Mechanisms of Urgently Presenting Acute Heart Failure

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Summary

The mechanisms of urgently presenting acute heart failure (AHF) are not clear. We evaluated the serum catecholamine values of AHF patients immediately after admission. A total of 1,475 AHF patients were screened, and 484 who were admitted from their homes and in whom serum catecholamine could be evaluated immediately after admission were analyzed. The patients were divided into three groups according to the time interval from the onset of symptoms to admission (OA): < 3 hours (early-OA group; n = 283), 3-24 hours (middle-OA group; n = 142), and ≥24 hours (late-OA group; n = 59). In the early-OA group, the systolic blood pressure (SBP) was significantly higher, orthopnea was more frequent, the pH value was significantly decreased, and the use of non invasive positive-pressure ventilation was required significantly more often than in the other groups. The serum noradrenaline level was significantly increased in the early-OA group (1.96 [0.73-3.41] ng/mL) than in the middle-OA (1.49 [0.73-3.41] ng/mL) and late-OA (1.40 [0.91-2.42] ng/mL) groups, and the adrenaline level was significantly increased in the early-OA group (0.36 [0.13-1.17] ng/mL) than in the late-OA (0.22 [0.09-0.52] ng/mL) group. A multivariate logistic regression model indicated the early-OA group was independently associated with the SBP > 140 mmHg (odds ratio [OR]: 2.199, 95% CI: 1.375-3.581), midnight/early morning admission (OR: 3.158, 95% CI: 2.048-4.868), and high serum catecholamine value (adrenaline > 0.96 ng/mL, noradrenaline > 3.39 ng/mL, and dopamine > 0.21 ng/mL) (OR 2.091, 95% CI: 1.161-3.767). In conclusion, urgently presented AHF might be induced by an endogenous catecholamine surge, which causes an excessive rise in blood pressure leading to increased after-load and volume-shift lung congestion.

Key words: Catecholamine, Norepinephrine, Symptom, Onset time, Admission time, Time interval, Vascular heart failure

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cute heart failure (AHF) occurs in various clinical settings. The European Society of Cardiology (ESC) guidelines classify patients with AHF into several clinical conditions.1,2 These include 1) acute decompensated heart failure (HF) and de novo or decompensated chronic HF; 2) hypertensive AHF; 3) pulmonary edema; 4) cardiogenic shock; 5) high-output HF; and 6) right HF. We focused on patients with 2) hypertensive AHF and 3) pulmonary edema. Patients with pulmonary edema could be divided into two categories: “vascular failure” and “cardiac failure.” In vascular HF, pulmonary congestion is induced by afterload mismatch or volume shift, which is often accompanied by an increase in systemic blood pressure. Most patients in this setting develop HF abruptly and present to an emergency department immediately after the onset of symptoms. This pathophysiology might be linked to hypertensive HF. Contrarily, patients with cardiac failure present pulmonary congestion caused by ventricular output failure, which is often accompanied by systemic fluid retention. In this setting, the symptoms develop gradually over days and weeks. These differences are important when deciding the initial management of AHF. However, the underlying mechanism of each of these entities has not been well elucidated.

The increased neuronal release of norepinephrine and the decreased efficiency of norepinephrine reuptake both contribute to the increased cardiac adrenergic drive in congestive HF.3 Plasma norepinephrine and epinephrine levels are increased in patients with HF as a result of increased sympathetic nerve activity.4,5 Furthermore, these increases in cardiac norepinephrine spillover have been shown to have a strong negative correlation with the long-term prognosis of HF.3,5 However, no reports have demonstrated the role of sympathetic nerve activity in AHF. We hypothesized that the serum catecholamine surge resulting from increased sympathetic nerve activity plays an important role in the worsening of AHF, especially in vascular HF. The present study evaluated the serum catecholamine

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1,475 patients who were admitted to the intensive care unit

732 patients who did not undergo catecholamine measurement within 15 minutes after admission

234 patients who were admitted from other hospitals or general wards

25 patients for whom the time of onset could not be investigated because of a lack of data

484 patients were enrolled in present study

Early-OA group (n=283)  Middle-OA group (n=142)  Late-OA group (n=59)

Figure 1. The patient selection process. Between January 2000 and December 2018, 1,475 patients who were admitted to the intensive care unit at Nippon Medical School Chiba Hokusoh Hospital were screened. Among these, 242 who did not undergo serum catecholamine measurement within 15 minutes after admission, 234 who were admitted from other institutes or general wards, and 25 whose time of onset was not described were excluded. Ultimately, 485 AHF patients were enrolled in the present study. The patients were divided into three groups according to the time interval from the onset of symptoms to admission: the early-OA group (n = 283), the middle-OA group (n = 142), and the late-OA group (n = 59). AHF indicates acute heart failure; OA indicates time from the onset to admission.

Methods

Subjects: A total of 1,475 AHF patients admitted to the intensive care unit (ICU) of Nippon Medical School Chiba Hokusoh Hospital between January 2000 and December 2018 were screened. Among these, 732 in whom the serum catecholamine level was not measured were excluded from this study. An additional 234 patients were later excluded as they were admitted from other hospitals or a general ward. Finally, 25 patients were excluded because data on the time of onset were missing from hospital medical records. Ultimately, 484 patients with AHF were enrolled in this study (Figure 1).

AHF is defined as a gradual or rapid change in the signs and symptoms of HF resulting in the need for urgent therapy.8) HF was comprehensively diagnosed based on clinical history (i.e., symptoms, functional limitation, prior cardiac disease, risk factors, exacerbating factors, comorbidities, and drugs), the results of a physical examination (i.e., vital signs, weight and volume status in heart, lung, abdomen, and peripheral vascular region), and initial investigations (i.e., chest radiography, 12-lead electrocardiography, laboratory measurements of troponins, blood urea nitrogen, creatinine, sodium, potassium, glucose, liver function, and complete blood count). Furthermore, the plasma natriuretic peptide was measured, and echocardiography was performed as supplementary evaluations for the diagnosis of HF. The treating physician in the emergency department diagnosed AHF based on the results of the abovementioned procedures within 30 minutes of admission. All patients had a New York Heart Association functional class of either III or IV.

Diuretics or vasodilators were administered to all of the included patients as treatment for AHF. Patients who satisfied one of the three following criteria required intensive care: 1) requirement of high-flow oxygen therapy (including mechanical support) to treat orthopnea; 2) requirement of inotropes or mechanical support due to low blood pressure; or 3) requirement of various types of diuretics to improve general or lung edema. Patients with HF caused by ST-T segment elevation acute coronary syndrome were excluded from the study. The physician chose the treatment strategy.

Blood sample measurements and procedure: Blood samples from the included patients were collected within 15 minutes of admission before the initial treatment. Samples were centrifuged within 5 minutes of collection at 4°C and then immediately frozen and stored at −80°C until the analysis. The data were retrospectively retrieved from hospital medical records.

The patients were divided into three groups according to the time interval from the onset of symptoms to admission (OA). As the purpose of the present study was to elucidate the characteristics and mechanisms of urgently presented AHF, we defined urgently presented AHF as
visiting the hospital within 3 hours after the onset of symptoms. Patients were divided into the following groups according to the time between the onset of symptoms and visiting the hospital: < 3 hours, early-OA group ($n = 283$); 3-24 hours, middle-OA group ($n = 142$); and > 24 (with a gradual worsening of symptoms), late-OA group ($n = 59$) (Figure 1). Symptoms were defined as the presence of dyspnea on exertion or at rest and paroxysmal nocturnal dyspnea, which were directly associated with visiting the emergency room.

The patients’ characteristics, including age, gender, presence of de novo or recurrent HF, etiology of HF, risk factors for atherosclerosis (diabetes mellitus, hypertension, and dyslipidemia), vital signs (systolic blood pressure [SBP] and HF), left ventricular ejection fraction (LVEF) on echocardiography, arterial blood gas data, laboratory data (e.g., blood urea nitrogen, total bilirubin, hemoglobin, brain natriuretic peptide [BNP], C-reactive protein [CRP]), mechanical support (noninvasive positive-pressure ventilation [NPPV] and endotracheal intubation [ETI]), medications administered during ICU admission, and duration of admission (duration of ICU stay and hospital stay) were compared among the three groups. The serum catecholamine values were evaluated within 15 minutes in all 484 cases to elucidate the mechanisms the type of AHF and were compared among the three groups. The LVEF was calculated using the Teichholz method or Simpson’s method at admission (Sonos 5500; Hewlett Packard, Palo Alto, CA, USA; or Vivid I; GE Yokogawa Medical, Tokyo, Japan). Since the LVEF was measured during the acute phase, it was not adequately evaluated because of severe orthopnea. The methodology of LVEF measurement (Teichholz method or Simpson’s method) was decided on a case-by-case basis.

The short- and mid-term prognosis: The short-term prognosis was evaluated as the duration of admission (duration of ICU stay and hospital stay) and in-hospital mortality. The mid-term prognosis, including all-cause death within 180 days, was also evaluated. Patients underwent clinical follow-up at routine outpatient visits. The prognosis of patients being followed at other institutes were determined by telephone. The prognostic value, in terms of 180-day all-cause death, was evaluated using a multivariate logistic regression model and a Kaplan-Meier curve. A log-rank test was conducted to determine the statistical significance of differences.

Statistical analyses: All data were statistically analyzed using the SPSS 22.0 software (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as median and range or interquartile range. The Kruskal-Wallis test was used for comparisons among the three groups. Post-test comparisons for multiple analysis were performed using the Bonferroni test. The chi-squared test was used to compare proportions. $P$-values < 0.05 were considered to indicate statistical significance.

The prognostic value of the middle-OA group and late-OA group (a reference group for the early-OA group) was assessed using a multivariate Cox proportional-hazards regression model. A multivariate Cox regression analysis was conducted to determine the hazard ratio (HR) for 180-day mortality. The cumulative survival rates in each of the three groups were analyzed using Kaplan-Meier curves, and a log-rank test was used to calculate the statistical significance of the differences.

A multivariate logistic regression analysis was conducted to determine the odds ratios (ORs) for the associated factors of the early-OA group. All clinically relevant factors affecting the time interval from the onset of symptoms to admission, including the age (per 1-year increase), gender (male), re-admission HF (yes), admission time (midnight and early morning), SBP (>140 mmHg), LVEF (per 1% increase), CKD (yes), pH (per 0.01 increase), serum catecholamine value (adrenaline > 0.96 ng/mL, noradrenaline > 3.39 ng/mL, and dopamine > 0.21 ng/mL), total bilirubin (per 1.0-mmol/L increase), hemoglobin (per 1.0-mg/dL increase), and CRP (per 1.0-mg/dL increase) were included in a multivariate logistic model. The multivariate logistic model was developed by simultaneous forced entry. Patients who visited the hospital between 23:00 and 06:59 were defined as the midnight/early morning group. The cutoff value of serum catecholamine was determined by quartiles, with high serum catecholamine defined as Q4 in each catecholamine value.

Ethical review: The research ethics committee of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol. The requirement for written informed consent was waived in accordance with the advice given by the ethics committee, because of the study’s retrospective design.

Results

Patient characteristics and differences among three groups: The study population included 309 (63.8%) men with a median age of 76 years and 180 (37.2%) patients who had been re-admitted for HF. A total of 210 (43.4%) patients had ischemic heart disease, and 274 (56.6%) had non-ischemic heart disease. Most patients were complicated with severe orthopnea ($n = 402$, 83.1%), and the median LVEF on admission was 32.0% (Table I).

The distribution of the time interval from the onset of symptoms to hospitalization is presented in Figure 2. Two hundred eighty-three patients (58.5%) visited the hospital within 3 hours after the onset of symptoms, and 59 (12.2%) were admitted to hospital with a gradual worsening of symptoms over 24 hours. The SBP and heart rate of the patients in the early-OA group were significantly higher compared with those of the middle- and late-OA groups. Acidosis (low pH, high CO2, and high lactate) was significantly more frequent, and the use of NPPV was required significantly more frequently in the early-OA group than in the middle- and late-OA groups. Furthermore, the serum total bilirubin, BUN, CRP, and BNP levels were significantly lower, whereas the serum hemoglobin levels were significantly higher in the middle- and late-OA groups (Table I). The medications before hospitalization were not associated with the time interval from the onset of symptoms to hospitalization. However, regarding the medication during ICU, administration of nitroglycerin decreased significantly, and administration of dobutamine increased significantly in the early-OA group than in the middle- and late-OA groups (Table I).
| Characteristics                        | Total (n = 484) | Early-OA group (n = 283) | Middle-OA group (n = 142) | Late-OA group (n = 59) | P value |
|----------------------------------------|-----------------|--------------------------|---------------------------|------------------------|---------|
| **Arterial blood gas**                 |                 |                          |                           |                        |         |
| pH                                     | 7.31 (7.19-7.40) | 7.25 (7.16-7.36)         | 7.33 (7.27-7.41)          | 7.43 (7.37-7.46)       | < 0.001 |
| PCO2 (mmHg)                            | 45 (36-57)      | 50 (38-63)               | 42 (34-52)                | 34 (30-41)             | 0.013   |
| PO2 (mmHg)                             | 100 (70-148)    | 102 (72-153)             | 98 (68-148)               | 93 (67-142)            | 0.769   |
| HCO3- (mmol/L)                         | 21.7 (19.0-24.3) | 21.4 (18.6-23.8)         | 21.9 (19.6-24.3)          | 22.5 (19.5-25.5)       | 0.092   |
| SaO2 (%)                               | 96 (91-98)      | 96 (90-98)               | 96 (91-98)                | 97 (93-99)             | 0.030   |
| Lactate (mmol/L)                       | 1.9 (1.2-3.7)   | 2.4 (1.4-4.8)            | 1.7 (1.1-2.8)             | 1.5 (1.1-2.3)          | < 0.001 |
| **Laboratory data**                    |                 |                          |                           |                        |         |
| Total bilirubin (mg/dL)                | 0.5 (0.4-0.8)   | 0.5 (0.4-0.7)            | 0.6 (0.4-0.8)             | 0.9 (0.5-1.2)          | < 0.001 |
| BUN (mg/dL)                            | 24.2 (17.5-35.9) | 22.8 (16.6-33.0)         | 25.0 (18.9-39.9)          | 29.8 (19.9-37.0)       | 0.013   |
| Creatinine (mg/dL)                     | 1.17 (0.86-1.82) | 1.14 (0.86-1.81)         | 1.20 (0.87-2.19)          | 1.21 (0.82-1.79)       | 0.508   |
| Sodium (mmol/L)                        | 140 (138-142)   | 140 (138-142)            | 140 (138-142)             | 139 (136-142)          | 0.404   |
| Potassium (mmol/L)                     | 4.3 (3.9-4.7)   | 4.3 (3.8-4.7)            | 4.4 (4.0-4.7)             | 4.3 (3.9-4.7)          | 0.448   |
| Uric acid (mg/dL)                      | 6.8 (5.5-8.0)   | 6.9 (5.5-8.0)            | 6.6 (5.5-7.8)             | 7.2 (5.5-8.1)          | 0.293   |
| Hemoglobin (g/dL)                      | 12.3 (10.6-14.0) | 12.7 (11.0-14.5)         | 11.8 (10.2-13.2)          | 11.9 (10.4-13.3)       | < 0.001 |
| CRP (mg/dL)                            | 0.54 (0.18-2.17) | 0.42 (0.14-1.50)         | 0.53 (0.18-1.95)          | 2.28 (0.66-5.73)       | < 0.001 |
| BNP (pg/mL)                            | 774 (435-1328)  | 700 (413-1,181)          | 842 (488-1,341)           | 1,081 (494-1,784)      | 0.006   |
| **Medication (cases) before hospitalization** |       |                          |                           |                        |         |
| Diuretics (yes, %)                     | 242 (50.0%)     | 132 (46.6%)              | 79 (55.6%)                | 31 (52.5%)             | 0.199   |
| Nitroglycerin (yes, %)                 | 58 (12.80%)     | 34 (12.0%)               | 18 (12.7%)                | 6 (10.2%)              | 0.300   |
| Nicorandil (yes, %)                    | 65 (13.4%)      | 32 (11.3%)               | 24 (16.9%)                | 9 (15.3%)              | 0.254   |
| ACE-I/ARB (yes, %)                     | 239 (49.4%)     | 143 (50.5%)              | 66 (46.5%)                | 30 (50.8%)             | 0.712   |
| β-blocker (yes, %)                     | 187 (38.6%)     | 105 (37.1%)              | 61 (43.0%)                | 21 (35.6%)             | 0.443   |
| Statin (yes, %)                        | 164 (33.6%)     | 94 (33.2%)               | 50 (35.2%)                | 20 (33.9%)             | 0.919   |
| MRA (yes, %)                           | 82 (16.9%)      | 42 (14.8%)               | 27 (19.0%)                | 13 (22.0%)             | 0.883   |
| **Medication (cases) during ICU**      |                 |                          |                           |                        |         |
| Intravenous injection                  |                 |                          |                           |                        |         |
| Furosemide (yes, %)                    | 449 (92.8%)     | 264 (93.3%)              | 129 (90.8%)               | 56 (94.9%)             | 0.522   |
| Nitroglycerin (yes, %)                 | 265 (54.8%)     | 181 (64.0%)              | 65 (45.8%)                | 19 (32.2%)             | < 0.001 |
| Nicorandil (yes, %)                    | 60 (12.4%)      | 36 (12.7%)               | 17 (12.0%)                | 7 (11.9%)              | 0.967   |
| Carperitide (yes, %)                   | 204 (42.1%)     | 114 (40.3%)              | 61 (43.0%)                | 29 (49.2%)             | 0.443   |
| Dopamine (yes, %)                      | 26 (5.4%)       | 16 (5.7%)                | 4 (2.8%)                  | 6 (10.2%)              | 0.103   |
| Dobutamine (yes, %)                    | 69 (13.4%)      | 28 (9.9%)                | 21 (14.8%)                | 20 (33.9%)             | < 0.001 |
| Internal medicine                      |                 |                          |                           |                        |         |
| ACE-I/ARB (yes, %)                     | 206 (42.6%)     | 123 (43.5%)              | 57 (40.1%)                | 26 (44.1%)             | 0.783   |
| β-blocker (yes, %)                     | 160 (33.1%)     | 90 (31.8%)               | 49 (34.5%)                | 21 (35.6%)             | 0.776   |
| Spiro lactone (yes, %)                 | 211 (43.6%)     | 120 (42.4%)              | 63 (44.4%)                | 28 (47.5%)             | 0.757   |
| **Short-term outcome**                 |                 |                          |                           |                        |         |
| ICU hospitalization (days)             | 4 (3-5)         | 3 (3-5)                  | 4 (3-5)                   | 5 (3-10)               | < 0.001 |
| Total hospitalization (days)           | 23 (16-37)      | 22 (16-36)               | 24 (15-37)                | 28 (20-45)             | 0.026   |
| In-hospital mortality (yes, %)         | 31 (6.4%)       | 15 (5.3%)                | 8 (5.6%)                  | 8 (13.6%)              | 0.056   |

OA indicates time from onset to admission; LVEF, left ventricular ejection fraction measured by echocardiography; CKD, chronic kidney disease; ETI, endotracheal intubation; NPPV, noninvasive positive-pressure ventilation; BUN, blood urea nitrogen; CRP, C-reactive protein; BNP; brain natriuretic peptide; ICU, intensive care unit; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and MRA, mineralocorticoid receptor antagonist. *P* values among the three groups were determined by the Kruskal-Wallis test or the χ² test. All numerical data are expressed as median (25%-75% interquartile range).
The distribution of AHF patients according to the onset-to-hospitalization time. Admission was achieved within 2 hours in 283 patients (58.4%), between 2 and 23 hours in 142 patients (29.3%) and > 24 hours in 59 patients (12.2%). AHF indicates acute heart failure; OA indicates time from the onset to admission.

The Kaplan-Meier survival curves, including all-cause death within 180-days, for the early-OA group are presented in Figure 3. The survival rate in the early-OA group was significantly higher than that in the late-OA group ($P = 0.035$). A multivariate Cox regression model revealed that late-OA was an independent predictor of 180-day mortality (HR 2.042, 95% CI: 1.039-4.014, $P = 0.038$) (Table II).

**Catecholamine values and associated factors in the early-OA group:** Interestingly, the serum levels of adrenaline in the early-OA group (0.36 [0.13-1.17]) were significantly increased in comparison to those in the late-OA (0.22 [0.09-0.52]) group. Moreover, the serum levels of noradrenaline in the early-OA group (1.96 [1.02-3.60] ng/mL) were significantly increased in comparison to those in the middle-OA (1.49 [0.73-3.41] ng/mL) and late-OA (1.40 [0.91-2.42] ng/mL) groups (Figure 4). The multivariate logistic regression model indicated the early-OA was independently associated with SBP > 140 mmHg (OR: 2.219, 95% CI: 1.375-3.581, $P = 0.001$), midnight/early morning admission (OR 3.158, 95% CI: 2.048-4.868, $P < 0.001$), and serum catecholamine value (adrenaline > 0.96 ng/mL, noradrenaline > 3.39 ng/mL, and dopamine > 0.21 ng/mL) (OR 2.091, 95% CI: 1.161-
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The catecholamine values in the three groups. A: The serum levels of adrenaline in the early-OA group (0.36 [0.13-1.17]) were significantly increased in comparison to the middle-OA (0.25 [0.08-0.71]) and late-OA (0.22 [0.09-0.52]) groups. B: The serum levels of noradrenaline were significantly increased in the early-OA group (1.96 [1.02-3.60] ng/mL) compared with those in the middle-OA (1.49 [0.73-3.41] ng/mL) and late-OA (1.40 [0.91-2.42] ng/mL) groups. C: The serum levels of dopamine tended to be increased in the early-OA group (0.10 [0.04-0.24] ng/mL) compared with those in the middle-OA (0.07 [0.03-0.18] ng/mL) and late-OA (0.05 [0.03-0.14] ng/mL) groups. OA indicates time from the onset to admission.

3.767, \( P = 0.014 \) (Table III).

Discussion

Our present study suggests that the status of patients with urgently presented AHF was critical in the emergency setting and required immediate treatment. However, they were not included sicker patients by the analysis of the mid-term follow-up. Early-OA was characterized by a more urgent AHF presentation, which was consistent with the pathophysiology of vascular HF. Thus, the present study demonstrated the role of sympathetic nerve activity in the super acute phase of vascular HF. Patients with a short interval from the onset of symptoms to admission

### Table II. Multivariate Analyses of the Associations between 180-Day All-Cause Death and the Time from Onset to Admission

| OA Category | All-cause death | Univariate | Multivariate (model 1) | Multivariate (model 2) |
|-------------|-----------------|------------|------------------------|------------------------|
|             | HR 95% CI       | HR 95% CI  | HR 95% CI  | HR 95% CI |
| Late-OA group (versus Early-OA group) | 1.956 1.037-3.689 0.038 | 2.042 1.039-4.014 0.038 | - | - |
| Middle-OA group (versus Early-OA group) | 1.066 0.612-1.858 0.822 | - | - | - |
| Age (per 10-years-old increase) | 1.339 1.052-1.704 0.018 | 1.491 1.041-2.14 0.009 | 1.246 0.940-1.653 0.126 | 1.015 0.990-1.041 0.236 | 1.003 0.966-1.041 0.882 | 1.009 0.973-1.045 0.639 |
| Gender (male) | 0.796 0.491-1.289 0.353 | 0.793 0.428-1.468 0.461 | 0.744 0.419-1.382 0.314 | 0.932 0.555-1.716 0.932 |
| Creatinine (per 0.1-mg/dL increase) | 1.008 0.998-1.018 0.123 | 1.012 0.997-1.028 0.114 | 0.013 1.002-1.025 0.025 | 0.093 0.083-1.099 0.025 |
| Total bilirubin (per 0.1-mg/dL increase) | 1.015 0.990-1.041 0.236 | 1.003 0.966-1.041 0.882 | 1.009 0.973-1.045 0.639 | 0.912 0.871-0.954 0.002 |
| CRP (per 1.0-mg/dL increase) | 1.083 1.037-1.131 < 0.001 | 1.069 1.009-1.133 0.024 | 1.083 1.029-1.139 0.002 | 0.983 0.932-1.036 0.247 |
| BNP (per 10-pg/dL increase) | 1.000 1.000-1.000 0.325 | 1.000 1.000-1.000 0.953 | 1.000 1.000-1.000 0.901 | 1.000 1.000-1.000 0.901 |
| LV EF (per 10% increase) | 0.962 0.832-1.112 0.598 | 0.881 0.732-1.060 0.181 | 0.923 0.782-1.090 0.347 | 0.983 0.932-1.036 0.247 |

OA indicates time from onset to admission; HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; BNP, brain natriuretic peptide; and LV EF, left ventricular ejection fraction measured by echocardiography.
exhibited higher serum catecholamine levels in comparison to those with a long interval. These results suggest that patients with vascular HF develop higher catecholamine levels and that this was not associated with a worse mid-term prognosis.

**Sympathetic nerve activity and HF:** The plasma levels of norepinephrine were traditionally evaluated in patients with HF. Cohn et al. first pointed out the presence of high plasma levels of norepinephrine in patients with HF in the 1980s and suggested that high plasma norepinephrine levels were associated with adverse outcomes. Kaye et al. also evaluated the plasma levels of norepinephrine in severe HF and demonstrated that sympathetic activation was due to both an increase in the whole body spillover rate of norepinephrine and a coexistent decrease in the norepinephrine clearance rate. These studies emphasized that the total systemic norepinephrine release by the sympathetic nervous system was significantly increased in patients with HF. They evaluated the cardiac spillover of norepinephrine in patients with HF using blood samples measured by echocardiography; CKD, chronic kidney disease; BUN, blood urea nitrogen; and CRP, C-reactive protein.

**Phenotype of HF and sympathetic nerve activity:** The ESC guidelines proposed several phenotypes of AHF. The concepts of “hypertensive AHF” and “pulmonary edema” were previously discussed in several reports and are sometimes referred to as “vascular failure” and “cardiac failure.” Cardiac failure was defined as the deterioration of cardiac performance over days to weeks leading to decompensation, whereas vascular failure was defined as acute hypertension and increased vascular stiffness. The concept of vascular failure is characterized by a transient volume shift from the peripheral veins to the pulmonary circulation, with slight fluid accumulation. It has been described as “fluid redistribution” and in general, it was associated with an urgent presentation. The patients in the early-OA group of the present study were characterized by high SBP and heart rates, acidosis (low pH, high CO2, and high lactate), frequent use of NPPV, and treatment with nitroglycerin, but not with dobutamine. These findings suggest that the patients with early-OA had a more urgent presentation, which seemed to include patients with vascular failure. Furthermore, the prevalence of hypertension was significantly high in patients with early-OA, suggesting that the baseline blood pressure was high and the control of usual blood pressure was poor. These facts would also lead to sudden increase in blood pressure at an emergency situation. From our perspective, vascular failure was strongly associated with high SBP, midnight/early morning admission, and high serum catecholamine values.

Interestingly, the patients who had a short time interval from the onset of symptoms to admission exhibited high serum catecholamine values, suggesting that certain types of stressor suddenly induce the general systemic catecholamine release, causing blood pressure values to suddenly become extremely high. This easily induces sudden after-overload mismatch, leading to volume shift from the peripheral veins to the pulmonary circulation with
slight fluid accumulation. Thus, the stressor associated with the sudden systemic catecholamine release might be a relatively common mechanism of vascular failure in cases with an urgent presentation. The sudden systemic catecholamine release in response to a stressor might be explained as the pathophysiological mechanism of urgently presented AHF.

Sleep apnea syndrome might be a stressor that induces the catecholamine surge in AHF. Approximately 30% of patients with moderate to severe chronic HF are reported to be complicated by obstructive or central sleep apnea syndrome. The activation of the sympathetic nervous system of HF patients might be exacerbated as a result of recurrent hypoxemia and hypercapnia arising during periods of sleep apnea. Naughton et al. investigated the overnight urinary norepinephrine excretion in patients with central sleep apnea complicated by HF and concluded that the levels of urinary norepinephrine excretion in patients with central sleep apnea were higher than those in patients with normal breathing patterns. Furthermore, the sudden catecholamine surge might be induced by the symptom of dyspnea. Slight volume accumulation might even be observed in patients with vascular failure. If they experience dyspnea due to slight volume accumulation in the lung (lung edema), it is a stressor that induces the catecholamine surge. Mental stress caused by HF might be another potential stressor. In any case, the administration of β blockers might be a reasonable approach to suppressing the catecholamine surge. Since the dose-dependent reduction of the serum norepinephrine level was suggested, the administration of β blockers would be recommended, and if possible, the dosage should be increased for patients who experience sudden onset of vascular failure. For the prevention of urgently presented AHF, it is necessary to implement procedures to block the endogenous catecholamine surge (e.g., β blocker administration).

Regarding the prognosis, several studies have reported that increased sympathetic activity leads to a worse prognosis in patients with chronic HF. In all of these cohorts, the sympathetic activity status or plasma norepinephrine levels were evaluated in the compensated phase of HF. In the present study, all cases were evaluated within 15 minutes after admission; thus, the serum catecholamine level was evaluated in the decompensated phase. As mentioned above, we hypothesized that a stressor that increases the serum catecholamine value would induce volume shift “vascular” failure with an urgent presentation. Patients with an early presentation were treated approximately and successfully by NPPV and nitroglycerin, which led to a better prognosis. For this reason, the results might have differed from previous studies; thus, the enhancement of sympathetic activity in the super acute phase was not associated with adverse outcomes in the AHF cohort. Although this might have been one of the limitations of the present study, no time-dependent change was observed in serum catecholamine at any time during the AHF treatment. If we evaluated the serum catecholamine value in the compensated phase, the prognosis might have been more clearly presented.

Study limitations: The present study was associated with several limitations. First, the study population was limited to patients who were admitted to the ICU. Thus, AHF patients admitted to general wards were excluded from this study. This exclusion may reduce the generalizability of the study. The patients were treated in a “closed ICU” by cardiologists in our institute. Thus, the majority of patients with severely decompensated AHF were admitted to the ICU. However, clear criteria regarding the dose of high-flow oxygen, inotropes, and diuretics have not been proposed. The admission criteria may have differed year by year. The responsible physician ultimately decided where each patient should be admitted (the ICU or general ward). Patient bias might have affected this decision. Second, the study was conducted at a single center and was not a prospective randomized controlled trial. It is, therefore, possible that unmeasured variables affected the results. Furthermore, the difficulty in standardizing care for each patient may have influenced the major findings of this study. Third, although the correlation between the response to sympathetic stimulation and the release of endogenous catecholamine was suggested in an experimental model, Mancia et al. reported that the plasma catecholamine value did not reflect sympathetically induced changes in blood pressure. Thus, the hypothesis that the serum level of catecholamine itself reflects the general activity of the sympathetic nerve system may be controversial. Fourth, 732 patients were missed the data of catecholamine within 15 minutes. Because of the retrospective study in an emergency situation, relatively a lot of cases were missed during the collection of samples. Although it was not arbitrary, patient selection bias might exist in the enrollment process. Finally, we did not present the time-dependent change in serum catecholamine throughout the AHF treatment. This is essential for determining whether the serum catecholamine value is a factor influenced by emergency stress.

Conclusions
Urgently presented AHF might be induced by the endogenous catecholamine surge, leading to an excessive increase in blood pressure followed by increased afterload and volume-shift lung congestion.

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Disclosure
Conflicts of interest: The authors declare no conflicts of interest in association with the present study.

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