63.1%, respectively, log-rank $p < 0.001$; Fig. 1a). Based on the unadjusted Cox proportional hazards analysis, both HC (HR: 0.759, 95% CI: 0.658–0.875, $p < 0.001$) and HN (HR: 1.471, 95% CI: 1.251–1.729, $p < 0.001$) were prognostic predictors. However, based on the adjusted Cox regression model, only HC (HR: 0.743 95% CI: 0.632–0.874, $p < 0.001$), but not HN (HR: 1.088, 95% CI: 0.896–1.322,

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