Original Paper

Relationship Between Short-Term Blood Pressure Variability and Incidence of Acute Kidney Injury in Critically Ill Patients

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Key Words

Blood pressure • Variability • AKI • Mortality

Abstract

Background/Aims: Blood pressure (BP) variability is associated with cardiovascular events, and cerebral and renal damage. The aim of this study was to investigate any potential relationship between short-term BP variability and incidence of acute onset conditions, such as acute kidney injury (AKI), in critically ill patients. **Methods:** BP was monitored to analyze its variability in critically ill patients in present study. Short-term BP variability was assessed as average real variability (ARV), standard deviation (SD) and coefficient of variation (CV) of 24-hour BP. **Results:** A total of 565 patients were included, 41.2% (n=233) of which presented with AKI after admission (AKI stage I, n = 94; stage II, n = 37; stage III, n = 102). The mean APACHE II score was 21.5 for all patients. ARV of 24 h systolic BP was significantly higher in patients with AKI (p<0.001). This association remained (p=0.006) after adjustment for potential confounders. The incidence of AKI increased with the ARV from 14.0% (ARV ≤6 mmHg) to 73.9% (ARV >14 mmHg). A weak association was also found between BP variability and hospital mortality in critically ill patients. **Conclusion:** BP variability is correlated with the incidence of AKI in critically ill patients.

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Introduction

Blood pressure (BP) is constantly fluctuating, and is characterized by short-term (minutes to hours) and long-term (days to months) fluctuations. Although not completely understood, these fluctuations are the consequence of intricate interactions between intrinsic and extrinsic factors, including neural reflex, humoral regulation, cardiovascular autoregulation, and environmental and behavioral conditions [1]. Evidence from clinical trials

and observational studies link short-term BP variability with incidence of cardiovascular events, cerebral and renal damage, as well as progression of vascular disease [2-4]. Elevated BP variability is also related to mortality, independent of increased BP levels [5, 6].

Renal dysfunction is a critical condition, with high incidence and morbidity. An association between increased short-term BP variability and subclinical renal damage, which includes the presence of microalbuminuria or decrease of estimated glomerular filtration rate (eGFR), has been observed in essential hypertensive patients [7]. Kidney hypoxia or ischemia-reperfusion injury is thought to occur during the course of BP fluctuations, [8] which could occasionally develop into acute kidney injury (AKI), particularly in critically ill patients. The incidence of AKI is high (>36%) in these patients, and could even exceed 60% during the ICU stay [9].

BP management is always a challenge when dealing with critically illnesses. However, most of the studies on BP variability are performed in the general population or hypertensive patients. Little is known about the clinical outcomes of critically ill patients with elevated BP variability. Therefore, we conducted this study to investigate any potential relationship between short-term BP variability and the incidence of AKI or mortality in an ICU setting.

Materials and Methods

We conducted a prospective, observational study of patients admitted to a 50-bed ICU of an academic teaching hospital over a 10-month period from March 2015 to December 2015. The Ethics Committee of the West China Hospital approved the study protocol.

Patients admitted to the ICU were included in this study. Those with one or more of the following conditions were excluded: 1) aged <18 years, 2) expected ICU stay <72 h (those who were expected to die in a short period of time, or postoperative patients who did not extubated but with stable condition), 3) previously treated in this ICU and 4) admitted with Chronic Kidney Disease (CKD).

All the patients underwent 24-h non-invasive BP monitoring after admission (IntelliVue MP60, Philips, Netherlands). The BP cuff was fitted to one of the arms; the cuff size was determined by the upper arm circumference. BP measurements were recorded at 30-min intervals. Short-term BP variability was estimated as the standard deviation (SD), coefficient of variation (CV), and average real variability (ARV) of 24-hour systolic BP. ARV was calculated using the following formula:

$$ARV = \frac{1}{\sum w} \times \sum_{k=1}^{N-1} (w \times |BP_{k+1} - BP_k|)$$

where n is the number of BP readings, and w refers to the time of each interval. The mean BP was calculated as an overall 24-h average of SBP for each patient.

AKI was defined and classified by the KDIGO definition according to creatinine change and urine output criteria, including any of 1), increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 hours; or 2), increase in SCr to ≥ 1.5 times baseline within the prior 7 days; or 3), urine volume <0.5 ml/kg/h for 6 hours [10]. AKI was staged for severity according to increase in SCr (1.5-1.9 times baseline or ≥ 0.3 mg/dl increase as stage I; 2.0 to 2.9 times baseline as stage II; 3.0 times baseline or ≥ 4.0 mg/dl increase as stage III); initiation of renal replacement therapy (stage III) or urine output (<0.5 ml/kg/h for 6 to 12 hours as stage I; <0.5 ml/kg/h for ≥ 12 hours as stage II; <0.3 ml/kg/h for ≥ 24 hours or anuria for ≥ 12 hours as stage III). Sepsis (previous severe sepsis) was identified by proven or suspected infection with dysfunction of at least one organ [11].

The demographic information, clinical and laboratory data were collected. The primary outcome was the incidence of AKI, and the secondary outcomes included hospital mortality, length of ICU stay, length of hospital stay, etc. The severity of illness was assessed according to the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Sequential Organ Failure Assessment (SOFA) scores.

Statistical analysis was performed with SPSS software (IBM, USA). For continuous variables, Student's t-test was used for normally distributed data and the Mann-Whitney U-test was used for skewed variables.

Table 1. Clinical and Demographic Characteristics of Patients With and Without AKI. BMI, Body Mass Index; eGFR, glomerular filtration rate estimate by MDRD study equation; CRRT, continuous renal replacement therapy

	Total n=565	AKI group n=233	Non-AKI group n=332	p value
Age (year)	57.0 ± 17.4	56.4 ± 16.9	57.4 ± 17.7	0.491
Male	364 (64.4%)	146 (62.7%)	218 (65.7%)	0.463
BMI (kg/m ²)	22.91 ± 3.47	23.03 ± 3.56	22.82 ± 3.42	0.559
APACHE II	21.54 ± 6.71	24.06 ± 7.11	19.77 ± 5.80	< 0.001
SOFA	9.45 ± 4.32	11.30 ± 4.51	8.04 ± 3.58	< 0.001
Sepsis	326 (57.7%)	149 (63.9%)	177 (53.3%)	0.012
Comorbidity				
Hypertension	144 (25.5%)	57 (24.5%)	87 (26.2%)	0.640
Diabetes mellitus	63 (11.2%)	26 (11.2%)	37 (11.1%)	0.996
COPD	61 (10.8%)	19 (8.2%)	42 (12.7%)	0.090
Malignant neoplasms	66 (11.7%)	23 (9.9%)	43 (13.0%)	0.262
Vasoactive drug usage	166 (29.4%)	94 (40.3%)	72 (21.7%)	< 0.001
Mean SBP (mmHg)	116.5 ± 11.7	115.6 ± 10.8	117.1 ± 12.2	0.139
CRP (mg/L)	93.4 (32.5, 165.0)	112.0 (41.3, 198.8)	84.0 (28.4, 138.0)	0.005
IL-6 (pg/mL)	104.3 (30.9, 293.2)	151.6 (57.8, 416.4)	73.4 (23.5, 212.6)	< 0.001
PCT (ng/mL)	1.56 (0.39, 7.41)	5.33 (1.18, 21.57)	0.78 (0.20, 2.50)	< 0.001
Lac (mmol/L)	1.5 (1.1, 2.3)	1.7 (1.2, 3.4)	1.4 (1.1, 2.0)	< 0.001
BUN (mmol/L)	10.65 ± 8.91	14.90 ± 10.88	7.67 ± 5.54	< 0.001
SCr (μmol/L)	116.93 ± 116.97	178.72 ± 158.37	73.57 ± 34.05	< 0.001
Alb (g/L)	30.96 ± 6.78	30.33 ± 6.58	31.40 ± 6.90	0.064
eGFR (mL/min/1.73m ²)	79.22 ± 48.63	53.93 ± 39.60	96.97 ± 46.52	< 0.001
CRRT	80 (14.2%)	73 (31.3%)	7 (2.1%)	< 0.001

Categorical variables were compared with the chi-square test or the Fisher's exact test. Risk factors for AKI, such as sepsis and severity of illness, could also affect BP variability. Therefore, multivariable logistic regression analysis was performed to evaluate the independent risk factors for AKI. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of 24 h ARV and APACHE II score in the multivariable logistic regression analysis, with hospital mortality as the dependent variable. Correlations between two quantitative variables were determined by Pearson correlation analysis. $P < 0.05$ was considered to indicate statistical significance.

Fig. 1. Screening flowchart of study patients.

Results

A total of 565 patients were included in this study. Of these, 364 (64.4%) were male (Table 1). Mean age was 57.0 years at admission. The mean BMI, SOFA and APACHE II scores were 22.9 kg/m², 9.45 and 21.5, respectively. A total of 326 (57.7%) patients were diagnosed with sepsis after admission, and 25.5% (144) patients were hypertensive. Fig. 1 shows the inclusion criteria of the patients.

A total of 233 (41.2%) patients presented with AKI within the first 3 days after admission (AKI stage I, $n = 94$; stage II, $n = 37$; stage III, $n = 102$), while the remaining 332 patients did not show any renal dysfunction (Table 2). Changes of patients' eGFR are shown in suppl. Fig. S1. For all supplemental material see www.karger.com/doi/10.1159/000485927.

Table 2. Clinical Outcomes of Patients With and Without AKI

	Total n=565	AKI group n=233	Non-AKI group n=332	p value
AKI stage				
Stage I	94 (16.6%)	94 (40.3%)		
Stage II	37 (6.5%)	37 (15.9%)		
Stage III	102 (18.1%)	102 (43.8%)		
Mechanical ventilation free ICU stay (day)	4 (1, 10)	4 (1, 10.5)	3 (1, 9)	0.907
ICU stay (day)	11 (6, 21)	12 (8, 22)	9 (4, 19.75)	< 0.001
Hospital stay (day)	21 (13, 34.5)	22 (13, 36.5)	20 (12, 33)	0.290
All-cause mortality in hospital	99 (17.5%)	66 (28.3%)	33 (9.9%)	< 0.001

Table 3. Short-Term BP Variability Indices in Patients With and Without AKI. SD, standard deviation of 24-hour SBP; CV, coefficient of variation of 24-hour SBP; ARV, average real variability of 24-hour SBP

	Total n=565	AKI group n=233	Non-AKI group n=332	p value
Mean SBP (mmHg)	116.5 ± 11.7	115.6 ± 10.8	117.1 ± 12.2	0.139
SD (mmHg)	15.04 ± 6.00	16.82 ± 5.78	13.80 ± 5.85	< 0.001
CV (%)	13.01 ± 5.25	14.64 ± 4.99	11.87 ± 5.13	< 0.001
ARV (mmHg)	9.80 ± 2.87	10.87 ± 3.03	9.04 ± 2.50	< 0.001

Table 4. Multivariable Logistic Regression Analysis with AKI as the Dependent Variable. ARV, average real variability of 24-hour SBP

	Odds Ratio	95% CI	p value
APACHE II	1.068	(1.012, 1.127)	0.017
Lac	1.618	(1.238, 2.116)	< 0.001
Mean SBP	1.005	(0.979, 1.031)	0.731
ARV	1.190	(1.055, 1.342)	0.005
SCr	1.016	(1.006, 1.026)	0.001

BMI, age, comorbidities and the proportion of male patients did not differ between the AKI and non-AKI groups. Inflammatory factors (CRP, IL-6, PCT) were significantly higher in the AKI group than in the non-AKI group. As compared to the non-AKI patients, AKI patients had more severe condition, worse organ function and higher rate of vasoactive drug usage (Table 1). The AKI group also had longer ICU stay and higher mortality rate. There was no difference in the mechanical ventilation-free ICU days between the two groups (Table 2).

As shown in Table 3, the patients with AKI exhibited higher BP variability in 24-hour SBP (SD, CV as well as ARV) with same mean SBP during the first 24 hours after admission, as compared to those without AKI (suppl. Fig. S2). The difference in ARV of 24-hour SBP was significant (Adjusted OR, 1.190 [1.055–1.342]; $p=0.005$) after adjustment for severity of illness (APACHE II score), Lac, sepsis, inflammatory factors, 24-hour mean SBP and vasoactive drug usage (Table 4 and suppl. Table S1). Moderate correlation was revealed between ARV and SD ($r = 0.691$, $p < 0.001$) or CV ($r = 0.697$, $p < 0.001$). The differences in both SD and CV of 24-hour SBP between two groups became insignificant after adjustment (suppl. Tables S2 and S3).

The incidence of AKI increased with the ARV from 14.0% (ARV ≤ 6 mmHg) to 73.9% (ARV > 14 mmHg) (Fig. 2). There was a moderate decrease in the incidence curve of AKI when the ARV was 7–10 mmHg, and 45.5% of the patients' ARV was clustered in this interval. The all-cause hospital mortality rate also rose from 4.7% to 28.3% along with the increase of ARV.

The multivariable logistic regression analysis revealed that death during hospital stay was associated with increased APACHE II score (Adjusted OR, 3.20 [1.91–5.34]; $p < 0.001$), presence of sepsis (Adjusted OR, 2.43 [1.36–4.33]; $p = 0.003$), vasoactive drug usage (Adjusted OR, 1.71 [1.02–2.88]; $p = 0.043$), as well as 24 h ARV > 12.7 mmHg (Adjusted OR, 2.72 [1.16–6.40]; $p = 0.021$) (Fig. 3 & suppl. Tables S4, S5, and S6). When factors correlated with hospital mortality were further examined in the subgroups of hypertensive or AKI patients, 24 h ARV showed no significant predictive value in both subgroups.

Fig. 2. Incidence of AKI and hospital mortality rate of patients with different level of 24 h ARV. Along with the increase of ARV, The incidence of AKI rose from 14.0% to 73.9% with a moderate decrease when the ARV was between 7 and 10 mmHg. The all-cause hospital mortality rate also increased gradually with the elevation of ARV. The number of death included the patients who died during hospital stay. ARV, average real variability of 24-hour SBP.

Fig. 3. Multivariable logistic regression analysis with hospital mortality as the dependent variable in all and subgroups of hypertensive and AKI patients.

Risk factors for CRRT were also explored in AKI patients, including increased APACHE II score (Adjusted OR, 1.082 [1.009–1.161]; $p = 0.027$), and decreased eGFR (Adjusted OR, 0.950 [0.931–0.969]; $p < 0.001$) (suppl. Table S7). Seven patients without AKI performed CRRT for extrarenal factors (2 with hyperkalemia; 4 with volume overload; and 1 for inflammatory mediators clearance).

Discussion

In this study, a significant association between the presence of AKI and elevated ARV of 24-hour SBP was identified in a cohort of critically ill patients. This association remained significant after adjustment for potential confounding factors, such as severity of illness, vasoactive drug usage and average SBP. The incidence of AKI rose in patients with higher degree of ARV. A weak association was found between ARV and hospital mortality in all patients, but not in hypertensive or AKI patients.

BP fluctuates with time. During several minutes or over a period of months, its variability is the manifestation of complex interactions between external factors and internal response of BP control mechanisms, which subsequently influence organ function [1]. The relationship between BP variability and its roles in the progression of organ damage and the initiation of vascular events is well established [12]. A recent systematic review revealed that BP variability facilitates the progression of preclinical cardiac, arterial and renal damage [13]. A study conducted mostly in patients with hypertension linked both short and long-term BP variability to several chronic conditions [14]. In addition, the present study indicated that 24 h BP variability was associated with acute onset conditions (in this case, with AKI) in critically ill patients.

Short-term BP variability has been usually described by several statistical parameters including SD, CV or ARV of either systolic or diastolic BP. Of which, SD is a commonly used measurement to quantify the dispersion of a set of data values around the mean but without any information about the order of these values [15]. Therefore, one of the most important drawbacks of this parameter is to describe how BP changes dynamically over time. ARV is the average of the absolute differences of consecutive BP measurements, which is sensitive to the consecutive BP measurements ordered with time manner [16]. Studies [17, 18] suggest that ARV is a more appropriate index of time series BP variability and a more useful predictor of outcomes. It is consistent with current study that ARV performed greater predictive value on AKI in critically ill patients.

Enhanced BP variability increases variations in blood perfusion of different organs; of which, kidneys are the most susceptible because of the low renal oxygen extraction proportion (approximately 10–15%) [19]. Thus, AKI is more common in critically ill patients with enhanced BP variability, after renal function is affected by altered renal perfusion. The incidence of AKI increased with the increase in BP variability, and rose to 73.9% when ARV was >14 mmHg in the present study. Few other studies have investigated the potential relationship between short-term BP variability and renal function. Despite different parameters of BP variability used, these studies indicated that increased BP variability was associated with signs of renal dysfunction, regardless of mean BP values. The 24-h rate of SBP variation was shown to be a strong predictor of impaired renal function (OR per 0.1 mmHg/min increase, 1.49 [1.18–1.88]; $p = 0.001$) [20]. Similar results were reported when linking other parameters of short-term BP variability (ARV of 24-hours SBP, weighted SD of 24-hours SBP) with eGFR in patients with microalbuminuria [7]. To the best of our knowledge, all the studies on BP variability and renal function were conducted in hypertensive patients; and data of critically ill patients, whose renal function was often impaired, was scarce. This is the first study to evaluate the relationship of short-term BP variability and AKI in critically ill patients.

Stable renal blood flow is maintained against changes of renal perfusion pressure over a range of 80–180 mmHg by renal autoregulatory mechanisms,[21] which are mainly mediated by the myogenic and the macula densa-tubuloglomerular feedback responses that involve comprehensive mechanisms of multiple pathways [22]. Increased NO production and inflammatory response attenuate renal autoregulation [23]. When these occur in critically ill patients, the renal blood flow is difficult to stabilize with damaged renal autoregulation after variations in BP. The association between AKI and elevated BP variability in the present study suggested early attenuated renal autoregulation in critically ill patients.

Data from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome,[24] which included 8938 subjects from 11 centers, demonstrated that the systolic BP variability could predict both total and cardiovascular mortality in adjusted models. ARV maintained its predictive value after adjustment for several confounders and additional 24-hour BP level. Results of a recent meta-analysis of 77, 299 patients also supported the relationship between BP variability and mortality [25]. After adjusting for age and mean BP, the relative risk of all-cause mortality and cardiovascular event-related mortality associated with BP variability was 1.03 (95% CI, 1.02–1.04; $p < 0.001$) and 1.10 (95% CI, 1.02–1.17; $p < 0.001$). In a small survey of patients with sepsis, a significant correlation was found between BP variability and APACHE II score ($r = 0.732$, $p < 0.001$), making it a potential risk factor for predicting the survival rate [26]. In the present study, patients with ARV ≤ 7.8 mmHg had a greater chance of survival than those with ARV > 12.7 mmHg. However, most of the included patients had an ARV between 7.8 and 12.7 mmHg. In addition, our study included critically ill patients with a mean APACHE II score of 21.5; and numerous factors are involved in the death of a critically ill patient. So we considered ARV as a cautionary factor when it increased significantly, but not strong enough to predict mortality as compared to other factors in critically ill patients, based on the multivariate analysis. This association became insignificant in subgroups of hypertensive or AKI patients, partly proving its weakness.

The meaning of short-term BP variability could differ if the frequency of intermittent BP readings changes in 24 hours. The minimal number of BP readings required to compute ARV without meaningful loss of prognostic information is 48 recordings, at 30-min intervals over 24 hours, according to an analysis of a large dataset [27]. The consistency of relationship between ARV calculated from different BP recording frequencies and all-cause mortality declines rapidly for < 48 recordings. In the present study, in order to maintain the accuracy of ARV and consistency among patients, the BP readings were obtained at 30-min intervals throughout 24 hours. This frequency was kept constant during daytime and nighttime.

Our study had some limitations. Firstly, the study was not blinded: the intensivists who managed the patients and made the diagnosis of AKI were aware of the patients' BP levels. Nevertheless, since the BP variability was subsequently calculated by a statistician, it is unlikely that the intensivists' knowledge of the patients' BP could cause significant bias in this study. Secondly, although invasive arterial pressure monitoring was performed for some patients, non-invasive BP data was primarily used in this study. Non-invasive BP monitoring has been shown to be as effective in detecting BP fluctuations as invasive BP monitoring in clinical practice [28]. Therefore, it can be assumed that this method had little influence on our results. Furthermore, patients included in the present study were diagnosed with sepsis (previous severe sepsis) by proven or suspected infection with dysfunction of at least one organ, which has been revised by the third international definitions for sepsis and septic shock [29]. However, we assumed that patients diagnosed with "old" severe sepsis underwent a similar pathophysiological process as the "new" sepsis patients.

Conclusion

The results of our study showed a significant association between BP variability and the incidence of AKI in critically ill patients. Both the incidence of AKI and hospital mortality increased with the increase in 24 h ARV. Weak association was also discovered between BP variability and hospital mortality in critically ill patients, making it a cautionary factor when the BP increased rapidly. Due to the cross-sectional nature of the present study, the results remain speculative and the importance of monitoring BP variability needs to be further confirmed.

Disclosure Statement

None.

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