

Early Drop in Systolic Blood Pressure and Worsening Renal Function in Elderly Patients With Acute Heart Failure: How Does the Heart Rate Interact?

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Abstract

Background: Regardless of patients' baseline renal function, worsening renal function (WRF) during hospitalization is associated with poor outcomes. In individuals with acute heart failure (AHF), one predictor of WRF is an early drop in systolic blood pressure (SBP). Few studies have investigated WRF in elderly AHF patients or the influence of these patients' at-admission heart rate (HR) on the relationship between an early SBP drop SBP and the AHF.

Methods: We measured the SBP and HR of 245 elderly AHF inpatients (82.9±6.0 years old, females 50.6%) at admission and another six times over the next 48 hr. We defined 'WRF' as a serum creatinine increase ≥ 0.3 mg/dL by Day 5 post-admission. We calculated the 'early SBP drop' as the difference between the admission SBP value and the lowest value during the first 48 hr of hospitalization.

Results: There were significant differences between the 36 patients with WRF and the 209 patients without WRF: early SBP drop (51.3 vs. 32.5 mmHg, $p < 0.01$) and at-admission HR (79.3 vs. 89.6 bpm, $p < 0.05$), respectively. In the multiple logistic regression analysis adjusted for the confounders, early SBP drop (OR: 1.003, 95%CI: 1.003–1.03, $p < 0.04$) and HR at-admission (OR: 0.98, 95%CI: 0.96–0.99, $p < 0.01$) were significantly associated with WRF. No significant association was shown for the interaction term of early SBP drop × at-admission HR with WRF ($p = 0.3$).

Conclusions: In these elderly AHF patients, exaggerated early SBP drop and lower at-admission HR were significant independent predictors of WRF, and these factors were additively associated with WRF.

Background

Approximately one-third of individuals with acute heart failure (AHF) experience worsening renal function (WRF) during hospitalization [1–7], and it has been demonstrated that WRF has a strong association with poorer patient outcomes regardless of the patients' baseline renal function [1–9]. It is thus crucial to identify patients who are at risk of developing WRF, at the earliest point possible. Higher blood pressure (BP) at a patient's admission to a hospital was shown to be linked to a greater risk of WRF [3–5, 10, 11], and a drop in a patient's systolic blood pressure (SBP) during the first days post-admission has also been shown to pose a risk of the development of WRF [1]. It was suggested that AHF patients' baseline heart rate (HR) can be used to predict in-hospital cardiac mortality, and in contrast to patients with chronic heart failure (CHF), among AHF patients a lower HR at baseline was shown to be associated with a higher in-hospital rate of cardiac death [8].

Few investigations have examined the relationships among WRF, early SBP drop, and the at-admission HR in elderly patients with AHF. Herein, we tested our hypothesis that an early drop in the SBP of an elderly AHF patient could be used to predict WRF in the patient. We also investigated the effect of at-admission HR on any interactions among these factors.

Methods

Study population

The study design was observational, and the study was conducted at Hiroshima City Asa Hospital from January 2013 to December 2015. We considered a patient as eligible for study enrollment if he or she had been hospitalized for the treatment of AHF, which we defined as a rapid onset or worsening of symptoms and/or signs of heart failure (HF). The HF symptoms were: fatigue, breathlessness, and ankle swelling. The signs were: peripheral edema, elevated jugular venous pressure, and pulmonary crackles [12, 13]. Each patient's diagnosis of AHF was based on a thorough medical history and assessment of the patient's symptoms, potential cardiac and noncardiac precipitants, and any prior cardiovascular history; the diagnosis also considered the signs/symptoms of hypoperfusion or congestion revealed by a physical examination and confirmed by appropriate additional investigations: i.e., laboratory assessments (including the measurement of B-type natriuretic peptide [BNP]), echocardiography, chest x-ray, and electrocardiography [13].

Regarding the patients' BNP levels used for the diagnosis of AHF, we set an exclusion cut-off point at 100 pg/mL based on current guidelines [13]. Each AHF diagnosis was made by experienced cardiologists. We excluded patients with multiple organ failure, shock, or sepsis, and those who were on chronic hemodialysis. The consecutive eligible elderly patients with AHF were enrolled after the study's purpose was fully explained to the patients and their informed consent was obtained. The Hiroshima City Asa Hospital Research Committee approved the study's protocol.

Procedures

The physician investigators were not prohibited from using any standard medication thought necessary to treat the enrolled patients, including additional vasodilators [1]. Each patient's HR and SBP were measured at their admission and measured another six times during the 48 hr immediately after their admission. At the baseline and 12 hr later, blood samples were taken for laboratory measurements, including serum creatinine. After that point, the blood samples and measurements were taken daily through Day 5 post-admission [1].

Definitions

We defined 'WRF' as a ≥ 0.3 mg/dL increase in the patient's serum creatinine level compared to his or her baseline value, at any time through Day 5 [1]. We examined the potential 'early drop in SBP' as the difference between the patient's SBP value taken at admission and the lowest SBP value measured during the first 48 hr of hospitalization [1]. For all of the blood pressure measurements, the patient was supine and had rested for ≥ 5 min.

Statistical Analyses

The data are presented as the mean \pm the standard deviation (SD) or as a percentage, and all analyses were performed with SPSS ver. 11.5J software (SPSS, Chicago, IL). We used the Chi-squared test for compare categorical variables among groups, and we performed an analysis of variance (ANOVA) for the continuous variables. For the multiple pairwise comparisons of proportions or means between pairs of groups, we used Bonferroni's correction or Tukey's honestly significant differences (HSD) test. We assessed the correlations between parametric variables by determining the Pearson's correlation coefficient. We assessed the correlations between nonparametric variables by determining Spearman's correlation. To estimate and test the independent effects of early SBP drop and the at-admission HR on WRF, we conducted a multiple logistic regression analysis. In addition to the patient age and gender, each of the baseline regression models used herein included factors that were significantly correlated with WRF as determined by either the Pearson or Spearman correlation. Probability (p)-values < 0.05 were accepted as significant.

Results

Patients

Creatinine values that allowed a classification of WRF were available for all 245 of the enrolled patients: mean age 82.9 ± 6.0 years, 124 females (50.6%), 121 males (49.4%). Among all patients, 78.3% had a history of hypertension, and 11.8% had ischemic heart failure.

Prevalence And Clinical Correlates Of Wrf

WRF was confirmed in 14.7% ($n = 36$) of the 245 evaluable patients. Table 1 summarizes the characteristics of patients with and without WRF. Compared to the 209 patients without WRF (85.3%), those with WRF had significantly higher prevalences of a history of hypertension, intravenous loop diuretic use, and intravenous nitroglycerin use; in addition, the WRF group had significantly higher baseline SBP values, significantly lower HR at admission, and significantly greater early drops in SBP through the first 48 hr post-admission (Table 1).

Table 1
Baseline characteristics of the elderly AHF patients with and without worsening renal function (WRF)

Baseline characteristics	WRF (n=36)	No WRF (n=209)
Age, yrs	82.3±6.4	83.1±6.0
Male, %	41.7	50.7
Body weight at assessment, kg	48.4±14.3	50.5 ±11.5
Clinical scenario 1, %	58.3*	38.3
Clinical scenario 2, %	16.7*	33.0
Clinical scenario 3, %	8.3	8.1
Clinical scenario 4, %	13.9	12.4
Ejection fraction, %	42.5±13.0	46.2±14.9
Current smoking, %	27.8	24.9
Daily alcohol intake, %	11.1	22.0
Hypertension, %	91.7*	76.0
Diabetes mellitus, %	33.3	34.0
Lipid disorder, %	44.4	38.8
Chronic atrial fibrillation, %	22.2	23.9
Baseline laboratory values:	6.38±0.9	6.01±1.2
Log BNP	11.7±2.2	11.8±2.1
Hemoglobin, g/dL	30.7±16.5	31.6±17.5
BUN, mg/dL	1.61±1.0	1.47±1.0
Serum creatinine, g/dL	2.78	9.1
Medication at baseline:	52.8	44.0
ACEI use, %	36.1	40.7
ARB use, %	36.1	27.8
CCB use, %	58.3	48.6
Beta-blocker, %	88.9*	73.2
Loop diuretics, %	50.0**	23.9
Medication during admission:	5.6	8.1
I.V. loop diuretic use, %	158±37***	137±30

I.V. isosorbide dinitrate, %	78.5±18	76.1±20
I.V. carperitide use, %	79.3±21*	89.6±29
BP and HR parameters:	51.3±30***	32.5±30
SBP admission, mmHg		
DBP at admission, mmHg		
HR at admission, mmHg		
Peak drop in SBP within 48 hr, mmHg		

Data are mean SD or as percentages. ANOVA for continuous variables and the χ^2 test for qualitative variables were used. *p<0.05, **p<0.01, ***p<0.001 compared to the no WRF group. I.V.: intravenous.

Correlations Of Wrf With Early Sbp Drop

As shown in Table 2, the following were significantly negatively correlated with WRF: hypertension, intravenous loop diuretic use, intravenous nitroglycerin, SBP at admission, HR at admission, and peak drop in SBP within 48 hr.

Table 2
Correlation between early SBP drop and worsening renal function

Correlation coefficients (ρ) by Spearman's test . *p<0.05. **p<0.001. Baseline characteristics	WRF (n=36)
Age, yrs	-0.038
Male, yes=1, no=0	-0.064
Body weight at assessment, kg	-0.075
Clinical scenario 1, yes=1, no=0	0.144*
Clinical scenario 2, yes=1, no=0	-.0126*
Clinical scenario 3, yes=1, no=0	0.003
Clinical scenario 4, yes=1, no=0	0.015
Ejection fraction, %	-0.068
Current smoking, yes=1, no=0	0.024
Daily alcohol intake, yes=1, no=0	-0.096
Hypertension, yes=1, no=0	0.135*
Diabetes mellitus, yes=1, no=0	-0.005
Lipid disorder, yes=1, no=0	0.041
Chronic atrial fibrillation, yes=1, no=0	-0.014
Baseline laboratory values:	0.122
Log BNP	-0.008
Hemoglobin, g/dL	-0.009
BUN, mg/dL	0.071
Serum creatinine, g/dL	-0.082
Medication at baseline:	0.062
ACEI use, yes=1, no=0	-0.033
ARB use, yes=1, no=0	0.065
CCB use, yes=1, no=0	0.069
Beta-blocker, yes=1, no=0	0.129*
Loop diuretics, yes=1, no=0	0.206**
Medication during admission:	-0.034
I.V. loop diuretic use, yes=1, no=0	0.182**

I.V. isosorbide dinitrate, yes=1, no=0	0.049
I.V. carperitide use, yes=1, no=0	-0.133*
BP and heart rate parameters	0.209**
SBP at admission, mmHg	
DBP at admission, mmHg	
HR at admission, mmHg	
Peak drop in SBP within 48 hr, mmHg	

Correlation coefficients (ρ) by Spearman's test . * $p < 0.05$. ** $p < 0.001$.

Determinants Of Wrf

The results of our multiple logistic regression analysis are presented in Table 2. The analysis was adjusted for the following confounders: patient age and gender, the presence/absence of hypertension, the left ventricular ejection fraction, the values of total cholesterol and BNP, the patients' baseline creatinine values, intravenous nitroglycerin and carperitide use, intravenous loop diuretic use, and beta blocker use. The two factors that were significantly associated with WRF were the patient's HR at admission ($p < 0.01$) and a peak drop in SBP within 48 hr post-admission ($p < 0.05$) (Table 2). The interaction term of early SBP drop · at-admission HR was not significantly associated with WRF ($p = 0.3$).

Table 3
Logistic regression model of early SBP drop for worsening renal function in the 36 patients with WRF

Trait	OR	95% CI	p-value
Age, yrs	0.95	0.88–1.02	0.13
Male, yes=1, no=0	0.54	0.22–1.33	0.18
Ejection fraction, %	0.97	0.94–1.01	0.09
Hypertension, yes=1, no=0	2.93	0.77–11.1	0.12
Beta-blocker at baseline, yes=1, no=0	1.44	0.60–3.44	0.41
Log BNP	1.05	0.65–1.70	0.85
I.V. loop diuretic use during admission , yes=1, no=0	2.21	0.58–8.35	0.24
I.V. isosorbide dinitrateduring admission, yes=1, no=0	1.80	0.73–4.48	0.20
I.V. carperitide use during admission , yes=1, no=0	0.68	0.13–3.57	0.65
Heart rate at admission, bpm	0.98	0.96–0.99	0.004
Peak drop in SBP within 48 hr, mmHg	1.02	1.004–1.03	0.02

Each BP parameter was added simultaneously to the regression model.

Discussion

The results of this observational study demonstrated that a greater drop in SBP within the first 48 hr after the hospitalization of an elderly patient with AHF – as well as the patient's HR at admission – were independently associated with a higher risk of the occurrence of WRF. This is the first investigation to report associations of an early SBP drop and the at-admission HR with WRF in patients with AHF.

Early Sbp Drop And Wrf

Our findings revealed that an early SBP drop after hospitalization in elderly patients with AHF was an independent determinant of the development of WRF. In the univariate analyses conducted in prior studies, the baseline SBP level itself was found to be positively correlated with WRF, and in those studies [10, 11], a higher risk of WRF during hospitalization was observed in AHF patients with hypertension. Forman et al.⁵ reported that an SBP value at admission > 160 mmHg was independently associated with an increased WRF risk. In the present study, although the baseline SBP level was significantly positively correlated with the early SBP drop ($r = 0.82$, $p < 0.001$), only early SBP drop remained independently related to a higher risk of WRF when either the baseline SBP level or the early SBP drop was included in the multiple regression model. This result suggests that a larger drop in SBP (and not a higher baseline SBP) was a significant risk factor for WRF in this series of elderly AHF patients.

We suspect that our present findings might be due to the auto-regulatory response in the kidneys [14]. The kidneys' vascular system will constrict (its afferent arterioles, specifically) when the renal perfusion pressure rises because of an increase in BP; the kidneys' inter-lobal arteries may also constrict. Afferent vasodilation occurs when the BP drops, and if the BP falls further, efferent vasoconstriction can also occur. The kidneys are thus able to maintain – over a wide range of BP values – constant glomerular capillary perfusion, pressure, and filtration. The pre-glomerular circulation of patients with long-standing hypertension has shown a blunted ability to dilate in response to a drop in SBP, and this can result in an exaggerated decrease in the intraglomerular pressure [15]. Our present observation that a higher drop in SBP is related to a higher risk of WRF is consistent with the above explanation, but our findings remain to be confirmed in further studies.

Although our results indicate that the use of an intravenous loop diuretic or isosorbide dinitrate during a patient's hospital admission was significantly and positively correlated with WRF, neither loop diuretic nor isosorbide dinitrate use was shown to be a significant indicator of WRF in the multivariate model. Diuretics are known to present a risk of impaired kidney function in patients with heart failure, probably by a so-called 'tubuloglomerular feedback' mechanism. The distal tubules of the kidneys sense a loss of salt, and this leads to a release of adenosine, which then binds to the adenosine A1-receptor. Afferent vasoconstriction is the result, with a subsequent reduction in the renal blood flow (a main determinant of renal function in heart failure patients) [16].

Nitrate is thought to dilate the renal microvascular flow and increase the renal blood flow when other aspects of the vascular status are normal. However, a systemic vasodilation of the systemic vasculature might completely decrease the renal blood flow in accord with an acute SBP reduction. Each deleterious impact of diuretics or nitrate on the renal blood flow would thus be observed in an AHF population such as our present patients, because both diuretics and nitrate would contribute to a higher drop in SBP during the acute phase of HF.

At-admission HR and WRF

Our analyses revealed that the at-admission HR values of the elderly patients with AHF were independently associated with a higher risk of WRF. This finding confirms that a lower HR at admission may be a marker and may also pose a direct increased risk of WRF in AHF patients [17]. In individuals with chronic HF, elevated resting HR was reported to be associated with increased risks of cardiovascular disease and mortality [18, 19]. In the hyperacute phase of AHF, tachycardia is a mostly beneficial physiological compensatory response. An increase in the HR is necessary to maintain the cardiac output, due to structural limitations of the stroke volume [20].

Although the details of the relationship between the pathophysiology of AHF and the HR remain unknown [21], our present data demonstrate that a lower HR at baseline in patients with AHF was associated with a much higher risk of WRF. Bainbridge showed in 1915 that rapid volume loading results in increases of both blood pressure and heart rate [22], and a 2009 review showed that a higher baseline SBP is

associated with a better outcome [23]. We speculate that in the urgent phase of AHF, a higher risk of WRF might be associated with an impaired ability to increase the heart rate to appropriate levels.

It should be noted that we did not observe a significant association between WRF and the interaction term of early SBP drop ´ at-admission HR. We thus suggest that the early SBP drop and at-admission HR each have an additive impact on WRF rather than a synergistic effect.

Conclusion

Among the 245 elderly patients hospitalized for AHF, WRF was independently predicted by a greater drop in SBP during the first 48 hr of hospitalization. The patients' at-admission HR also independently predicted WRF. Because WRF is strongly related to poorer clinical outcomes up to 180 days post-admission, an early SBP drop and the at-admission HR might serve as additive surrogate markers of clinical outcomes in AHF patients.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Hiroshima City Asa Hospital Research Committee, Hiroshima, Japan and was conducted in accordance with the principles stated in the Declaration of Helsinki. All participants provided informed written consent.

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