Early Blood Pressure Reduction by Intravenous Vasodilators Is Associated With Acute Kidney Injury in Patients With Hypertensive Acute Decompensated Heart

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Background: Intravenous vasodilators are commonly used in patients with hypertensive acute decompensated heart failure (ADHF), but little is known about their optimal use in blood pressure (BP) management to avoid acute kidney injury (AKI). The purpose of this study was to investigate the association between systolic BP (SBP) changes and the incidence of AKI in patients with hypertensive ADHF.

Methods and Results: Post-hoc analysis was performed on a prospectively enrolled cohort. We investigated 245 patients with ADHF and SBP >140 mmHg on arrival (mean age, 76 years; 40% female). We defined “SBP-fall” as the maximum percent reduction in SBP 6 h after intravenous treatment. AKI was defined as serum creatinine (SCr) ≥0.3 mg/dL, or urine output <0.5 mL/kg/h (n=66) at 48 h. Mean SBP and SCr levels on arrival were 180 mmHg and 1.21 mg/dL, respectively. Patients with AKI had significantly larger SBP-fall than the others (36.7±15.3% vs. 27.2±15.3%, P<0.0001). Logistic regression analysis showed an odds ratio per 10% SBP-fall for AKI of 1.49 (95% confidence interval 1.29–1.90, P=0.001). SBP-fall was significantly associated with the number of concomitant used intravenous vasodilators (P=0.001). The administration of carperitide was also independently associated with increased incidence of AKI.

Conclusions: Larger SBP-fall from excessive vasodilator use is associated with increased incidence of AKI in patients with hypertensive ADHF.

Key Words: Acute decompensated heart failure; Acute kidney injury; Blood pressure reduction; Vasodilators
Methods

A retrospective analysis of a prospectively collected cohort was performed. A total of 569 patients who were hospitalized with ADHF between January 2012 and January 2018 were enrolled. The diagnosis of ADHF was based on the Framingham criteria. Of all patients, we excluded 2 with insufficient data, 278 with SBP ≤140 mmHg, 15 with end-stage renal disease defined as eGFR <15 mL/min/1.73 m², 3 with acute myocardial infarction, 1 with right ventricular failure. We also excluded 24 patients who did not receive intravenous agents within 6 h of arrival, because this study focused on the association between BP reduction caused by medical intervention, in particular, intravenous vasodilators, and the incidence of early-phase AKI. Finally, we analyzed 245 patients with ADHF. The study protocol was approved by the institutional ethical review board (approval no. 20111323). All participants provided written informed consent.

AKI and Outcome

In this study, we calculated the incidence of AKI 48 h after the patient’s arrival. According to the Kidney Disease Improving Global Outcome (KDIGO) definitions, we defined the development of AKI as an increased level of serum creatinine (SCr) ≥0.3 mg/dL after arrival or urine volume <0.5 mL/kg/h for 6 h. All 245 patients were divided into 2 groups according to incidence of AKI: AKI group (n=66) or Non-AKI group (n=179). Blood samples for laboratory measurement of SCr were taken on arrival and at 24 h, and 48 h. We also recorded in-hospital deaths and

Table 1. Patients’ Characteristics

| Overall (n=245) | AKI (n=66) | Non-AKI (n=179) | P value |
|----------------|------------|-----------------|---------|
| Age, years     | 76±11      | 77±11           | 76±12   | 0.73    |
| Female, n (%)  | 98 (40)    | 27 (41)         | 71 (40) | 0.88    |
| NYHA III/IV, n | 82/113     | 17/37           | 65/76   | 0.15    |
| BMI, kg/m²     | 23.4±4.9   | 23.4±4.9        | 23.1±4.6| 0.65    |
| SBP, mmHg      | 180±31     | 180±34          | 179±30  | 0.77    |
| DBP, mmHg      | 96±24      | 98±22           | 95±25   | 0.32    |
| Lowest SBP within 6 h, mmHg | 122±20 | 111±18          | 127±19  | <0.0001 |
| SBP-fall, %    | 29.7±15.9  | 36.7±15.3       | 27.2±15.3| <0.0001 |
| Heart rate, beats/min | 98±25 | 103±25          | 96±25   | 0.047   |
| LVEF >50%, n (%) | 122 (50) | 29 (44)         | 94 (52) | 0.31    |

Previous history

|                        | Overall (n=245) | AKI (n=66) | Non-AKI (n=179) | P value |
|------------------------|-----------------|------------|-----------------|---------|
| AF/AFL, n (%)          | 71 (29)         | 16 (24)    | 55 (31)         | 0.35    |
| CHF, n (%)             | 122 (50)        | 34 (52)    | 88 (49)         | 0.77    |
| DM, n (%)              | 86 (35)         | 26 (39)    | 60 (34)         | 0.45    |
| HTN, n (%)             | 162 (66)        | 42 (64)    | 120 (67)        | 0.65    |
| DL, n (%)              | 88 (36)         | 27 (41)    | 61 (34)         | 0.37    |
| COPD, n (%)            | 16 (7)          | 8 (12)     | 8 (5)           | 0.04    |

Baseline medications

|                         | Overall (n=245) | AKI (n=66) | Non-AKI (n=179) | P value |
|------------------------|-----------------|------------|-----------------|---------|
| ACEI/ARB, n (%)        | 134 (55)        | 36 (55)    | 98 (55)         | 1.00    |
| β-blocker, n (%)       | 102 (42)        | 23 (35)    | 79 (44)         | 0.24    |
| MRA, n (%)             | 48 (20)         | 16 (24)    | 32 (18)         | 0.28    |
| CCB, n (%)             | 81 (33)         | 18 (27)    | 63 (35)         | 0.29    |
| Loop diuretic, n (%)   | 112 (41)        | 37 (45)    | 75 (39)         | 0.35    |

Laboratory data

|                         | Overall (n=245) | AKI (n=66) | Non-AKI (n=179) | P value |
|------------------------|-----------------|------------|-----------------|---------|
| Hb, g/dL               | 12.1±2.3        | 12.1±2.3   | 12.1±2.2        | 0.97    |
| Alb, g/dL              | 3.6±0.5         | 3.5±0.6    | 3.6±0.5         | 0.58    |
| AST, U/L               | 31 (21–41)      | 29 (20–46) | 31 (22–40)      | 0.95    |
| ALT, U/L               | 20 (12–33)      | 20 (12–35) | 19 (13–32)      | 0.86    |
| BUN, mg/dL             | 25±11.4         | 26±11.9    | 24±11.2         | 0.29    |
| SCr, mg/dL             | 1.21±0.52       | 1.28±0.55  | 1.18±0.51       | 0.20    |
| eGFR, mL/min/1.73 m²   | 48.5±19.7       | 45.4±18.6  | 49.6±20.0       | 0.14    |
| Sodium, mEq/L          | 140±4           | 140±4      | 140±4           | 0.81    |
| BNP, pg/mL             | 656 (364–1,022) | 654 (348–1,022) | 657 (180–1,019) | 0.80    |

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist; AKI, acute kidney injury; AF/AFL, atrial fibrillation/atrial flutter; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CCB, calcium-channel blocker; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DL, dyslipidemia; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HTN, hypertension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SCr, serum creatinine.
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The Bonferroni correction was applied to correct the multiple comparisons, and the Dunnett’s t-test was used to compare patients treated with 1, 2, and 3 vasodilators with those treated with loop diuretics alone. We performed univariable logistic analyses to evaluate the odds ratio (OR) and 95% confidence interval (95% CI) and thus assess the influence of each variable on the development of AKI. In the multivariable logistic analysis, variables with P<0.05 in the univariable analyses were selected. The restricted cubic spline was used for visualization of the continuous relationship between SBP-fall and adjusted OR for AKI by multivariate logistic regression model with the adjustment for chronic obstructive pulmonary disease, heart rate, and carperitide. Knots were placed at the 10th, 50th, and 90th percentiles (8.6%, 28.7%, 52.3%).

In the present study, we converted loop diuretic dose to furosemide equivalents with 20 mg oral furosemide, 5 mg oral torasemide, and 30 mg oral azosemide.

The logistic regression analysis with restricted cubic spline analysis was performed on rms of the R package. Other statistical analyses were performed with JMP pro version 13.0 (SAS Institute, Cary, NC, USA). A value of P<0.05 was considered to indicate statistical significance.

Results

The patients’ characteristics on arrival at hospital are shown in Table 1. There were no significant differences in age, NYHA functional class, SBP, and SCr on admission between the 2 groups. Of all subjects, 41% were prescribed

| Table 2. Treatment From Hospital Arrival to 6h |
|-----------------------------------------------|
| Overall (n=245) | AKI (n=66) | Non-AKI (n=179) | P value |
|-----------------|-----------|-----------------|---------|
| Furosemide i.v., n (%) | 221 (90) | 60 (91) | 161 (90) | 0.47 |
| Carperitide, n (%) | 143 (58) | 51 (77) | 92 (51) | 0.0002 |
| NTG/ISDN i.v., n (%) | 94 (38) | 25 (38) | 69 (38) | 1.00 |
| CCB i.v., n (%) | 23 (10) | 9 (14) | 14 (8) | 0.22 |

AKI, acute kidney injury; CCB, calcium-channel blocker; i.v., intravenous; ISDN, isosorbide dinitrate; NTG, nitroglycerin.
### Table 3. Logistic Regression Analyses for Acute Kidney Injury

|                                | Univariate |           | Multivariate |           | AUC  |
|--------------------------------|------------|-----------|--------------|-----------|------|
|                                | OR         | 95% CI    | P value      | OR        | 95% CI| P value |       |
| **Ages, years, per 10 years**  | 1.04       | 0.82–1.33 | 0.17         |           |       |         | 0.75  |
| **Female**                     | 1.05       | 0.59–1.87 | 0.86         |           |       |         |       |
| **SBP at arrival, per 10 mmHg  | 1.01       | 0.93–1.11 | 0.77         |           |       |         |       |
| **SBP-fall, per 10%**          | 1.49       | 1.22–1.81 | <0.001       | 1.54      | 1.24–1.91| <0.001  |
| **HR, per 10 beat/min**        | 1.12       | 1.00–1.25 | 0.049        | 1.07      | 0.95–1.21| 0.28   |
| **AF/AFL**                     | 1.46       | 0.80–2.67 | 0.22         |           |       |         |       |
| **CHF**                        | 1.10       | 0.62–1.93 | 0.74         |           |       |         |       |
| **HTN**                        | 0.86       | 0.48–1.55 | 0.62         |           |       |         |       |
| **CHF**                        | 1.10       | 0.62–1.93 | 0.74         |           |       |         |       |
| **COPD**                       | 2.95       | 1.06–8.21 | 0.04         | 3.06      | 0.99–9.43| 0.054  |
| **SCr, per 1 mg/dL**           | 1.40       | 0.83–2.37 | 0.21         |           |       |         |       |
| **Sodium, per 1 mEq/L**        | 1.01       | 0.94–1.08 | 0.81         |           |       |         |       |
| **Alb, per 1 g/dL**            | 0.82       | 0.49–1.37 | 0.44         |           |       |         |       |
| **Hb, per 1 g/dL**             | 1.00       | 0.88–1.13 | 0.97         |           |       |         |       |
| **NYHA IV**                    | 1.73       | 0.98–3.06 | 0.06         |           |       |         |       |
| **Time to treatment, per 1 min**| 0.98     | 0.94–1.02 | 0.32         |           |       |         |       |
| **Furosemide i.v.**            | 1.12       | 0.42–2.95 | 0.82         |           |       |         |       |
| **Carpentide**                 | 3.22       | 1.69–6.13 | <0.001       | 4.39      | 2.16–8.93| <0.001  |
| **NTG/ISDN i.v.**              | 0.97       | 0.54–1.70 | 0.92         |           |       |         |       |
| **CCB i.v.**                   | 1.86       | 0.76–4.53 | 0.18         |           |       |         |       |

AUC, area under the curve; CI, confidence interval; OR, odds ratio. Other abbreviations as in Tables 1 and 2.

![Figure 2](image.png)

**Figure 2.** Odds ratio (OR) for acute kidney injury (AKI) and in-hospital outcome by the interquartile range of SBP-fall. The error bars indicate 95% confidence interval. Data presented as n (%), median and interquartile range. SBP, systolic blood pressure.
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Increased the risk of AKI. SBP-fall was 27.5%, even in patients not administered any vasodilators. Regarding the details of the vasodilators, carperitide was a significant predictor of AKI, whereas NTG/ISDN or CCB had no predictive value. In addition, the predictive value of carperitide was independent of SBP-fall (Table 3). In fact, in patients treated with 1 vasodilator, the SBP-fall with carperitide (n=95) was smaller than that with other agents (NTG/ISDN or CCB) (n=61) (23.6% vs. 38.5%, P≤0.001).

Discussion

In the present study, we investigated early-phase BP changes in patients with hypertensive ADHF, and report 3 main findings. First, SBP-fall within the first 6 h predicted the incidence of AKI at 48 h. Second, the SBP-fall was associated with the number of vasodilators administered. Third, a larger SBP-fall did not improve the duration of hospital stay or in-hospital mortality.

SBP-Fall and Vasodilator Use

The associations between the number of administered vasodilators and SBP-fall and OR for AKI are shown in Figure 4. The incidence of AKI in patients treated with diuretics alone was defined as the reference (OR=1). Compared with the reference, an increased number of administered vasodilators induced a larger SBP-fall, and accordingly increased the risk of AKI. SBP-fall was 27.5%, even in patients not administered any vasodilators. Regarding the details of the vasodilators, carperitide was a significant predictor of AKI, whereas NTG/ISDN or CCB had no predictive value. In addition, the predictive value of carperitide was independent of SBP-fall (Table 3). In fact, in patients who treated with 1 vasodilator, the SBP-fall with carperitide (n=95) was smaller than that with other agents (NTG/ISDN or CCB) (n=61) (23.6% vs. 38.5%, P≤0.001).

Table 4. 1-Year Outcomes After Discharge

| Outcome                              | Overall (n=241) | AKI (n=64) | Non-AKI (n=177) | P value |
|--------------------------------------|-----------------|------------|-----------------|---------|
| All-cause death, n (%)               | 22 (9)          | 5 (8)      | 17 (10)         | 0.80    |
| CV death, n (%)                      | 7 (3)           | 4 (6)      | 3 (3)           | 0.08    |
| HF rehospitalization, n (%)          | 48 (20)         | 17 (26)    | 31 (18)         | 0.15    |
| CV death or HF rehospitalization, n (%) | 50 (21)       | 18 (28)    | 32 (18)         | 0.37    |
| All-cause death or HF rehospitalization, n (%) | 59 (24)       | 19 (29)    | 40 (23)         | 0.32    |

AKI, acute kidney injury; CV death, cardiovascular death; HF, heart failure.
leaves to AKI.\textsuperscript{17} Indeed, several previous studies have shown that BP reduction is associated with increased incidence of AKI in patients with ADHF.\textsuperscript{3,18,19} However, those studies included patients with mean SBP of 130–140 mmHg at baseline. We guessed that, in patients with normotensive or hypotensive ADHF, BP reduction during the early phase would indicate arterial underfilling rather than optimization of cardiac afterload. Conversely, we expected that patients with hypertensive ADHF would possibly benefit from BP reduction in the early phase. However, unexpectedly, we showed that SBP-fall was associated with the risk of AKI, even in patients with SBP >140 mmHg. In addition, the continuous relationship between SBP-fall and the OR for AKI showed a positive correlation (Figure 3). We considered it significant that there was not a U-shaped relationship between SBP-fall and the incidence of AKI. These results indicated that, consistent with a previous study,\textsuperscript{20} there is no SBP threshold for the incidence of AKI in patients with hypertensive ADHF. When we performed the receiver-operator characteristic analysis, the best cutoff value of SBP-fall was 30.9\%, with 66.7\% sensitivity and 60.2\% specificity (c-statistic 0.676, P<0.001) (Supplementary Figure). However we thought that this cutoff value would be inappropriate as a target SBP level in the early-phase management of hypertensive ADHF, because in the clinical setting, it is important to minimize the risk of AKI rather than improve the accuracy of prediction of AKI. In terms of the target level of SBP-fall, the current ESC guideline recommends within 25\% reduction of SBP, which is not based on established evidence. In our cohort, 25\% SBP-fall had high sensitivity (77.2\%) with low specificity (43.6\%) for the incidence of AKI. Therefore, we consider that in the range of 25\% SBP reduction would be reasonable even in patients with hypertensive ADHF.

The progression of left ventricular hypertrophy and increased vascular stiffness are considered important inducible factors of hypertensive ADHF.\textsuperscript{21} It is known that these structural and functional cardiovascular changes reflect impairment of the renal autoregulatory function.\textsuperscript{22} The susceptibility of intraglomerular pressure to impairment of renal autoregulation explains why AKI can result from BP reduction even in patients with hypertension.

We also clarified that the number of administered vasodilators was significantly associated with SBP-fall and the risk of AKI (Figure 4). This result suggested that combined use of intravenous vasodilators is associated with SBP-fall and risk of AKI. Some clinicians assert that aggressive BP reduction is reasonable for prompt improvement of ADHF symptoms; however, we should note that, with a higher incidence of AKI, a larger SBP-fall did not reduce in-hospital deaths or shorten the duration of in-hospital stay (Figure 2).

Of course, we do not deny the effectiveness of vasodilator use in patients with ADHF.\textsuperscript{23} Rapid fluid redistribution caused by venous vasocontraction is considered a mechanism responsible for ADHF. Vasodilators work by reducing vessel tone not only in arteries, but also in veins. Therefore, it is important to counteract unnecessary venous vasoconstriction to decrease central venous pressure (CVP) by using vasodilators. Mullens et al reported that higher CVP is associated with worsening renal function in patients with decompensated HF.\textsuperscript{24} Although the present study had no data on CVP or serial changes in jugular venous distention, we speculate that the ideal ADHF treatment may be to use vasodilators to reduce CVP with a minimal SBP-fall.
Clinicians should minimize the SBP-fall and usage of intravenous vasodilators as long as HF symptoms are improved. Conversely, it would be inappropriate to use vasodilators aggressively to decrease the SBP to an arbitrary target level, particularly within the first 6 h after hospital arrival. In addition, the patients who were administered intravenous loop diuretics alone presented with a certain degree of reduction in SBP (Figure 4). Of course, other interventions such as oxygen administration or artificial ventilation would have a substantial effect on the reduction in SBP. From these perspectives, for management of hypertensive ADHF, clinicians should avoid abrupt BP reduction within the first 6 h resulting from combined use of vasodilators.

We also clarified that the administration of carperitide was also independently associated with increased incidence of AKI (Table 3). Matsue et al reported that carperitide was significantly associated with increased in-hospital deaths of patients with acute HF. We thought that the concomitant use of intravenous furosemide and carperitide might be a risk for excessive reduction of effective plasma volume, which contributes to AKI. A previous study showed that nesiritide, a recombinant B-type natriuretic peptide, was not associated with worsened renal function, but it was associated with an increase in the rate of hypotension. Interestingly, the predictive value of carperitide for the incidence of AKI was independent of SBP-fall in the present study (Table 3). Although there might be different properties between carperitide and nesiritide, we should take care about excessive reduction of effective plasma volume when using carperitide, even if patients do not present an excessive SBP-fall.

We showed that the SBP on arrival had no association with the incidence of AKI, although previous studies reported an association between higher SBP and risk of AKI. We were able to explain this result by the homogeneity of our population; we included only patients with SBP > 140 mmHg. In addition, the association between higher SBP and incidence of AKI might derive from larger SBP reductions in the early phase.

Recent previous studies reported that the prognostic ability of AKI on admission may be superior to AKI occurring within the first 5 days, and a transient elevation of SCR level does not predict poor outcome because it would reflect the process of decongestion. However, it is also well known that the complication of AKI predicts poor outcome in patients with ADHF. Actually, in the clinical setting, it is not easy to distinguish true AKI from pseudo AKI when the SCr increases. In the present study, 68% patients in the AKI group experienced decreased urine output. Low urine output or poor diuretic response inhibits decongestion. Therefore, clinicians should take care with excessive SBP reductions that would cause AKI.

Study Limitations

There were several limitations to the present study. First, we could not determine whether smaller SBP-fall directed management would decrease the risk of AKI, because this study was performed in a post-hoc manner. Second, we could not investigate the dosages and duration of administration of intravenous vasodilators; it was difficult to define their equivalent doses. Third, we could not take into consideration changes in effective fluid volume, which is an important determinant of the incidence of AKI.

Conclusions

In the first 6 h of management of hypertensive ADHF patients, aggressive SBP reduction by combination use of vasodilator agents predicted the incidence of AKI. In addition, a larger SBP reduction was not associated with the in-hospital outcome. The risks and benefits of BP reduction should be considered in patients with hypertensive ADHF.

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Conflicts of Interest / Source of Funding

None declared.

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Supplementary Files

Please find supplementary file(s);
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