

Mean arterial pressure within 24 hours of admission predicts short-term prognosis in patients with intermediate-risk and high-risk pulmonary embolism

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Research

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Abstract

OBJECTIVE

Pulmonary embolism is a terrible cardiovascular condition with considerable morbidity and mortality. Previous studies have investigated that systolic blood pressure (Systolic BP) and diastolic blood pressure (Diastolic BP) were related to 30-day and in-hospital mortality. We aimed to determine if the average mean arterial pressure (aMAP) in the first 24 hours of hospital admission is useful to predict short-term outcomes of intermediate-risk and high-risk PE patients.

Method

We conducted a single center retrospective study. From May 2012 and April 2019, 122 intermediate-risk and high-risk PE patients were included. The primary outcome was in-hospital mortality. The secondary outcome was adverse events. ROC curves and cut-off values for aMAP predicting in-hospital-death were computed. According to cut-off values, we categorized five groups defined as followed: group

1: aMAP < 70 mmHg; group 2: 70 mmHg ≤ aMAP < 80 mmHg; group 3: 80 mmHg ≤ aMAP < 90 mmHg; group 4: 90 mmHg ≤ aMAP < 100 mmHg; group 5: aMAP ≥ 100 mmHg. Co-regression models were calculated to investigate associations between aMAP and in-hospital-death.

Result

In the study group of 122 patients, 15 patients (12.30%) died in hospital due to PE. ROC analysis for MAP predicting in-hospital-death revealed an AUC of 0.729 with cut-off value of 79.4 mmHg. Cox regression models showed a significant association between in-hospital death and aMAP group 1 (Ref), aMAP group 2 (OR 1.680, 95% CI 0.020-140.335), aMAP group 3 (OR 0.003, 95% CI 0.0001-0.343), aMAP group 4 (OR 0.006, 95% CI 0.0001-1.671), aMAP group 5 (OR 0.003, 95% CI 0.0001-9.744). It is aMAP 80-90 mmHg that suffer from minimum adverse events.

Conclusion

Prognostic role of MAP at the first 24 hours of hospital admission should be emphasized in patients with PE. 80 to 90 mmHg may be the optimal range of MAP for intermediate-risk and high-risk PE patients.

Introduction

Acute pulmonary embolism (PE) is the third most common diagnosis in cardiovascular disease and can be the source of significant morbidity and mortality, especially in intermediate-risk and high-risk patients, whose mortality in 30 days is > 10%^[1, 2]. For low-risk patients, mortality at 30 days was rarely 1.0%. Thus, intermediate-risk and high-risk PE patients should receive more attention.

Latest guideline emphasized the central role of early risk assessment of patients with an acute pulmonary embolism (PE)^[3]. Systolic blood pressure (Systolic BP) and diastolic blood pressure (Diastolic BP) values are fundamental and integral to severity assessment. Previous articles have already proved the prognostic role of systolic blood pressure (Systolic BP) in acute PE patients^[4, 5]. Thereby, Systolic BP < 100 mmHg was incorporated into simplified Pulmonary Embolism Severity Index (sPESI)^[6] and Pulmonary Embolism Severity Index (PESI)^[1]. In addition, Diastolic BP ≤ 65 mmHg at admission was relevant by in-hospital mortality^[4]. Literally, mean arterial pressure (MAP), which is important to organ and tissue perfusion, is calculated as 1/3 Systolic BP plus 2/3 Diastolic BP. Moreover, MAP is proved to be relevant with heart rate, left ventricular contractility and right heart dysfunction^[7]. For critically ill patients, MAP level was closely related to mortality^[8]. However, no study to date has investigated the relationship between MAP and outcome of PE patients.

In this study, we sought to determine if the average MAP (aMAP) in the first 24 hours of hospital admission is useful to predict short-term outcomes of intermediate-risk and high-risk PE patients.

Methods And Patients

We performed a retrospective analysis of acute intermediate-risk and high-risk PE patients, who were treated in the Fujian Provincial Hospital between May 2012 and April 2019. The local editorial board approved the study.

In our retrospective study, eligible patients were required to be confirmed by computed tomography pulmonary angiography (CTPA) or pulmonary angiography, availability of patient records, and age ≥ 18 years. Conversely, pregnant women were excluded from the study. Classification of pulmonary embolism severity was according to 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society.

The final study group included 122 patients (age median 68.5 years, 60 female). Treatment methodology was same during the study period following the guidelines on the diagnosis and management of acute pulmonary embolism^[9, 10]. The primary outcome of this study was in-hospital mortality. The secondary outcome of this study was adverse events.

Definitions

Adverse events were defined as cardiogenic shock (Systolic BP < 90 mmHg), cardiopulmonary resuscitation, mechanical ventilation, vasopressor therapy, thrombolysis.

Clinical and instrumental evaluation of PE

Blood pressure measurement frequencies at the first 24 hours of hospital admission were depending on their severity. For intermediate-risk PE patients, BP was measured with a 6-hour interval by an automated non-invasive blood pressure machine. For high-risk PE patients, BP needed to be measured with a 2-hour interval by an automated invasive or non-invasive blood pressure machine. The aMAP was established by using the sum of MAP divided by the number of BP measurements during the 24 hours.

Classification of pulmonary embolism severity

Haemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on transthoracic echocardiogram (TTE), is sufficient to classify a patient into the high-risk PE category. Haemodynamic instability was determined as followed: cardiac arrest, obstructive shock (Systolic BP < 90 mmHg or vasopressors required to achieve a BP \geq 90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (Systolic BP < 90 mmHg or a systolic BP drop \geq 40 mmHg for > 15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis). Patients with Signs of RV dysfunction on TTE (or CTPA), elevated cardiac biomarker levels, and PESI class III–V or sPESI \geq I should be classified into the intermediate–high-risk category. Patients with signs of RV dysfunction or elevated cardiac biomarkers, despite a low PESI or an sPESI of 0, should be classified into the intermediate–low-risk category.

Statistical analysis

The Kolmogorov-Smirnov test was performed to verify the normality of the distribution of the data. Data are presented as the mean \pm SD if normally distributed or median (interquartile range) if not normally distributed. Continuous variables were compared by analysis of Student's t test if the data had normal distribution or by Mann-Whitney-U test or Wilcoxon rank sum test for non-normally distributed variables between the 2 groups. The Kruskal-Wallis (non-normal distribution) test was used for comparing \geq 2 groups. Categorical variables, presented as a percentage, were compared by the Pearson's χ^2 test. We calculated a receiver operating characteristic (ROC) curve with the area under curve (AUC) to establish the optimal cut-off for aMAP as a predictor of in-hospital mortality. In particular, Youden's index (YI = sensitivity + specificity - 1) was also adopted to estimate and confirm the optimal cut-off value from the ROC curve analysis. Univariate and multivariate analyses for the assessment of independent risk predictors were performed by use of the Cox regression model.

We performed statistical analyses with the use of SPSS Version 24, (SPSS, Chicago, IL). All hypothesis tests were two-sided, with a significance level of 0.05.

Results

In the study group of 122 patients, 15 patients (12.30%) died in hospital due to PE. The baseline characteristics of the study groups are outlined in Table 1.

Survival group and non-survival group had comparable rates of previous conditions like hypertension, diabetes, chronic heart failure. Comparing to the survival group, the non-survival group had higher white blood cell count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), d-dimer. And aMAP, Systolic BP, Diastolic BP, Glomerular filtration rate were significantly lower in the non-survival group. The non-survival group had higher percent of high-risk (53.3% vs 11.2%, $p < 0.001$) and lower percent intermediate-low risk patients (20.0% vs 75.7%, $p < 0.001$), more severe classification.

Calculated ROC analysis for aMAP predicting in-hospital death revealed an AUC of 0.729 with aMAP cut-off value of 79.4 mmHg for PE patients included. The percentage of sensitivity, specificity, Youden's index were calculated as 80.5%, 60.0%, 0.405 respectively (Fig. 1)

According to aMAP cut-off value, we categorize five groups defined as followed: group 1: aMAP < 70 mmHg; group 2: 70 mmHg \leq aMAP < 80 mmHg; group 3: 80 mmHg \leq aMAP < 90 mmHg; group 4: 90 mmHg \leq aMAP < 100 mmHg; group 5: aMAP \geq 100 mmHg. Comparing adverse events amounts among different groups, we found that group 1 had most adverse events. Conversely, the amount of group 2 was least. (Fig. 2)

The characteristics of the MAP groups are outlined in Table 2. Group 4 was eldest when compared with other groups ($p = 0.023$). Among groups above, albumin in group 1 was lowest. There were no differences in hemoglobin, ALT, AST, uric acid, glomerular filtration rate and troponin I among groups above.

Cox proportional hazards regression method was used for univariable and multivariable analysis. For univariable analysis, group 3 was a protector factor for in-hospital death (OR 0.051, 95% CI 0.006–0.460). In multivariable analysis (model 2 and model 3 in Table 3), group 3 remained a protector factor for in-hospital death (OR: 0.011, 95% CI 0.0001–0.442, OR 0.003, 95% CI 0.0001–0.343, respectively) compared with group 1. In model 2 and model 3, group 1, group 4 and group 5 were not a protective or hazardous factor for in-hospital mortality.

Discussion

In this study, we found that in-hospital mortality of patients with aMAP < 80 mmHg was considerably higher than that of patients with aMAP \geq 80 mmHg. It seems that aMAP ranging from 80 to 90 mmHg was beneficial to PE patients.

PE was one of the most common critically diseases nowadays. Longitudinal studies indicated the incidence of PE was keeping climbing^[11, 12]. But with different severities, mortality varied widely. For intermediate-risk and high-risk PE patients, mortality was more than 10 fold than that of low-risk patients^[1]. That is to say they account for most part of PE patients who died in 30 days. In my view, they need to achieve more attention. That is why only intermediate-risk and high-risk PE patients were included in this study.

As we know, this is the first study that investigated the relationship between aMAP and in-hospital death of PE patients. Previous studies indicated MAP was involved with right heart dysfunction which was generally acknowledged pertinent to adverse outcomes. When pulmonary arterial bed is occluded by

thromboembolism, pulmonary vascular resistance (PVR) and right ventricular(RV) after-load increased.As a result,RV contraction time prolonged and leftward bowing of the interventricular septum occurred.And this may result in a decreasing in the cardiac output (CO), and contribute to systemic hypotension and hemodynamics instability.In the pulmonary embolism severity index (PESI) and the simplified PESI, Systolic BP of < 100 mmHg is one of the parameters to predict adverse outcomes^[1].While limited studies focused on Diastolic BP.Coronary arteries perfuse cardiac myocytes during diastole.Diastolic BP is essential to coronary flow.Patients with PE often complicated with myocardial infarction.Waits GS^[13] et al found out that low Diastolic BP < 70 mmHg in participants without history of cardiovascular disease whose Systolic BP > 140 mmHg still carries increased risk of subclinical myocardial injury.There is a J shaped curve relation between Diastolic BP during treatment and myocardial infarction,the optimal Diastolic BP was between 85 and 90 mmHg^[14].Recent study demonstrated that PE patients with Diastolic BP \leq 65 mmHg at admission are susceptible to in-hospital death^[4].

MAP is determined as 1/3 Systolic BP plus 2/3 Diastolic BP.The evaluation of MAP has turned out to improve the outcome in different life-threatening illness as sepsis resuscitation, ischemic stroke and distributive shock^[15].Moreover,MAP fluctuations between - 5% and 5% were significantly related to ICU mortality (odds ratio, 1.296; 95% CI, 1.103–1.521; p = 0.002) and hospital mortality (odds ratio, 1.323; 95% CI, 1.142–1.531; p < 0.001)^[16]. Consequently,MAP may be a better indicator that reflects the hemodynamics profile than Systolic BP.

MAP at admission has been identified as a risk factor for ICU mortality and indicator of kidney perfusion^[8, 17]. Computed ROC analysis showed an optimal aMAP cut-off value of 79.4 mmHg for the prediction of in-hospital death in PE patients (specificity 0.805,sensitivity 0.600,AUROC 0.729).Current guidelines recommend targeting a MAP \geq 65 mmHg in septic patients^[18].But the optimal MAP remains an area of debate.In this study,we found that optimal aMAP for patients with PE was 80–90 mmHg.In group 4 and group5,four patients died in hospital(2 received vasopressor therapy,1 with uncontrolled hypertension).It seems that keeping aMAP \geq 90 mmHg would not benefit PE patients.It has been proved out that higher MAP was detrimental to patients,especially to patients without hypertension^[19, 20].Too much dose of vasopressors like norepinephrine and dobutamine, may contribute to higher MAP level.Excessive vasoconstriction may deteriorate tissue perfusion and trigger or aggravate arrhythmias^[21].Vasopressors could increase RV inotropy and systemic BP,promote positive ventricular,interactions lowers filling pressures^[3],however,raising the cardiac output may aggravate the ventilation/perfusion mismatch by further redistributing flow from(partly) occluded to unoccupied artery^[22].Uncontrolled hypertension could increased left ventricular after-load.

Previous researches have demonstrated no significant improvement in renal function when targeting higher MAP value in septic shock^[23, 24].We also found no differences in kidney function among different MAP groups in this article.

We defined adverse clinical events as cardiogenic shock,cardiopulmonary resuscitation, mechanical ventilation, vasopressor therapy, thrombolysis.Honestly,low level of MAP may be a presentation of cardiogenic shock and an indication of vasopressor therapy.That is the reason why patients with aMAP < 70 mmHg suffer from maximum adverse events.However,it is aMAP 80–90 mmHg that suffer from minimum adverse events.Interestingly,aMAP from 80 to 90 was also a protective factor of in-hospital mortality.

There are some limitations to this study that should be considered. First, this was a single-center study conducted in a hospital,susceptible to sampling bias.Second, this study was retrospectively conducted with reference to the electronic medical record. The aMAP values may not reflect actual hemodynamic status. Third, we only included first 24 hours of MAP for analysis but subsequent MAP were not considered.Fourth, MAP between patients with hypertension and without hypertension did not compare.

Conclusion

In conclusion,prognostic role of MAP at the first 24 hours of hospital admission should be emphasized in patients with PE.80 to 90 mmHg may be the optimal range of MAP for intermediate-risk and high-risk PE patients.

Declarations

Acknowledgement

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Contribution

JL,C, J L contributed equally to this work and acquired the data,drafted and revised the manuscript. SJ S and DS W designed the study, provided supervision and critically revised the manuscript. All authors approve the final version of the manuscript and agree to be accountable for all aspects of the study.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Fujian Provincial Hospital (Fujian, China) in accordance with 1964 Helsinki declaration. Consent was not required due to the retrospective nature of the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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Tables

Due to technical limitations, Tables 1-3 are provided as Supplementary Files.

Figures

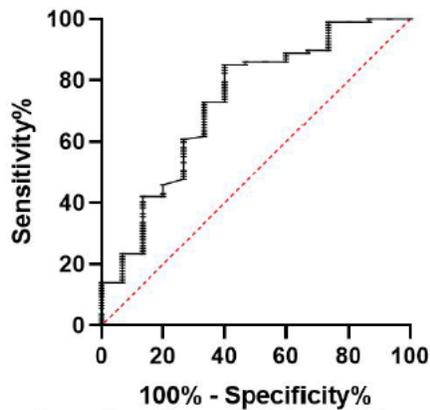


Figure 1

Calculated ROC analysis for aMAP predicting in-hospital death revealed an AUC of 0.729 with aMAP cut-off value of 79.4mmHg for PE patients included. The percentage of sensitivity, specificity, Youden's index were calculated as 80.5%, 60.0%,0.405 respectively.

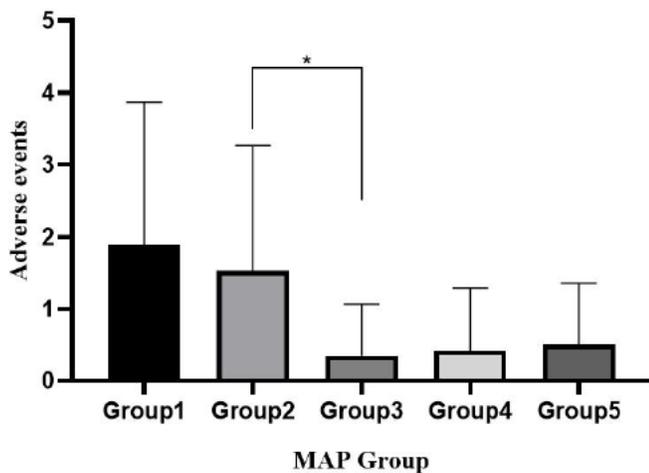


Figure 2

According to aMAP cut-off value, we categorize five groups defined as followed: group 1: aMAP <70mmHg; group 2: 70 mmHg ≤ aMAP <80mmHg; group 3: 80 mmHg ≤ aMAP <90mmHg; group 4: 90mmHg ≤ aMAP <100 mmHg; group 5: aMAP ≥ 100 mmHg. Comparing adverse events amounts among different groups, we found that group1 had most adverse events. Conversely, the amount of group2 was least.

Supplementary Files

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