CTPA pulmonary artery distensibility in assessment of severity of acute pulmonary embolism and right ventricular function

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Abstract
To investigate the characteristics of pulmonary artery distensibility (PAD) in patients with acute pulmonary embolism (APE) and to assess the correlation of PAD with APE severity and right ventricular function. A total of 33 patients who underwent retrospective electrocardiogram (ECG)-gated computed tomography pulmonary angiography (CTPA) with a definite diagnosis of APE were included in the study. According to APE severity, the patients were divided into severe (SPE) and non-severe (NSPE) groups. Data from a control group without APE matching the basic demographics of the APE patients were collected. Pulmonary artery distensibility (PAD) and right ventricular function parameters were compared among the 3 groups, their relationships were investigated, and receiver operating characteristic (ROC) curves were used to determine the sensitivity and specificity of the above parameters for the diagnosis of APE severity. The PAD values of the control, NSPE, and SPE groups were (7.877 ± 2.637) × 10⁻³ mm/Hg, (6.050 ± 2.011) × 10⁻³ mm/Hg, (4.321 ± 1.717) × 10⁻³ mm/Hg, respectively (P < .01). There were statistically significant differences in right ventricular function parameters among the 3 groups (P < .05). The correlation analysis between PAD and right ventricular function parameters showed a weak negative correlation (r = −0.281−−0.392). The area under the ROC curve of PAD was 0.743, the critical value was 4.200, and the sensitivity and specificity were 42.5% and 94.1%, respectively. The PAD obtained by retrospective ECG-gated CTPA could accurately evaluate APE severity and right ventricular function. As the severity of APE increases, PAD decreases, which is helpful to identify patients at high risk of APE.

Abbreviations: LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, NSPE = non-severe pulmonary embolism, PAD = pulmonary artery distensibility, RVEDV = right ventricular end-diastolic volume, RVESV = right ventricular end-systolic volume, SPE = severe pulmonary embolism.

Keywords: acute pulmonary embolism, CT pulmonary angiography, ECG-gating, pulmonary artery distensibility, right ventricular function

1. Introduction
Acute pulmonary embolism (APE) is a common condition associated with high morbidity and mortality.[1] Right ventricular dysfunction is a reliable prognostic predictor, and right ventricular failure is a major cause of death related to APE within 30 days.[2,3] Therefore, a timely and accurate assessment of right ventricular failure and APE severity is of high importance.
In recent years, pulmonary artery distensibility (PAD) has been suggested to be a sensitive and specific marker for pulmonary hypertension, and this is generally measured by cardiovascular magnetic resonance and echocardiography. However, the use of CTPA on PAD is rarely reported. One study showed that PAD measured using ECG-gated CTPA correlated with pulmonary hemodynamics measured by right heart catheterization in subjects with chronic thromboembolic pulmonary hypertension. Our previous research confirmed that retrospective ECG-gated CTPA could be used to evaluate PAD. In this study, we evaluated PAD in patients with APE and assessed its correlation with right ventricular function by retrospective ECG-gated CTPA.

2. Materials and methods

2.1. Subjects

This study was approved by the hospital ethics committee of the First Affiliated Hospital of Hebei North University (IRB2020103), which waived the requirement for written informed consent because of the retrospective nature of the study. All accessed patient data were de-identified.

The study group consisted of patients with suspected APE who underwent retrospective ECG-gated CTPA on 640 slice-volume CT in our institution from May 2016 to May 2019, and all the patients had signed informed consent forms for the examination. Participants were excluded if there were:

1. previous history of serious heart disease, such as valvular disease, cardiomyopathy, congenital heart disease, etc.;
2. previous history of pulmonary hypertension;
3. CTPA showed right ventricular wall hypertrophy; or
4. inadequate CTPA images.

Of all the patients that received CTPA at our institution during the study period, 163 subjects were identified that received retrospective ECG-gated CTPA. After excluding valvular disease (15 cases), cardiomyopathy (3 cases), congenital heart disease (10 cases), previous history of pulmonary hypertension (24 cases), right ventricular wall hypertrophy (11 cases), and inadequate CTPA images (4 cases), a total of 96 subjects were identified.

The APE diagnostic criteria were CTPA showed low-density filling defects, stenosis, or occlusion of pulmonary arteries on more than 2 consecutive slices. There were 33 subjects who met the diagnostic criteria for APE, and 63 subjects without APE. All APE patients were divided into 2 groups according to APE severity: severe PE (SPE) and non-severe PE (NSPE). Patients in the SPE group had at least one of the following clinical manifestations:

1. systolic blood pressure (SBP) <90 mm Hg, >15 minutes;
2. tachycardia >100 beats per minute (bpm), or bradycardia <40 bpm, an SBP drop by >40 mm Hg;
3. partial pressure of oxygen <60 mm Hg; or
4. respiratory rate >25 breaths/minutes.

The control group were selected from the remaining 63 subjects who had no embolisms to approximately match the age, sex distribution and body mass index (BMI) of the APE patients group.

2.2. Scanning protocol

CT scanning was performed using a 640 slice-volume CT (Aquilion ONE, Toshiba Medical Systems Corporation, Tokyo, Japan). The tube current was determined with the automatic exposure control (SUREExposure3D, Toshiba Medical Systems). Tube voltage was manually set by the operator with the default of 100 kVp, and adjusted to 120 kVp when the automatic tube current selected the maximum. Retrospective ECG-gated scanning low-dose mode, heart rate ≤65 bpm: full-dose exposure at 70% to 80% phase (half-dose exposure for other phases); heart rate >65 bpm, full-dose exposure at 30% to 80% phase (half-dose exposure for other phases). Slice thickness: 1 mm, interval: 1 mm. Adaptive iterative dose reduction: AIDR3D, FC43.

The volume of isotonic contrast medium was adapted to the patient’s body weight (1.1 ml/kg) (iodixanol, 320 mgI/ml; Yangtze River Pharmaceutical Group, Taizhou, China) at a rate of 4 ml/second, followed by 30 ml of 0.9% saline solution injected at the same flow rate as the contrast material. With a dual-shot injector (OptiVantageDH, Mallinckrodt, Staines-upon-Thames, UK), the contrast material and saline solution were injected through a 18-gauge intravenous injection catheter inserted into the antecubital vein.

2.3. Reconstruction and measurements

2.3.1. CT image post-processing. Retrospective reconstruction was completed in the 5% to 95% phases at 10% intervals. The 10 sets of images were sent to an image post-processing workstation (Vitrea, Version 6.7.2). To ensure study objectivity, the data were measured by 2 physicians with extensive experience who were skilled in using the software and had no knowledge of patient information, and the mean values were calculated.

2.3.2. PAD evaluation. On the first set of reconstructed images, a cross-section of the main pulmonary artery was identified midway between the origin and its furcation, and it was adjusted to be perpendicular to the long axis in both the axial and coronal planes (Fig. 1). The measurements were repeated on the other 9 image sets. The maximum cross-sectional area (Ss) and minimum cross-sectional area (Sd) of the pulmonary artery were recorded.

In this study, artery distensibility (AD) was chosen to evaluate pulmonary artery elastic properties (i.e., pulmonary artery distensibility [PAD]), which was reported by previous publications:

\[ \text{PAD} = \frac{(S_s - S_d)/S_d}{(\text{SBP} - \text{DBP})} \]

Ss and Sd were defined as maximum luminal area and minimum luminal area, respectively.

SBP: systolic blood pressure. DBP: diastolic blood pressure.

2.3.3. Right ventricular function evaluation. The raw data were transferred to the cardiac function analysis software on the post-processing workstation of Vitrea FX for cardiac function evaluation. Right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) were automatically calculated by the computer. RVEDVLVEDV and RVESV/LVESV ratios were calculated separately.

2.4. Statistical analysis

Data analysis was performed with SPSS 17.0 statistical software (SPSS Inc, Chicago, IL), with P < .05 indicating significant differences. First, normality was assessed with Shapiro–Wilk testing, and homogeneity of variance was determined by Levene tests. One-way analysis of variance (ANOVA) was used to
compare measurements among groups (Welch test used for variance nonhomogeneity), and Least Significant Difference (homogeneity of variance) or Games–Howell (variance nonhomogeneity) tests were carried out for comparisons between groups. χ² tests were used to compare categorical data. The correlations between RVDSV, RVESV, RVEDV/LVEDV, RVESV/LVESV, and PAD were analyzed by Pearson correlation analysis. Receiver operating characteristic (ROC) curve analysis was used to evaluate the accuracy of each parameter to assess APE severity and to determine the best critical point and the sensitivity and specificity.

3. Results

3.1. General clinical information of patients

There were 33 subjects (16 males, 17 females) in the APE group with an age range of 47 to 83 years (mean 65.2 ± 8.7). The mean body mass index (BMI) of these patients was 23.5 ± 3.2 kg/m². This group was further divided into NSPE (17 cases) and SPE (16 cases). The control group included 30 subjects (14 males, 16 females) with an age range of 42 to 73 years (mean 62.0 ± 7.3). The mean BMI of the control group was 23.2 ± 2.9 kg/m². There were no significant differences in age, gender composition, or BMI among the 3 groups. Their basic demographic characteristics were shown in Table 1.

Figure 1. Measurement of cross-sectional area of pulmonary artery. (A) The coronal plane of reconstruction used for cross-sectional area measurement was adjusted to be perpendicular to the pulmonary artery on both (B) sagittal and (C) axial views. The manual measurement of pulmonary artery in (D) systole and (E) diastole.

### Table 1
Comparison of basic data among the three groups.

| Group          | Control | NSPE  | SPE  | F/χ² | P    |
|----------------|---------|-------|------|------|------|
| Sex (female/total) | 16/30   | 9/17  | 8/16 | 0.049 | .976 |
| Age (years ± SD)       | 62.0 ± 7.3 | 63.1 ± 9.1 | 67.5 ± 7.9 | 2.547 | .087 |
| BMI (kg/m² ± SD)        | 23.2 ± 2.9 | 22.7 ± 2.5 | 24.4 ± 3.1 | 1.418 | .250 |
| Smoking status          |         |       |      |      |      |
| Ever-smoker             | 12      | 9     | 10   | 2.244 | .326 |
| Never-smoker            | 18      | 8     | 6    |      |      |
| Hypertension            | 9       | 4     | 4    | 0.297 | .935 |
| Diabetes mellitus       | 2       | 2     | 1    | 0.703 | .843 |

3.2. Comparison of PAD among the 3 groups

The PAD of the control, NSPE, and SPE groups were (7.877 ± 2.637) × 10⁻³ mmHg, (6.050 ± 2.011) × 10⁻³ mmHg, and (4.321 ± 1.717) × 10⁻³ mmHg, respectively (Table 2). There were significant differences among the 3 groups (P < .01).

### Table 2
Comparison of PAD among the three groups.

| Group | Control | NSPE  | SPE  | F     | P    |
|-------|---------|-------|------|-------|------|
| PAD   | 7.877 ± 2.637 | 6.050 ± 2.011 | 4.321 ± 1.717 | 13.161 | .000 |
3.3. Comparison of right ventricular function among the 3 groups

The overall differences of RVEDV, RVESV, RVEDV/LVEDV, RVESV/LVESV between the 3 groups were statistically significant ($P < .05$, Table 3).

Pairwise comparison showed significant differences in RVEDV between the control and SPE groups ($P = .027$) and the SPE and NSPE groups ($P = .042$). There was a significant difference in RVESV between the control and SPE groups ($P = .009$). There were significant differences in RVEDV/LVEDV between the control and SPE group ($P = .004$) and the SPE and NSPE groups ($P = .007$), and for RVESV/LVESV between the control and SPE groups ($P = .020$) and the NSPE and SPE groups ($P = .030$).

3.4. Correlation between PAD and right ventricular function

There was a weak negative correlation between PAD and right ventricular function parameters ($r = -0.281–0.392$, Table 4).

Three decimal five. ROC curve analysis of the diagnostic accuracy of PAD and functional parameters. The areas under ROC curve of PAD, RVEDV, RVEDV/LVEDV, RVESV/LVESV were all >0.7 (Table 5). The area under the ROC curve of PAD was 0.743, the critical value of differentiation was 4.200, and the sensitivity and specificity were 62.5% and 94.1%, respectively (Fig. 2).

4. Discussion

To the best of our knowledge, this is the first study to apply PAD obtained by retrospective ECG-gated CTPA to evaluate APE severity and right ventricular function. There are 2 main findings. First, retrospective ECG-gated CTPA could reflect the characteristics of PAD and right ventricular function in APE patients while accurately diagnosing APE. Second, PAD was related to APE severity and right ventricular function, which helped identify high-risk patients. As APE severity increased, PAD was reduced. There was a slight-to-moderate negative correlation between PAD and right ventricular function parameters in subjects with APE.

APE is one of the leading causes of death in subjects with cardiovascular disease and is commonly encountered in clinical practice. The mortality rate of diagnosed and treated APE ranges from 3% to 8%, but increases to ∼30% for untreated APE.[15] The recommended treatment and prognosis vary widely according to APE severity,[16] so timely risk stratification is essential to optimize patient management.[17] Rapid integration of historical information and physical findings with readily available laboratory data and various imaging examinations including echocardiography and CTPA are necessary for this process.
Studies have shown that ECG-gated CTPA can provide a definitive diagnosis of APE and also reflect cardiac function information such as ejection fraction, RV/LV ratio, wall motion abnormality, and atrial thrombosis. This method is therefore helpful for risk stratification in APE patients, including emergency patients as it is fast and non-invasive.

Our study revealed significant differences in right ventricular function parameters among the 3 groups. The only significant difference in RVESV was between the control and SPE groups. There were significant differences in RVEDV/LVEDV and RVESV/LVESV between the control and SPE groups and NSPE and SPE groups. As APE severity increased, so did the ratios of RVEDV/LVEDV and RVESV/LVESV, which is consistent with previous reports. APE leads to hemodynamic abnormality, presenting as sudden pulmonary hypertension. This event increases the RV after load, which manifests as RV dilation and interventricular septal bulging. The sudden drop of RV cardiac output leads to decreased LV filling. Therefore, the RVEDV/LVED and RVESV/LVESV increase significantly. The ratio parameters eliminated the effects of individual differences and basic cardiac function, which could more objectively reflect right ventricular function impairment. The areas under the ROC curve for the accuracy of RVEDV/LVEDV and RVESV/LVESV in the diagnosis of severe APE were all >0.7, which was helpful to identify severe APE and guide further treatment.

Pulmonary artery elasticity can reflect the degree of pulmonary hypertension and is a powerful predictor of death in patients with pulmonary hypertension. Direct PAD evaluation is only possible with invasive right heart catheterization, which is the current gold standard. Frequent follow-up, screening tests or treatment responses are needed clinically, so an alternative non-invasive method is desirable. CTPA is now widely used in clinical practice. Many studies have demonstrated that this rapid, accurate, and non-invasive method can acquire embolism information for APE and also provide functional RV information. Previous reports confirmed that retrospective ECG-gated CTPA could be used to evaluate PAD. Therefore, this study adopted retrospective ECG-gated CTPA performed with 64 slice-Volume CT to evaluate APE severity and right ventricular function.

PAD values were significantly different among the 3 groups and decreased with greater APE severity. Previous reports described reduced PAD in patients with pulmonary hypertension compared to normal subjects; it was sensitive to early increased vascular resistance in pulmonary hypertension and was a predictor of adverse outcome. The present study found that the pulmonary artery expanded and was difficult to dilate when the pulmonary circulation resistance increased after APE, so PAD decreased. The area under the ROC curve of PAD in the diagnosis of SPE was 0.743 with sensitivity and specificity of 62.5% and 94.1%, respectively, which was helpful for risk stratification. We also found a weak negative correlation between PAD and right ventricular function parameters in APE patients. As PAD decreased, and right ventricular function parameters increased accordingly, indicating that PAD could indirectly reflect impaired right ventricular function in patients with APE.

This study has several limitations. First, the sample size was small, and we did not perform invasive right heart catheterization to evaluate pulmonary artery pressure. Secondly, this study involved exclusively oriental/Chinese subjects and would limit its utility, particularly in terms of generalizing this study to other ethnicities. Thirdly, the method only reflected the elastic characteristics of a certain segment of pulmonary artery, not the entire artery, but the results were quite obvious and reasonable in terms of severity correlation. Furthermore, the patients with heart disease/valvular diseases, existing pulmonary hypertension (in whom the PA is already dilated), and those with right ventricular hypertrophy were also excluded. In the future, a larger population including various pathological states will be assessed to achieve a better understanding of vascular pathology in APE patients.

In conclusion, this study established the feasibility of risk stratification using PAD non-invasively measured with retrospective ECG-gated CTPA. The decrease in PAD with increasing APE severity and the significant negative correlation relationship between PAD and right ventricular function should be taken into account in clinical trials and treatments for APE. The ability of retrospective ECG-gated CTPA to acquire both structural and functional information in APE patients enhances the clinical application of this approach.

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