Differential diagnosis of acute pulmonary embolism using contrast echocardiography

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Introduction

Acute pulmonary embolism (aPE) is a common life-threatening disease, with high mortality rate if not diagnosed and treated timely. Computed tomography pulmonary angiography (CTPA) has been considered to be the gold standard for the diagnosis, differential diagnosis and prognosis of pulmonary embolism. However, CTPA is not easily available, with X-ray radiation and possible allergic reaction and nephrotoxicity of contrast, so it is not always suitable for long-term follow-up of PE.

The pulmonary embolus may detach and occlude the branches of the pulmonary artery, even the main branches of the pulmonary artery, which causes a reduction of antegrade pulmonary blood volume (PBV) and a striking rise of the blood pressure in these vessels before embolic obstruction. This rise of pulmonary artery pressure, which the right heart must fight in order to ensure circulation, may sometimes lead to cardiac arrest [1,2].

Pulmonary transit time (PTT) is the time for a sample of blood to pass through the pulmonary circulation [3-6]. It depends on PBV and cardiac output (CO) according to the formula $PTT = \frac{PBV}{CO}$ [3-6]. Here, the PTT refers to the nPTT (normalized PTT; the PTT divided by the mean
R-R interval of electrocardiogram and CO refers to the right ventricular stroke volume (SV$_{RV}$). Previous studies have demonstrated PTT can be measured using real time contrast echocardiography of low mechanical index, such as myocardial contrast echocardiography, with high accuracy and reproducibility [6-8]. Meanwhile, CO can also be measured by conventional echocardiography. So, PBV can be obtained by the product of PTT and CO using echocardiographic method.

In the present study, we analyzed the feasibility and the performance of PBV differentiating between patients with and without PE, clarified the correlation between PBV and aPE severity marked by Mastora pulmonary artery obstruction index (PAOI) [8] on CTPA and aimed to provide a complementary approach for the diagnosis, differential diagnosis and prognosis of PE.

**Methods and methods**

**Study population**

This retrospective investigation was approved by the Human Research Ethics Committee of our Institute. Free informed consent was obtained from all participants. All cases of CTPA performed for suspected PE at our emergency or respiratory intensive care unit between 2018 and 2021 were reviewed. All patients were required to have undergone transthoracic echocardiography within 2 hours of computed tomographic angiographic diagnosis of PE. Exclusion criteria were: the use of chemotherapy and vasoactive drugs [6], hepatopulmonary syndrome, pulmonary arteriovenous fistula and standard echo images of inadequate quality.

**CTPA**

Chest CTPA was carried out with commercially available 64 computed tomography scans GE VCT (General Electric Healthcare, Milwaukee, WI, USA) using Omni- paque 350 intravenous contrast. PE scope was evaluated using the Mastora method and PE severity was assessed using the Mastora obstruction score as previous reported [9].

**Conventional ultrasound examination**

The conventional and contrast echocardiographic data were acquired with a commercially available ultrasound system (Philips EPIQ 7C, Netherlands) equipped with an X5-1 PureWave xMATRIX transducer (1-5MHz) at bedside. Left atrial end-systolic anteroposterior diameter (D$_{LA}$), left ventricular end-diastolic anteroposterior diameter (D$_{LV}$), right atrial end-systolic transverse diameter (D$_{RA}$), right ventricular end-diastolic anteroposterior diameter (D$_{RV}$), pulmonary artery diameter (D$_{PA}$), right ventricular fractional area change (FAC$_{RV}$), left ventricular ejection fraction (LVEF) and left ventricular mass index (LVM index), were obtained by real time 2D echo method. Tricuspid annular plane systolic excursion (TAPSE) was obtained by M-mode echo method. The peak early diastolic transmitral filling velocities (E), the peak tricuspid regurgitation velocity (TRV), right ventricular systolic pressure (RVSP), the velocity time integral at right ventricular outflow tract (VTI$_{RVOT}$), and the velocity time integral at pulmonary artery (VTI$_{PA}$) were obtained by the Doppler echo method. The peak early diastolic lateral mitral annulus tissue velocities (E’) were obtained by the Tissue Doppler echo method. Finally, the ratio of E/E’ and ratio of TRV/VTI$_{RVOT}$ were calculated, respectively.

**Real time contrast echocardiography**

All examinations were performed by a single physician experienced with contrast echocardiography. A commercially available second-generation contrast agent, SonoVue® phospholipid- shell sulfur hexafluoride microbubbles (Bracco, Milan, Italy) was used. A total of 59 mg of Sonovue® was diluted in 5 mL of saline according to the manufacturer’s protocol. At the beginning 1 mL of SonoVue® solution was administered intravenously at an infusion rate of about 0.5 mL/s in order to gain a visible ventricular opacification and myocardial enhancement, quickly followed by the administration of 1.5 mL at an infusion rate of about 0.75 mL/min to assure optimal myocardial enhancement. Examination was performed from the apical 4-chamber view and it was ascertained that the right ventricle, left atrium, and left ventricle were clearly visible by adjusting the probe position. Gain, depth, transmit focus, and post-processing were optimized at the beginning of the study and held constant throughout.

The optimal balance between myocardial contrast enhancement and attenuation in our setting was achieved at a very low mechanical index of 0.07. The mechanical index of destructive pulse was set at 1.35. The whole process, i.e., from the gradually visible ventricular opacification to the plateau of myocardial enhancement, and then to the peak replenishment of myocardial Sonovue® microbubbles at consecutive pulsing intervals after a destructive pulse, about 120-135s, was stored digitally.

Image analysis was performed off-line by two experienced operators. The clip containing contrast agent entry and passage through the heart was carefully reviewed. PTT, the time for the SonoVue® contrast agent to travel from the peak opacification in RV to the peak opacification in LV was determined by the time-intensity curves of contrast echocardiography (fig 1). To generate the nPTT value, the PTT was divided by the mean R-R interval (nPTT=PTT/mRR). The mean R-R interval was calculated from the heart rates that were measured by the ECG.
during the contrast studies. Finally, PBV was calculated, according to the formula:

\[
PBV (\text{ml}) = SV_{RV} \times \text{nPTT} = \left( \frac{D_{PA}}{2} \right) \times \pi \times VTI_{PA} \times nPTT [3-5].
\]

Intraobserver and interobserver variability for the measurement of PBV and Mastora PAOI were obtained by repeated, blinded analysis of 20 randomly selected patients after a minimum time interval of 2 weeks.

**Statistical analysis**

Results are expressed as mean ± standard deviation. Differences between the mean values of the 2 groups were analyzed by unpaired \( t \) tests. A receiver operating characteristic curve (ROC) analysis of PBV was used to differentiate between patients with aPE or not, determine the optimal cut-off points and validity parameters. The Pearson correlation analysis was used for determining the significance of correlations between PBV and Mastora PAOI. Bland & Altman was used to measure the inter/intra observer variability. A value of \( p<0.05 \) was considered statistically significant. All statistical analysis was performed with SPSS version 16 software for Windows (SPSS Inc, Chicago, IL).

**Results**

A total of 89 patients underwent CTPA for suspected PE, 57 of whom had positive results for PE, including 13 cases with massive pulmonary embolus, 19 cases with submassive pulmonary embolus and 25 with subsegmental pulmonary embolus. The mean Mastora PAOI was 56.14±33.49 (%), the maximum value was 95%, and the minimum value was 10%.

Differences in baseline characteristics and hemodynamics between the patients with aPE or not are presented in Table I. There was no significant difference in age, sex, diastolic blood pressure as well as the prevalence of chronic obstructive pulmonary disease and malignancy between the patients with aPE or not. Patients with aPE had a faster heart rate, lower systolic blood pressure, higher smoking rate and higher prevalence of hypertension and diabetes than those of patients without aPE.

The bedside echocardiographic measurements were successfully completed in all subjects but 7 ones due to low quality echo images. The echocardiographic characteristics of the entire cohort are presented in Table II. The diameter of RV, RA, RVSP and TRV/VTI RVOT was higher in patients with aPE than in those without \( (p<0.05) \), PTT, R-R interval, nPTT, VTI PA and PBV in patients with PE was significantly less than those in patients without PE \( (p<0.05) \) (also shown in fig 1), while the diameter of LV, LA, PA, LVEF, E/e’, TAPSE, FAC RV, SV RV, and LVM index were not significantly different between the patients with aPE or not \( (p>0.05) \). It is worth noting that PTT, nPTT and PBV in patients with aPE was even less than one half of those in patients without aPE \( (p<0.05) \).

As shown in fig 2A, none of these conventional echocardiographic parameters \( (D_{RV}, D_{RA}, RVSP \text{ and TRV/VTI}_{RVOT}) \) had an area under the ROC curve (AUC) of >0.5 in differentiating between patients with or without aPE. The AUC were 0.458(0.196-0.720), 0.484(0.238-0.730), 0.498(0.254-0.742) and 0.461(0.238-0.684) for \( D_{RV}, D_{RA}, \text{RVSP and TRV/VTI}_{RVOT} \) respectively. The AUC of PBV was 0.997(0.984~1.010) in differentiating between patients with or without aPE (fig 2B). The optimal cutoff value of PBV was 370 ml with a sensitivity of 100%, a specificity of 95.45%, false negative of 0%, false positive

![Fig 1. The comparison of pulmonary blood volume in a patient without pulmonary embolus (A, B, C) and a patient with massive acute pulmonary embolus in the right main pulmonary artery (D, E, F).](image-url)
of 4.55%, positive predictive value of 87.5%, negative predictive value of 100% and accuracy of 96.55%.

The Pearson correlation analysis showed that PBV correlated significantly with Mastora PAOI ($r=-0.897$, $p<0.01$). The linear regression equation was $y=114.5-0.269x$, where $x$ and $y$ represent PBV and Mastora PAOI, respectively (fig 3).

Interobserver and intraobserver agreement for the measurement of PBV and Mastora PAOI was fairly good: intraclass correlation coefficients were all more than 0.95 for interobserver and intraobserver variability.

**Discussion**

This is the first report on the application of PBV for the quantitative diagnosis and differential diagnosis of aPE using contrast echocardiography. It is a practical, feasible, accurate and convenient approach.

In this study, the conventional echocardiographic parameters, such as right ventricular size (represented by $D_{RV}$, $D_{RA}$), pulmonary artery pressure (represented by RVSP) and pulmonary resistance (represented by TRV/VTI$_{RVOT}$) was greater in patients with aPE than in those without aPE. These parameters were expected to be useful in the diagnosis of aPE. However, it was confirmed by ROC analysis that none of them had an AUC of >0.5; that is, none of them could be used in the diagnosis and differential diagnosis of aPE. This finding is consistent with the previous scholars’ claim that conventional echocardiography cannot reliably diagnose aPE [10,11].

Real time contrast echocardiography is a recently developed technique that utilizes low mechanical index to minimize microbubble destruction and permits quantitative measurements of cardiac cavity and myocardial perfusion. In our study, we used a commercially available second-generation contrast agent, SonoVue® phospho-

**Table II. Echocardiographic characteristics of entire cohort**

| Variables | No PE (n=32) | PE (n=57) | p-value |
|-----------|-------------|------------|---------|
| $D_{RV}$, mm | 18.9±5.26 | 25.7±6.9 | 0.03 |
| $D_{RA}$, mm | 32.4±5.58 | 37.8±5.3 | 0.04 |
| $D_{LA}$, mm | 45.8±6.7 | 43.9±5.7 | 0.72 |
| $D_{LV}$, mm | 32.2±5.3 | 33.8±6.2 | 0.69 |
| LVEF, % | 69.5±9.3 | 71.3±8.9 | 0.43 |
| LVM index, g/m$^2$ | 69.6±19.3 | 74.6±20.3 | 0.22 |
| E/E’ | 9.7±6.8 | 7.4±5.5 | 0.06 |
| TAPSE | 22.9±7.5 | 25.7±10.3 | 0.09 |
| FAC$_{RV}$ % | 45.9±10.3 | 49.2±11.5 | 0.18 |
| RVSP, mmHg | 26.3±7.2 | 35.7±9.8 | 0.03 |
| TRV/VTI$_{RVOT}$ | 0.068±0.029 | 0.177±0.043 | 0.04 |
| PTT | 6.98±1.31 | 2.64±1.04 | 0.006 |
| R-R interval | 0.86±0.03 | 0.74±0.03 | 0.04 |
| nPTT | 8.67±1.93 | 3.37±0.16 | 0.001 |
| FAC$_{LA}$ cm | 2.26±1.31 | 2.46±1.55 | 0.06 |
| VTI$_{PA}$ | 22.19±5.69 | 13.49±8.83 | 0.04 |
| SV$_{RV}$ | 65.76±21.95 | 64.08±5.59 | 0.85 |
| PBV | 558.86±159.24 | 211.46±96.75 | 0.003 |

Data are expressed as mean±standard deviation. DBP, diastolic blood pressure; DLA, left atrial end-systolic anteroposterior diameter; DLV, left ventricular end-diastolic anteroposterior diameter; DPA, pulmonary artery diameter; DRA, right atrial end-systolic transverse diameter; DRV, right ventricular end-diastolic anteroposterior diameter; E/E’, the ratio of peak early diastolic transmitral filling velocity (E) and peak early diastolic lateral mitral annulus tissue velocity(E’); FAC$_{RV}$, right ventricular fractional area change; LVM, left ventricular mass; nPTT, normalized PTT, the PTT divided by the mean R-R interval (nPTT=PPT/mRR); PE, pulmonary embolism; PBV, pulmonary blood volume; PTT, pulmonary transit time; RVSP, right ventricular systolic pressure; SVR, right ventricular stroke volume; TAPSE, tricuspid annular plane systolic excursion; TRV, the peak tricuspid regurgitation velocity; VTI$_{PA}$, velocity time integral at pulmonary artery; VTI$_{RVOT}$, velocity time integral at right ventricular outflow tract.
lipid-shell sulfur hexafluoride microbubbles. The microbubbles are haemodynamically inert and have the same size and the same intravascular rheology as red blood cells. They can pass through the right atrium, right ventricle, pulmonary arteries, pulmonary arterioles, capillaries, pulmonary veins and finally reach the left atrium as freely as red blood cells. Using real time contrast echocardiography, the track of contrast agent microbubbles from the right ventricle to the left atrium can be easily monitored, and from which PTT can be measured highly reproducibly and accurately [7,12] and PBV can be calculated according to the formula PTT = PBV/CO [3-5]. Real time contrast echocardiography, in fact, provides a simple method of calculation of the blood volume passing through the pulmonary vascular bed.

In this study, a PeakRV-PeakLV PTT, the time for the SonoVue® contrast agent to travel from the peak opacification in RV to the peak opacification in LV determined by the time-intensity curves of contrast echocardiography, was used, which could fully reflect the maximum open state of the pulmonary vascular bed (i.e., the maximal PBV) according to our previous study (data unpublished). Compared to patients without aPE, a significant reduced PTT and PBV in patients with aPE was consistent with a shorter transit time and less blood flow returned to the left atrium only from the remaining pulmonary vascular bed due to an obstruction of pulmonary embolus. Using ROC analysis, we confirmed that PBV is a powerful marker for the diagnosis and differential diagnosis of PE, with a very high sensitivity, specificity and an accuracy. Moreover, there was significant negative correlation between PBV and Mastora PAOI, which further confirms that PBV can be used in the quantitative diagnosis and differential diagnosis of pulmonary embolism.

Our study had several limitations that that have to be mentioned. First, the sample size was small. It is hard to avoid the deviation of statistical results. Studies based on larger populations would carry more weight. Second, during echo examination, patients with aPE were often being treated with thrombolytic and anticoagulant drugs. These drugs might have an impact on the measurement of PTT and SV_{RV}, and the calculation of PBV. Third, patients with aPE were often accompanied by changes in pulmonary artery resistance, pulmonary artery pressure and right ventricular function, which would further affect the measurement of PTT and SV_{RV}, and the calculation of PBV. Finally, a certain proportion of aPT patients had difficult echocardiographic examinations due to psychomotor agitation or obesity, the limitation of posture and the interference of ECG and other monitoring devices, especially at the level of pulmonary artery. In future, we should try our best to overcome these difficulties.

Conclusions

Our study demonstrated that PBV had a powerful performance in differentiating between patients with or without aPE and a PBV of <370 ml indicated aPE. Contrast combined with conventional echocardiography is enormously useful in an emergency setting because it is readily available and repeatable, is useful in the recognition and differentiation of PE, and is capable of assessing the severity of the PE and the patient’s response to therapy. Although it has some limitations, this study still holds considerable clinical promise for the diagnosis, differential diagnosis and follow-up of aPE.

Conflict of interest: none

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