Elevated Heart Rate in Combination with Elevated Blood Pressure Predicts Lower Cardiovascular Mortality in Acute Decompensated Heart Failure

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Summary

Despite its clinical relevance, a subclass of acute decompensated heart failure (ADHF) with elevated blood pressure, known as hypertensive ADHF (HT-ADHF), has been less intensively evaluated. This study aimed to characterize the prognostic nature and pathophysiology of HT-ADHF. A total of 509 consecutive patients with first-time ADHF hospitalization were subjects of the study. Participants were divided into two groups: an HT-ADHF group (systolic blood pressure, SBP > 140 mmHg at presentation) and a non-HT-ADHF group (SBP ≤ 140 mmHg). Median follow-up duration measured 253 days. Unadjusted Kaplan-Meier analysis demonstrated both a lower cardiovascular mortality rate in the HT-ADHF group and similar incidences of heart failure rehospitalization in both groups. Adjusted Cox hazard analysis showed an association of elevated SBP at presentation with significantly lower cardiovascular mortality, though no such association was observed with heart failure rehospitalization. Moreover, elevated heart rate in combination with elevated SBP at presentation predicted a significantly lower risk of cardiovascular mortality (Hazard Ratio: 0.32, 95% CI: 0.14-0.77, *p* = 0.01). Also, significantly lower cardiovascular mortality was observed in this subtype, compared with other types of ADHF. (Int Heart J 2020; 61: 308-315)

Key words: Hypertension, Sympathetic activation

Acute decompensated heart failure (ADHF) is the sudden or progressive worsening syndrome of heart failure, which is characterized by exacerbation of HF signs and symptoms resulting in the need for urgent treatment with hospitalization. ADHF constitutes a complex clinical syndrome, representing a broad spectrum of diseases and statuses with heterogeneous clinical presentations. Despite intensive research interest in the field, the pathophysiological mechanisms involved in the development and progression of ADHF have yet to be fully elucidated. To date, several clinical classifications of ADHF have been proposed based on subtypes of onset, etiology, and physiological conditions. While a classification consisting of 5 clinical scenarios (CS) mainly according to systolic blood pressure to guide early management of ADHF was suggested by Mebazaa, *et al.*,1 the European Society of Cardiology (ESC) guidelines recommended a different classification mainly based on etiologies.3 Among the subtypes of ADHF in these two classifications, a subgroup with elevated blood pressure, defined as hypertension in the ESC guidelines and CS1 in the classification by Mebazaa, *et al.*, has been less studied compared to other subtypes of ADHF, such as gradual/progressive amelioration of chronic HF and decompensated chronic heart failure. Clinically, hypertensive ADHF (HT-ADHF) generally comprises flash pulmonary congestion with relatively preserved left ventricular systolic function leading to favorable prognosis.3 We hypothesized that the excess of inappropriate sympathetic activation is associated with the pathophysiology in this clinically relevant subtype of ADHF. Therefore, this study primarily aimed to clarify the demographic characteristics and prognosis in HT-ADHF. Moreover, as a potential pathophysiological mechanism of this subtype of ADHF, the association between sympathetic overactivation represented by not only elevated blood pressure, but also higher heart rate, and time of the development of heart failure symptoms was evaluated.

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Received for publication October 7, 2019. Revised and accepted December 23, 2019. Released in advance online on J-STAGE March 14, 2020. doi: 10.1536/ihj.19-521
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Methods

Study participants and classification of ADHF based on systolic blood pressure (SBP) at initial presentation: A total of 535 consecutive patients who were admitted to one of two Juntendo University Hospitals in Metropolitan Tokyo with a diagnosis of ADHF from January 1, 2014 to December 31, 2016 were enrolled as subjects in this study. A consort diagram of this study is presented in Supplemental Figure 1. A diagnosis of ADHF requiring hospitalization was made based on signs and symptoms of pulmonary congestion, pleural effusion, and peripheral edema. Patients who presented with the following specific etiologies were excluded from analysis: pulmonary edema induced by overhydration in end-stage renal disease under chronic hemodialysis (n = 10), acute coronary syndromes (n = 5), and isolated right heart failure with minimal or no pulmonary congestion (n = 11). Other than patients on chronic hemodialysis, these subclasses of ADHF were previously defined as heart failure by acute coronary syndromes (HF-ACS) and right heart failure (RHF) in ESC guidelines, as well as CS-4 and 5 in the classification by Mебазза, et al. The remaining ADHF patients (n = 509) were included in the analysis and divided into two subgroups according to their systolic blood pressure (SBP) at initial presentation for detailed characterization. ESC guidelines and studies classify patients with elevated SBP as hypertensive heart failure (HT-HF), yet no clear definition has been proposed. Classification based on clinical scenarios with an initial SBP presentation greater than 140 mmHg was defined as clinical scenario 1 (CS 1). In this study, we accordingly set the cut-off value for SBP at 140 mmHg for the classification of hypertensive (HT-ADHF) and non-hypertensive ADHF (non-HT-ADHF). Median SBP and SBP interquartile ranges (IQR) in all participants were 144 mmHg and 122-167 mmHg, respectively. Moreover, to stratify patients by heart rate, the median of heart rate in all participants, 94 beats per minute (bpm), was used as a cut-off value. Heart rate data was not available in one patient. In this study, the time of ADHF onset was substituted as the time of presentation, arrival at the hospital, or the time the patient was transferred to the intensive cardiac care unit in cases in which they were already hospitalized for reasons other than ADHF.

Data collection, outcome measures, and follow-up period: All clinical data at initial presentation and endpoints, such as cardiovascular mortality and heart failure rehospitalization, were retrospectively collected by reviewing electronic medical charts. Cardiovascular mortality was defined as death by heart failure, coronary artery disease, critical arrhythmias, aortic disease, stroke, or sudden cardiac death (SCD) during follow-up. As another endpoint, rehospitalization due to heart failure, as a marker of heart failure recurrence, was counted. The median follow-up period and follow-up range were 253 and 0-1166 days, respectively. This study was approved by the Institutional Review Board of Juntendo University and has been registered in the University Hospital Medical Information Network - Clinical Trials Registry (UMIN-CTR) (ID: UMIN 000007555).

Statistical analysis: Continuous variables are presented as the mean ± standard deviation or median with the interquartile range per the results of the Shapiro-Wilk normality test and were compared using the non-parametric Mann-Whitney test. Categorical data are shown as numbers and percentages and were compared using the Fisher exact test. Kaplan-Meier curves for evaluation of time to cardiovascular death and time to heart failure rehospitalization were drawn, and the curves were compared using the log-rank test. In addition to unadjusted Kaplan-Meier analysis, multivariate Cox proportional hazard analysis was also conducted. Variables used in the multivariate model were selected per the results of univariate Cox hazard analysis when p-values were less than 0.1. Categorical hazard ratios of 4 subgroups divided by median systolic blood pressure and heart rate were adjusted by age, gender, anemia, history of HF hospitalization, chronic kidney disease, and use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor antagonists (ARBs). All probability values (P-values) were two-tailed and considered to be significant when less than 0.05.

Results

Baseline demographics in HT-ADHF (n = 245) and non-HT-ADHF patients (n = 264): A total of 509 ADHF patients (average age, 75.4 years, 199 females) were included in the analysis. Participants were divided into two groups, an HT-ADHF group and a non-HT-ADHF group, based on > or ≤ 140 mmHg of SBP at initial presentation (Table 1). Overall, patients with HT-ADHF were older, had a higher heart rate, and had a higher incidence of current/former smoking, though they had similar incidences of coronary artery disease (CAD), atrial flutter/fibrillation (AFL/AF), chronic kidney disease (CKD), and previous history of HF hospitalization compared to those with non-HT-ADHF. Patients with HT-ADHF received more antihypertensive agents, such as angiotensin receptor antagonists (ARBs) and calcium channel blockers (CCBs), but fewer loop diuretics and mineral corticoid receptor antagonists. Patients with HT-ADHF had a relatively preserved left ventricular ejection fraction (LVEF). Additionally, systemic inflammation implied by C-reactive protein (CRP) was lower in the HT-ADHF group.

HT-ADHF was associated with lower cardiovascular mortality, but not with a lower incidence of heart failure rehospitalization: Cardiovascular death and heart failure rehospitalization occurred in 57 (11.2%) and 124 patients (24.4%) through the follow-up period, respectively. Unadjusted Kaplan-Meier analysis showed lower cardiovascular mortality in patients with HT-ADHF (Figure 1A), but a similar incidence of heart failure rehospitalization (Figure 1B). Univariate Cox proportional hazard analysis showed age, high heart rate (HR) (> 94 beats per minute (bpm), median), anemia, history of heart failure, use of loop diuretics, and HT-ADHF were significantly associated with cardiovascular mortality. In multivariate Cox hazard analysis using a model consisting of variables with P-value < 0.1 in univariate analysis, age, male gender, high HR (> 94 bpm), anemia, history of heart failure, HT-ADHF, CKD, and use of ACEI/ARB and loop diuret-
Table I. Baseline Demographics and Medications in Patients with or without Hypertensive ADHF

|                      | Non-hypertensive | Hypertensive | P   |
|----------------------|------------------|--------------|-----|
| Gender, male         | 158, 59.8%       | 152, 62.0%   | 0.65|
| Age                  | 77.0, 65.0-84.8  | 80.0, 72.0-85.0 | 0.021|
| BMI                  | 22.4, 20.4-25    | 22.2, 19.8-25 | 0.871|
| SBP, mmHg            | 125.0, 110-136   | 165.0, 151-186 | <0.001|
| DBP, mmHg            | 74.5, 65-87      | 96.0, 81-110  | <0.001|
| HR, bpm              | 90.5, 74.3-112   | 97.5, 79-115  | 0.034|
| History of HF hospitalization | 94, 35.6%      | 77, 31.4%     | 0.348|
| Coronary artery disease | 103, 39.0%     | 92, 37.6%     | 0.784|
| AF/AFL               | 157, 59.7%       | 124, 51.0%    | 0.06|
| LVEF, %              | 40, 29-53        | 43, 30-58.8   | 0.021|
| Impaired LVEF < 40%  | 137, 55.2%       | 108, 45.8%    | 0.045|
| Anemia               | 151, 57.2%       | 148, 60.4%    | 0.472|
| Alb, mg/dL           | 3.40, 3-3.8      | 3.50, 3-3.9   | 0.114|
| BUN, mg/dL           | 23.00, 16-34     | 21.00, 16-29  | 0.027|
| Cr, mg/dL            | 1.04, 0.8-1.5    | 0.99, 0.8-1.4 | 0.626|
| eGFR, L/minute/1.72*2| 50.00, 30.0-69.4 | 49.80, 35.3-66.5 | 0.959|
| CKD                  | 163, 61.7%       | 163, 66.5%    | 0.269|
| HbA1c, mg/dL         | 6.0, 5.6-6.6    | 5.9, 5.5-6.5  | 0.406|
| CRP, mg/dL           | 0.9, 0.3-3.7    | 0.7, 0.2-2.0  | 0.019|
| high CRP > 1 mg/dL   | 122, 47.1%       | 92, 38.3%     | 0.057|
| ProBNP, pg/L         | 4708, 2317-10337 | 4787, 2008-9249 | 0.058|
| Smoking habit        | 125, 48.8%       | 138, 58.0%    | 0.047|
| Alcohol habit        | 124, 48.6%       | 115, 49.8%    | 0.856|
| ACEIs                | 40, 15.2%        | 25, 10.2%     | 0.111|
| ARBs                 | 74, 28.1%        | 96, 39.2%     | 0.009|
| Beta blockers        | 115, 43.9%       | 91, 37.1%     | 0.125|
| MRAs                 | 58, 22.1%        | 28, 11.4%     | 0.001|
| Loop diuretics       | 133, 50.6%       | 94, 38.4%     | 0.007|
| CCBs                 | 66, 25.1%        | 94, 38.7%     | 0.001|

Continuous variables are presented as the mean ± standard deviation or median with the interquartile range per the results of the Shapiro-Wilk normality test. SBP/DBP indicates systolic/diastolic blood pressure; HR, heart rate; AF/AFL, atrial fibrillation/atrial flutter; CKD, chronic kidney disease; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; and MRAs, mineralocorticoid receptor antagonists.

ics, HT-ADHF was shown to be independently associated with decreased cardiovascular mortality (Table II). In contrast, HT-ADHF was not associated with HF rehospitalization in either univariate or multivariate analysis (Table III). High HR (> 94 bpm) was associated with cardiovascular mortality, but not with heart failure rehospitalization in univariate analysis, and was slightly associated with a decreased risk of cardiovascular mortality in multivariate analysis. Stepwise higher hazard ratios for cardiovascular mortality with lower SBP (100-140 and < 100 mmHg) were demonstrated by adjusted Cox hazard analysis, where SBP > 140 mmHg was set as the reference control (Figure 2).

High HR in combination with high SBP predicts low cardiovascular mortality, but not heart failure rehospitalization: Unadjusted Kaplan-Meier analysis when the participants were divided into 4 subgroups, by SBP (>140 or ≤ 140 mmHg) and heart rate (>94 or ≤ 94 bpm), revealed a significantly higher incidence of cardiovascular death in patients with low SBP and HR than in the other 3 groups (Figure 3A). Cox proportional hazard analysis adjusted by age, gender, history of HF hospitalization, CKD, and use of beta blockers, ACEI and/or ARB, measured the categorical hazard ratios of these four subgroups and showed significantly lower risk for cardiovascular mortality in the subgroup having high SBP, as well as high HR when the hazard ratio in a group of low SBP and low HR was set as the reference (Figure 3B). However, neither SBP nor HR had an impact on the incidence of heart failure rehospitalization (Supplemental Figure 2A, B).

Diurnal change in symptom development and blood pressure at initial presentation in HT- and non-HT-ADHF: To determine whether circadian changes in hemodynamics may play a role in the pathogenesis of HT- and non-HT-ADHF, such as morning blood pressure surge, the incidence of ADHF symptom development by time period, 0:00-8:00, 8:00-16:00 (4:00 PM), 16:00-0:00, and intraday fluctuation of initial blood pressure at the presentation of ADHF patients were evaluated. The ratio of patients whose symptoms of ADHF developed at night (0:00 AM and 8:00 AM) was significantly higher in the HT-ADHF group compared to the non-HT-ADHF group (Tables IV, V). Consistently, mean SBP and diastolic BP (DBP) at initial presentation of all participants were highest for 4:00-8:00 AM (Supplemental Figure 3A). Similarly, the fre-
In the Heart Journal
March 2020

Higher Heart Rate Predicts Better Outcomes in ADHF

Table II. Cox Proportional Hazard Analysis to Identify Risk Factors of Cardiovascular Mortality in ADHF Patients

| Risk Factor                              | Univariate HR | 95% CI       | P   | Multivariate HR | 95% CI       | P   |
|------------------------------------------|---------------|--------------|-----|----------------|--------------|-----|
| Age                                      | 1.07          | (1.04-1.11)  | <0.001 | 1.07           | (1.03-1.11)  | 0.00 |
| Gender, male                             | 0.60          | (0.35-1.01)  | 0.05 | 0.77           | (0.45-1.32)  | 0.34 |
| High HR > 94 bpm                         | 0.48          | (0.28-0.85)  | 0.01 | 0.57           | (0.32-1.02)  | 0.06 |
| Anemia                                   | 2.85          | (1.50-5.40)  | 0.00 | 1.91           | (0.98-3.72)  | 0.06 |
| History of HF hospitalization            | 2.18          | (1.29-3.69)  | 0.00 | 1.70           | (0.94-3.08)  | 0.08 |
| Hypertensive ADHF                        | 0.48          | (0.28-0.84)  | 0.01 | 0.45           | (0.25-0.78)  | 0.01 |
| CAD                                      | 1.51          | (0.89-2.55)  | 0.13 |               |              |     |
| AF/AFL                                   | 0.77          | (0.45-1.29)  | 0.32 |               |              |     |
| CKD (eGFR < 60 L/minute/1.73*2)          | 1.78          | (0.97-3.27)  | 0.06 | 0.94           | (0.48-1.86)  | 0.87 |
| ACEIs                                    | 1.39          | (0.70-2.76)  | 0.34 |               |              |     |
| ARBs                                     | 1.42          | (0.84-2.42)  | 0.19 |               |              |     |
| ACEIs and/or ARBs                       | 1.70          | (1.00-2.91)  | 0.05 | 1.18           | (0.67-2.07)  | 0.56 |
| Beta blockers                            | 0.91          | (0.54-1.55)  | 0.73 |               |              |     |
| Loop diuretics                           | 2.13          | (1.24-3.67)  | 0.01 | 1.13           | (0.58-2.20)  | 0.71 |
| Calcium channel blockers                 | 1.27          | (0.74-2.17)  | 0.40 |               |              |     |
| Low LVEF < 40%                           | 0.89          | (0.52-1.54)  | 0.68 |               |              |     |
| CRP > 1.0 mg/dL                          | 1.54          | (0.91-2.60)  | 0.11 |               |              |     |

CAD indicates coronary artery disease; AF/AFL, atrial fibrillation/atrial flutter; CKD, chronic kidney disease; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; and LVEF, left ventricular ejection fraction.

Discussion

This study illustrates a clinically relevant, but not intensively investigated subtype of acute heart failure with the pathophysiology in which inappropriate sympathetic overactivation, represented by elevated blood pressure and heart rate, may play pivotal roles.

Acute heart failure is a syndrome of heterogeneous pathophysiological conditions or a cluster of diseases sharing similar symptoms, signs, and laboratory findings.
ADHF with elevated SBP (> 140 mmHg) has been previously reported as common, although the incidence varies among studies. A large-scale registry of ADHF in the United States showed 50% of ADHF patients have an associated elevated SBP (> 140 mmHg)\(^5\) and the frequency of such a population was found to vary between 67.4% and 30.3% among all ADHF patients in two European ADHF registries.\(^3,6\) In this study, the incidence of HT-ADHF (> 140 mmHg, 48.1%) was comparable with these previous studies, indicating the clinical relevance of HT-ADHF. In this study, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) were more prescribed, while fewer received mineral corticoid receptor antagonists and loop diuretics among HT-ADHF patients. These findings indicate that patients with HT-ADHF were hypertensive and fewer were complicated by chronic heart failure.

Unadjusted Kaplan-Meier analysis and univariate and multivariate Cox proportional hazard analyses consistently showed that HT-ADHF was associated with a decreased risk of cardiovascular mortality, but not with heart failure rehospitalization. Results regarding the impact of HT-ADHF on mortality in this study were consistent with those of previous studies,\(^7\) while there was no impact on rehospitalization due to heart failure, which has not been previously reported. Although detailed data regarding cardiovascular mortality is not available in this study and the precise mechanism of the discrepancy in the prognostic impact of HT-ADHF on cardiovascular mortality with heart failure rehospitalization remains unknown, it may be caused by sudden cardiac death in association with inappropriate sympathetic overactivation.\(^8\)

This study indicates that the pathophysiology in HT- and non-HT ADHF are substantially different, al-

### Table III. Cox Proportional Hazard Analysis for ADHF Rehospitalization

|                     | Univariate |            | P     | Multivariate |            | P     |
|---------------------|------------|------------|-------|--------------|------------|-------|
|                     | HRs        | 95% CI     |       | HRs          | 95% CI     |       |
| Age                 | 1.03       | (1.01-1.04)| < 0.001 | 1.01         | (1.00-1.03)| 0.15  |
| Gender, male        | 0.92       | (0.64-1.32)| 0.64  | 0.95         | (0.64-1.39)| 0.77  |
| High HR > 94 bpm    | 0.84       | (0.59-1.21)| 0.35  |              |            |       |
| Anemia              | 1.93       | (1.32-2.83)| < 0.001| 1.26         | (0.82-1.92)| 0.29  |
| History of HF hospitalization | 2.17 | (1.52-3.09) < 0.001 | 1.03 | (0.71-1.49)  | 0.88     |
| Hypertensive ADHF    | 0.98       | (0.69-1.40)| 0.92  |              |            |       |
| CAD                 | 2.18       | (1.53-3.10)| < 0.001| 1.85         | (1.27-2.68)| < 0.001|
| AF/AFL              | 1.11       | (0.78-1.59)| 0.56  |              |            |       |
| CKD (eGFR < 60 L/minute/1.73^2) | 2.17 | (1.43-3.29) < 0.001 | 1.34 | (0.85-2.13)  | 0.21     |
| ACEIs               | 1.31       | (0.80-2.13)| 0.29  |              |            |       |
| ARBs                | 1.06       | (0.74-1.54)| 0.74  |              |            |       |
| ACEIs and/or ARBs   | 1.23       | (0.86-1.75)| 0.26  |              |            |       |
| Beta blockers       | 1.43       | (1.01-2.04)| 0.05  |              |            |       |
| Loop diuretics      | 2.08       | (1.45-2.97)| < 0.001| 1.52         | (1.00-2.29)| 0.05  |
| Calcium channel blockers | 1.39 | (0.97-2.00) 0.07 | 1.20 | (0.83-1.74)  | 0.34     |
| Low LVEF < 40%      | 0.87       | (0.60-1.26)| 0.46  |              |            |       |
| CRP > 1.0 mg/dL     | 1.25       | (0.88-1.79)| 0.22  |              |            |       |

CAD indicates coronary artery disease; AF/AFL, atrial fibrillation/atrial flutter; CKD, chronic kidney disease; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; and LVEF, left ventricular ejection fraction.

Figure 2. Decreased risk of cardiovascular mortality in accordance with elevated SBP at presentation in ADHF patients. Multivariate Cox proportional hazard analysis, which was adjusted by age, gender, anemia, history of heart failure hospitalization, and use of ACEI/ARB or loop diuretics, showed a stepwise increase of SBP in hazard ratio for cardiovascular mortality (left panel), but not for heart failure rehospitalization (right panel). Bold horizontal line in combination with crossing vertical line indicate hazard ratios (HR) and 95% confident interval (95% CI), respectively.
though they share common signs and symptoms. Risk stratification by HR in addition to SBP showed a significantly lower cardiovascular mortality rate when the patients had higher levels, even after adjustment by AF/AFL and beta-blocker use, which may alter HR. These findings in this study, indicating a favorable prognostic impact of elevated HR in ADHF patients, are inconsistent with those in a previous cohort study in Japanese patients with chronic heart failure. Differences in the population and patient status, decompensated and compensated, may cause the opposing results for HR between the two studies. In this study, SBP and HR were considered as indicators of sympathetic activation. Therefore, these findings suggest that a subtype of ADHF accompanied by sympathetic activation leads to lower cardiovascular mortality with a similar incidence of heart failure readmission, although the exact cause of such a difference remains obscure. Accordingly, in respect of the prognosis of ADHF, the sympathetic activation in this subtype of ADHF may need to be considered rather “appropriate” than “over-” or “excessive”.

Furthermore, the significantly higher frequency of HT-ADHF in the nighttime (0:00-8:00) and the peak mean SBP/DBP for admission times between 4:00-6:00 in HT-ADHF patients may reflect circadian fluctuation of sympathetic activity. A body of evidence has suggested that

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**Figure 3.** Kaplan-Meier analysis and categorical hazard ratios for cardiovascular mortality when ADHF patients were divided into 4 groups by SBP and HR. A: Kaplan-Meier analysis showed a significantly higher incidence of cardiovascular mortality in the group with lower BP and lower HR, compared to the other 3 subgroups. *P < 0.05 when curves were compared to the group with low BP and low HR by Log-rank test. B: Adjusted categorical hazard ratio for cardiovascular mortality in patients with high SBP and HR was significantly low, when those with low SBP and HR were used as reference control.

**Table IV.** Frequency of Tachycardia and Hypertensive Heart Failure by Presentation Time

| Time of presentation | Frequency of tachycardia (HR > 100 bpm, n = 507*) | Frequency of hypertensive ADHF (SBP > 140 mmHg, n = 508*) |
|----------------------|----------------------------------------------------|--------------------------------------------------------|
| 0:00 AM - 8:00 AM    | 49/90, 54.4%                                       | 58/90, 64.4%                                           |
| 8:00 AM - 4:00 PM    | 92/252, 36.5%                                       | 110/252, 43.7%                                         |
| 4:00 PM - 0:00 AM    | 65/165, 39.4%                                       | 76/166, 45.8%                                          |

*Time of presentation data was not available in one patient and that of heart rate was not available in one patient.

**Table V.** Distribution of Presentation Time within Hypertensive and Non-Hypertensive ADHF

| Time of presentation | Non-hypertensiveADHF n = 264 | HypertensiveADHF n = 244* |
|----------------------|------------------------------|---------------------------|
| 0:00 AM - 8:00 AM    | 32, 12.1%                    | 58, 23.8%                 |
| 8:00 AM - 4:00 PM    | 142, 53.8%                   | 110, 45.1%                |
| 4:00 PM - 0:00 AM    | 90, 34.1%                    | 76, 31.1%                 |

*Data of time of presentation data was not available in one patient.
overactivation of the sympathetic nervous system is one of the major components in the pathophysiology of a non-dipper or rise in blood pressure during the nighttime or early morning in hypertensive individuals. Such a pathological diurnal change in blood pressure is associated with cardiovascular events, including coronary artery disease and heart failure. A previous study has also demonstrated that blood pressure in ADHF patients was significantly higher in the night. These studies may suggest that excessively elevated blood pressure by sympathetic overactivation, which may predominantly occur in the night to early morning, is one of the significant pathophysiologies of developing symptoms in hypertensive ADHF. Acute fluid redistribution is caused by a disturbance in the ventricular-vascular coupling relationship. In this relationship, acute alterations in vascular elasticity and vasoconstriction lead to cardiac overload and contribute to decompensated LV function. Although ADHF is generally accompanied by an increase in LV end-diastolic pressure (LVEDP), there are specific subgroups for which afterload reduction is appropriate, and others where volume removal or inotropic support is needed. HT-ADHF is a subgroup whose primary pathophysiological insult is an increase in afterload, which leads to volume redistribution with a shift of fluid from systemic to pulmonary circulation, such as “flash” pulmonary edema. A normal ventricular-vascular interaction maintains homeostasis in the cardiovascular system, including appropriate fluid distribution among periphery and pulmonary/systemic circulations. A mismatch in the ventricular-vascular coupling relationship plays a crucial role in the pathogenesis of HT-ADHF. A sharp increase in LVEDP induced by an abrupt rise in vascular tone, causing a progressive mismatch of that relationship in the setting of a non-compliant ventricle, is a particularly important contributor to the development of HT-ADHF. Moreover, in patients with poorly controlled hypertension, pathological sympathetic blood pressure surge occurs in the night and early morning. The findings in the present study regarding the diurnal distribution of the incidence in the presentation and peak blood pressure in the early morning of HT-ADHF may indicate a significant role for sympathetic activation in its pathophysiology. To date, there is no established treatment or preventative strategies specified for HT-ADHF. Potent and long-acting antihypertensive agents in combination including intensive beta blockers may be an option and should be considered. In addition, the timing of taking beta blockers and antihypertensive drugs at night might be somewhat efficient at blocking a nighttime sympathetic surge. Furthermore, sleep apnea may also be a critical component of the pathophysiology in HT-ADHF. Sympathetic alterations play a pivotal role in the pathophysiology of cardiovascular disease with obstructive sleep apnea (OSA). In OSA, an inappropriate balance between sympathetic and parasympathetic activation during sleep is closely associated with an alteration in hemodynamics and fluid distribution that result in cardiovascular morbidity and mortality. In particular, treatment by continuous positive airway pressure (CPAP) reduced hypertension and led to a reduction of cardiovascular events.

For acute treatments of ADHF associated with sympathetic overactivation, appropriate blood pressure control using vasodilators is essential. In addition, in patients with a higher heart rate, those with atrial fibrillation in particular, an ultra-short-acting beta blocker landiolol might be effective.

Our study is subject to some limitations. Its retrospective nature can identify correlations, but it was not designed to evaluate causality. Moreover, as the number of participants is limited and the underlying mechanisms have yet to be elucidated in this study, a larger-scale prospective registry exploring detailed clinical characterizations regarding HT-ADHF, such as heart rate variability and parameters related to sleep apnea, are needed to generalize the findings in this study. Subgroup analyses may be needed in a larger sample size study, such as subgroups by gender, age, anti-hypertensive medications and AF/AFL.

**Conclusions**

Among the subclasses in ADHF, one with elevated SBP at initial presentation, HT-ADHF, was associated with reduced cardiovascular mortality, albeit with a similar incidence of heart failure rehospitalization. Moreover, an elevated HR (> 94 bpm) at initial presentation in combination with an elevated SBP predicted a further lower risk of cardiovascular death. The findings in this study may indicate the significant contribution of sympathetic overactivation, represented by elevated SBP and HR, in the pathophysiology of HT-ADHF. Although further detailed and large-scale investigations are warranted, the findings of this study may indicate the therapeutic significance of controlling sympathetic overreaction to prevent HT-ADHF.

**Acknowledgments**

The authors thank all the patients and physicians who participated in this study.

**Disclosure**

Conflicts of interest: None.

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Supplemental Files
Supplemental Figures 1-3
Please see supplemental files; https://doi.org/10.1536/ihj.19-521