Association of Mean Perfusion Pressure Variability and Short-Term Mortality in Critically Ill Patients

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Abstract

Abnormal blood pressure variability (BPV) is associated with various organ injuries, high risk of cardio-cerebrovascular events and mortality. To investigate the association between mean perfusion pressure variability (MPPV) and mortality in critically ill patients admitted to the Intensive Care Unit (ICU), we analyzed data stored in the eICU-CRD database. MPPV was measured as the standard deviation (SD), coefficient of variation (CV), average real variability (ARV) and variation independent of the mean (VIM) of the first 24 hours MPP data within the first 72 hours in the first ICU stay. A total of 6049 patients were included. Apart from SD, survivors had significantly lower MPPV in ARV, CV but higher VIM compared with non-survivors. After accounting for confounders, highest MPPV in decile using four measurements were associated with increased risk of hospital mortality compared with those in the fifth and sixth decile. In addition, lowest MPPV with dimension (mmHg) in decile also correlated to an increase in the risk of hospital mortality compared with the fifth and sixth decile. These relationships remained remarkable in the sensitive analyses. Increased MPPV and decreased MPPV with dimension were associated with short-term mortality in critically ill patients.

Introduction

During hospitalization in the intensive care unit (ICU), blood pressure (BP) is regularly monitored to observe organ perfusion in a safe, non-invasive or invasive manner. BP is a substitute index for blood perfusion of terminal organs such as brain, heart and kidney which are prone to ischemia ¹. And variability is a normal physiological property of BP, which may contribute to morbidity and mortality through unbalanced load ^{2,3}.

For a long time, studies on long-term blood pressure variability (BPV) have confirmed that abnormal BPV is associated with various organ injuries, high risk of cardio-cerebrovascular events and mortality ⁴⁻⁸. Short term high BPV in critically ill patients is also found to be linked to mortality and organ injuries like acute kidney injury (AKI) ⁹. In contrast, a recent study showed that the decrease (between - 5% and 5%) in mean arterial pressure (MAP) fluctuation calculated by (nighttime MAP – daytime MAP) / 24-hour MAP may be related to adverse outcomes in critically ill patients ¹⁰. However, the threshold at which variability is too high or too low to be clinically significant remains unclear. And previous studies about the impact of short-term BPV on critically ill patients are limited by sample and evidence is not strong enough. Moreover, traditional index like MAP has some physiological deficiencies, especially the failure to consider venous outflow pressure. Obtained by the difference between MAP and central venous pressure (CVP), mean perfusion pressure (MPP) was recently proposed to personalized management tissue perfusion pressure instead of MAP ^{11,12}.

Therefore, we sought to describe the relationship between MPP variability (MPPV) and hospital mortality among critically ill patients. We hypothesized that an optimal range of MPPV can be determined to reduce hospital mortality in critically ill patients.

Methods

Study population

This study utilized data stored in the eICU Collaborative Research Database (eICU-CRD) v2.0 ¹³, which is a unique and publicly accessible multicenter database covering more than 200,000 ICU admissions ¹⁴. The inclusion criteria were (1) age 16 years or more; (2) at least 24 hours of continuous MAP and CVP invasive monitoring within the first 72 hours in the first ICU stay and (3) at least 20 MPP readings in the daytime and at least seven in the nighttime ¹⁵. Daytime is defined as 7 am to 11 pm, otherwise as nighttime. Those who received dialysis, died during the first 24 hours, complicated with chronic kidney disease stage 5, and with incomplete data or extreme MPP data were excluded.

Data extraction

We extracted MPP data, demographic data, baseline ICU characteristics, Charlson comorbidity index ¹⁶, and admission illness severity scores [including the Sequential Organ Failure Assessment (SOFA) ¹⁷ and Oxford Acute Severity of Illness Score (OASIS) ¹⁸]. Criteria for sepsis were defined based on those described earlier by Angus et al ¹⁹ instead of sepsis 3.0 because most microbiology data was unavailable in eICU-CRD. Additionally, the need for mechanical ventilation, incidence of AKI, use of vasopressor, antihypertensive drugs and sedatives were also collected.

Data cleaning

We chose the values of MAP between 0 mmHg and 150 mmHg, and the values of CVP between -10 mmHg and 50 mmHg. Furthermore, we deleted the outliers which were defined as larger than the average MPP values plus four standard deviation (SD) in each patient. Considering the influence of the extreme value on the result, we removed a total of 1% of patients with extreme high (> 99.5th percentile) and low value (< 0.05th percentile) of the coefficient of variation (CV) of MPP in further analysis.

Exposure

Short-term MPPV was measured as the SD, CV, average real variability (ARV) and variation independent of the mean (VIM) ²⁰ of 24-hour MPP data. The SD and ARV were thought as variability with dimension (mmHg). And CV and VIM were thought as variability without dimension. Detailed formulas are displayed in supplementary Table 1.

Outcomes

The primary outcome was in-hospital mortality.

Statistical analysis

Statistical analyses were performed using R version 3.63 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). Categorical variables were presented as percentages and compared using a chi-square test. Continuous variables were expressed as median (25th, 75th percentile) and compared using Wilcoxon rank-sum test.

MPPV parameters of the first complete 24 hours of ICU stay were taken as a continuous variable for the primary analysis. Firstly, general additive models with a logit link function were built to plot associations between MPPV and in-hospital mortality, adjusted by age, gender, BMI, ethnicity, Charlson comorbidity index, SOFA score, OASIS, history of tachyarrhythmia, sepsis, incidence of AKI in the first day of ICU admission, the need for mechanical ventilation, the use of vasopressor, antihypertensive drug and sedatives. Second, we used multivariable logistic regression models to assess the relationship between the outcome and deciles of each parameter adjusted by the same confounders mentioned before.

There were missing values for body mass index (BMI) (3.2 %) and multiple imputation was used to handle the missing with the mice package in R. In order to verify the robustness of the results, we explored the association of MPPV and ICU mortality. And the association of daytime and nighttime MPPV and hospital mortality were also analyzed. Furthermore, subgroup analyses were conducted in patients who were male or female, elderly (age ≥ 65 years) or not, with or without hypertension, sepsis, median SOFA score on the first day of ICU admission. For all analyses, a two-tailed P value less than 0.05 was considered statistically significant.

Ethics approval and consent to participate

The study was conducted entirely on a publicly available, third-party anonymous public database which was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. The re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (HIPAA Certification no. 1031219-2). The ethics committee of The First Affiliated Hospital of Nanjing Medical University waived the requirement for approval of this study (2021-QT-08). To apply for access to the database, we completed the National Institutes of Health's web-based course and passed the Protecting Human Research Participants exam (record ID. 32559175, ID. 38120064). All methods were performed in accordance with the relevant guidelines and regulations.

Results

Patient characteristics

After reviewing 166,355 first ICU stays in eICU-CRD, we finally included 6,049 fulfilling the inclusion and exclusion criteria (Fig.1). The baseline characteristics between survivors and non-survivors are shown in Table 1. Though there was no significant difference in the use of sedatives and the history of tachyarrhythmia, the survivors were, on average, younger, predominantly male and lower in BMI. Non-survivors were significantly complicated with more comorbidities, more severe in diseases (higher SOFA score and OASIS), needing more support (mechanical ventilation and vasopressors), less use of

antihypertensive drug, higher incidence of AKI and sepsis and lower MPP compared with survivors. More non-survivors had tachyarrhythmia history and less use of sedatives, but the difference did not reach statistical significance. Other information about hospitals, initial diagnosis, comorbidities and MPP data of the whole cohort were listed in supplementary Table 2.

The median of the four MPPV parameters were 7.8 mmHg (SD), 12.3% (CV), 2.8 mmHg (ARV) and 0.40 units (VIM) in the whole cohort. The 10th percentile and 90th percentile for the four MPPV parameters were 5.1 mmHg and 12.2 mmHg for SD, 8.2% and 12.2% for CV, 1.6 mmHg and 5.6 mmHg for ARV, 0.27 units and 0.62 units for VIM, respectively. The survivors had higher CV (13.0% vs 12.2%, $p<0.001$) and VIM (0.42 units vs 0.40 units, $p<0.001$), lower ARV (2.7mmHg vs 2.8 mmHg, $p=0.014$) and similar SD (7.9 mmHg vs 7.8 mmHg, $p=0.269$) as compared with non-survivors.

Association with MPP and other BPV

The scatter plots and the fitting curves of time-weighted average MPP (TWA-MPP) and MPPV showed us the relationship intuitively. The SD and ARV increased with the increase of the TWA-MPP. In the contrast, CV had a downward trend with the increase of the TWA-MPP. VIM did not change with the TWA-MPP (supplementary Fig.1). The correlation coefficient for CV and VIM was 0.98, which was the strongest (supplementary Fig.2).

There was also a strong correlation between MPPV and other BPV like MAP, systolic BP (SBP) and diastolic BP (supplementary Fig.3), among which the correlation coefficients of ARV were higher.

Association with hospital mortality

After adjusting for age, gender, BMI, ethnicity, Charlson score, SOFA score, OASIS, history of tachyarrhythmia, sepsis, incidence of AKI in the first day of ICU admission, the need for mechanical ventilation, the use of vasopressor, antihypertensive drug and sedatives, we found a 'U' shaped curve between variability with dimension indicators (SD and ARV) and hospital mortality using general additive models (Fig. 2A, 2C). However, hospital mortality simply increased with the dimensionless variability (CV and VIM) increasing (Fig. 2B, 2D).

After grouping in deciles (Fig. 3), multiple logistic regression revealed that both higher and lower MPPV with dimension were related to an increase in the risk of hospital mortality compared with the fifth and sixth decile (SD: adjusted odds ratio [OR] in the first decile: 1.64, 95% confidence interval [CI]:1.25-2.15, adjusted OR in the tenth decile: 1.83, 95% CI: 1.40-2.40; ARV: adjusted OR in the first decile: 2.10, 95% CI:1.62-2.73, adjusted OR in the tenth decile: 1.74, 95% CI: 1.33-2.27). But in dimensionless variability indicators, only higher MPPV (Fig. 3B, 3D) were associated with increased risk of hospital mortality compared with the fifth and sixth decile (CV: adjusted OR in the tenth decile: 1.50, 95% CI: 1.16-1.93; VIM: adjusted OR in the tenth decile: 1.51, 95% CI: 1.17-1.96). These results were consistent with the changing trend of general additive models.

Sensitivity and subgroup analyses

For the sensitivity analyses, we analyzed the association between MPPV and ICU mortality. We observed similar trends in each variability index (supplementary Fig.5). Multiple logistic regression also confirmed our findings (supplementary Fig.6). Higher MPPV increases the risk of ICU mortality without exception (adjusted OR in the tenth decile: SD: 1.90, 95% CI: 1.39-2.58; CV: 1.57, 95% CI: 1.18-2.09; ARV: 1.78, 95% CI: 1.32-2.39; VIM: 1.47, 95% CI: 1.10-1.96). In two MPPV with dimension indicators, lower variability also increased the risk of ICU mortality. (adjusted OR in the first decile: SD: 1.64, 95% CI: 1.20-2.22; ARV: 2.25, 95% CI: 1.69-3.00).

Since there was time interval in the calculation of daytime or nighttime ARV, we chose SD and CV representatively to analyze the association between day and night MPPV and hospital mortality. The results still showed good consistency (supplementary Fig.7, supplementary Fig.8).

The association of high MPPV and in-hospital mortality was analyzed across patients who were male or female, elderly (age ≥ 65 years) or not, with or without hypertension, sepsis, median SOFA score on the first day of ICU admission (Fig. 4). In patients who had SOFA score of $\geq$ eight or had hypertension history, higher variability is associated with higher risk of death in hospital. Surprisingly, sepsis patients with high variability did not increase hospital death risk.

Discussion

In this multicenter, retrospective, cohort study among critically ill patients, we clarified the clinically significant range of MPP abnormalities for the first time, and found that (1) increased MPPV (SD > 10.4 mmHg, CV $> 19\%$, ARV > 5.6 mmHg, VIM > 0.62 units) was associated with the risk of hospital mortality which was not influenced by confounding factors including absolute blood pressure levels. (2) decreased MPPV with dimension instead of those without dimension (SD < 5.9 mmHg, ARV < 2.2 mmHg) was also associated with the risk of hospital mortality.

Increased BPV is related to the prognosis of critically ill patients. A prospective, observational study conducted by Xie et al. reported a significant relationship between systolic BPV and the occurrence of AKI as well as a weak link with hospital mortality after adjusting potential confounding factors⁹. Two studies about intraoperative BPV also confirmed that a higher BPV is linked with postoperative AKI and postoperative mortality in noncardiac surgery^{20,21}. A post hoc analysis of the HeadPoST study has reported that increased BPV was associated with poor stroke outcome²². In endovascular therapy treated acute stroke patients, higher BPV in the first 24 hours was associated with poor 90-day neurological outcome²³. In our study, all variability indicators confirmed the link between high variability and increased risk of hospital mortality as well as ICU mortality. In addition, same conclusion could also be drawn when we analyzed daytime and nighttime MPPV separately.

Why is increased MPPV related to prognosis? As we all know, human body is always in dynamic balance to regulate a variety of external stimuli to maintain homeostasis. Critically ill patients are known for high incidence of anxiety²⁴, delirium²⁵, sleep loss²⁶, abnormal central and autonomic nervous regulation²⁷,

which are all related to increased morbidity and mortality²⁷⁻²⁹, and the patients in ICU are constantly affected by the environment day and night. Among previous randomized controlled trial studies in non-critically ill patients, it has been confirmed that generalized anxiety disorder was associated with a significant increase in systolic BPV, which may increase the variability by increasing sympathetic dominance³⁰. The addition of an anxiolytic to the pharmacotherapy regimens could reduce and stabilize the circadian rhythm of blood pressure³¹. Moreover, partial sleep deprivation³², fragmented sleep³³ and cold weather³⁴ could also lead to an increased BPV. In our study, we chose MPP as the target of variability study to explain the effect of organ perfusion variation on prognosis more pertinently. In addition to the above possible speculation, we supposed that this may be due to the ischemia-reperfusion injury. Prolonged ischemia can cause cell dysfunction and death³⁵. Increased BPV can be observed in the animal model of ischemia-reperfusion and lead to various organ injuries^{36,37}. Whether improving MPPV can affect the prognosis of critically ill patients still needs further study.

Decrease MPPV can also associated with an increased risk of death in hospital. This kind of patients may lose the function of physiological regulation and circadian rhythm of blood pressure. The blood pressure of normal people shows a dipper pattern. Abnormal diurnal variation of blood pressure was a risk factor for cardiovascular disease³⁸. Previous studies have investigated that reduced day/night fluctuations were associated with ICU and hospital mortality¹⁰ and nocturnal mean arterial pressure rising may be an important risk factor for high short-term and long-term mortality in critically ill patients³⁹. In our study, decreased MPPV with dimension was linked to hospital mortality and the risks were even higher as had been expected in ARV, an indicator closely related to time. However, this connection was affected by absolute blood pressure levels, which made the dimensionless MPPV without statistical significance. Besides, for the time series nature of ARV, it showed better sensitivity to identify MPP which changed little over time and to predict poor prognosis. Early studies have proposed that ARV was a more reliable representation of time series variability and added more prognostic value than SD^{40,41}. Our subgroup analyses for SD and ARV also displayed a better stability of ARV.

Our subgroup analyses showed that higher MPPV did not associate with in-hospital mortality in patients with sepsis. Though a prospective study with a small sample size observed a possible association between early SBP complexity and 28-day mortality in patients with severe sepsis⁴², they only analyzed SBP variability on the first five-minute window. Patients with sepsis are often characterized with increased MPPV during fluid resuscitation, but would not develop adverse outcomes. Given patients with hypertension who seem to be more susceptible to higher MPPV, more attention may be paid to the ICU MPP stability management of patients with hypertension in the future.

This is the first clinical investigation to explore the association between the variability of MPP and hospital mortality in critically ill patients. The advantage of this post hoc analysis was that the eICU-CRD database contained comprehensive and high-quality data and had an average five-minute of measurement interval of MAP and CVP which guaranteed the reliability of variability calculation. Moreover, the inclusion of the 24-hour measurement ensured that all patients were exposed to a complete

diurnal cycle. Finally, we combined four variability indicators, and conducted sensitivity and subgroup analyses to make the results more robust.

Our study has some limitations. First, although the data stored in eICU-CRD database was multicenter, effective external verification was not been carried out due to the lack of sufficient monitoring frequency in other databases. Second, due to the heterogeneity of monitoring methods and frequency, it is hard to determine the reference values of the MPPV results of each parameter. Third, the post hoc analysis has its inherent defects and unavoidable bias.

Conclusion

Increased MPPV and decreased MPPV with dimension were associated with short-term mortality in critically ill patients.

List Of Abbreviations

AKI: acute kidney injury; ARV: average real variability; BMI: body mass index; BP: blood pressure; BPV: blood pressure variability; CI: confidence interval; CV: coefficient of variation; CVP: central venous pressure; ICU: intensive care unit; MAP: mean arterial pressure; MPP: mean perfusion pressure; MPPV: mean perfusion pressure variability; OASIS: Oxford Acute Severity of Illness Score; OR: odds ratio; SBP: systolic blood pressure; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; TWA-MPP: time-weighted average mean perfusion pressure; VIM: variation independent of the mean;

Declarations

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Ethics approval and consent to participate

The database is released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. The re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (HIPAA Certification no. 1031219-2).

Consent for publication

Not applicable

Availability of data and material

The datasets generated and analyzed during the current study are available in the eICU-CRD repository, DOI: 10.1038/sdata.2018.178.

Competing interests

Yudie Peng, Buyun Wu, Changying Xing, Huijuan Mao declare that they have no competing interests.

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Authors' contributions

YDP and BYW designed the study, conducted the data collection, data analysis, data interpretation, and wrote the manuscript. CYX designed the study and reviewed the manuscript. HJM designed the study, conducted the data interpretation, and reviewed the manuscript. All authors reviewed and approved the version submitted for publication.

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Tables

Table 1

Baseline characteristics of the study population in the first 24 hours and MPP characteristics of the exposure time among survivors and non-survivors.

Variables	Survivors	Non-Survivors	<i>p</i>
N	4992	1057	
Age	66 (56, 75)	68 (57, 77)	< 0.001
Male (%)	3035 (60.8)	604 (57.1)	0.03
BMI (kg/m ²)	28.6 (24.6, 33.5)	28.2 (23.6, 33.6)	0.023
White (%)	3779 (75.7)	834 (78.9)	0.029
Charlson	1 (0, 2)	1 (0, 3)	0.006
SOFA score	8 (6, 10)	10 (8, 13)	< 0.001
OASIS	30 (23, 37)	37 (30, 43)	< 0.001
Sepsis (%)	963 (19.3)	357 (33.8)	< 0.001
History of Tachyarrhythmia (%)	670 (13.4)	166 (15.7)	0.057
First day AKI (%)	1839 (36.8)	582 (55.1)	< 0.001
Ventilation (%)	3507 (70.3)	865 (81.8)	< 0.001
Vasopressors (%)	1998 (40.0)	537 (50.8)	< 0.001
Sedatives (%)	2537 (50.8)	518 (49.0)	0.299
Antihypertensive drugs (%)	1713 (34.3)	251 (23.7)	< 0.001
Measurement times of MPP	284. (265, 288)	279 (247, 288)	< 0.001
TWA MPP (mmHg)	63.3 (57.8, 70.0)	60.6 (53.8, 69.1)	< 0.001
MPP-SD (mmHg)	7.8 (6.2, 9.8)	7.9 (6.1, 10.2)	0.269
MPP-CV (%)	12.2 (9.9, 15.2)	13.0 (10.3, 16.6)	< 0.001
MPP-ARV (mmHg)	2.8 (2.1, 3.8)	2.7 (1.9, 4.0)	0.014
MPP-VIM (units)	0.40 (0.32, 0.50)	0.42 (0.33, 0.53)	< 0.001
AKI: acute kidney injury; ARV: average real variability; BMI: body mass index; CV: coefficient of variation; ICU: intensive care unit; MPP: mean perfusion pressure; OASIS: Oxford Acute Severity of Illness Score; SD: standard deviation; SOFA: Sequential Organ Failure Assessment; TWA: time weighted-average; VIM: variation independent of the mean.			

Figures

Figure 1

Patient flow chart.

Figure 2

The associations between adjusted in-hospital mortality risk and MPPV fitted by general additive models and the histograms of MPPV. The figure shows that in all MPPV parameters, in-hospital mortality increases with variability. In two absolute MPPV parameters, SD and ARV, decreased variability also associated with high in-hospital mortality. The above associations were adjusted by age, gender, BMI, ethnicity, Charlson comorbidity index, SOFA score, OASIS score, history of tachyarrhythmia, sepsis, incidence of AKI in the first day of ICU admission, the need for mechanical ventilation, the use of vasopressor, antihypertensive drug and sedatives.

Figure 3

The deciles of MPP variability and adjusted odds ratio of in-hospital mortality using the fifth and sixth deciles as a reference. Multiple logistic regression reveals that for absolute variability indicators, both increased and decreased MPPV would lead to an increase in the risk of hospital mortality compared with the fifth and sixth decile. But in relative variability indicators, only higher MPPV were associated with increased risk of hospital mortality compared with the fifth and sixth decile, which were consistent with the change trend of general additive models.

Figure 4

Forest plot displaying the subgroup analyses of increased MPP variability (10th decile of CV and VIM). The reference groups were 1-9th deciles of CV and VIM. Note: Abbreviations: aOR: adjusted odds ratio; HTN: hypertension.

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