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# Analysis of elasticity characteristics of ascending aorta, descending aorta and pulmonary artery using 640 slice-volume CT

Fei Yang, MD[a], Dawei Wang, MD[c], Huaijun Liu, MD[a,*], Xiaolong Zhu, MD[b], Dianjun Zou, MD[b], Xiaocan Wang, MB[b], Zhenshun Hu, MD[b], Mengmeng Ji, MD[b], Shujun Cui, MB[b], Yue xiang Zhu, MB[b], Jing Wen, MB[d]

**Abstract**

As the prevalence of coronary computed tomographic angiography (CCTA), it is meaningful that CCTA can provide not only the structural details of artery, but also functional information of vessel elasticity. Our aim was to explore the elasticity characteristics of ascending aorta (AA), descending aorta (DA), main pulmonary artery (MPA), left pulmonary artery (LPA), right pulmonary artery (RPA), and their relationship between each other using 640 slice-volume computed tomography (CT). Furthermore, this study will also observe their relations with age.

A total of 42 subjects that were free of cardiovascular disease, high blood pressure, diabetes, and hyperlipidemia underwent CCTA on 640 slice-volume CT and were enrolled in this study. The subjects were divided into 2 groups: Group 1, age $<46$; Group 2, age $\geq 46$. The aortic distensibility (AD) and aortic compliance (AC) of aorta and pulmonary artery (PA) of each group were compared.

The AD and AC of PA decreased in the following order: MPA, RPA, and LPA. The correlation coefficients of different elastic parameters between different vessels were found to be different. The correlation coefficient of AD between AA and DA, AA and MPA, DA and MPA, RPA and MPA, LPA and MPA, and RPA and LPA were 0.689 ($P=.000$), 0.520 ($P=.000$), 0.393 ($P=.010$), 0.329 ($P=.033$), 0.579 ($P=.000$), and 0.534 ($P=.000$), respectively. The correlation coefficients of AC for the 6 groups mentioned above were 0.351 ($P=.023$), 0.470 ($P=.002$), 0.249 ($P=.112$), 0.190 ($P=.228$), 0.441 ($P=.005$), and 0.409 ($P=.010$), respectively. There was an age-dependent decrease of AD and AC in AA, DA, MPA, LPA ($P<.05$), but no difference in RPA ($P>.05$).

The elasticity characteristics of AA, DA, MPA, LPA, and RPA could be well shown by 640 slice-volume CT. The elasticity relativity was observed and was different between AA and DA, AA and MPA, LPA and MPA, LPA and RPA. An obvious age-related decrease in vascular elasticity was found in AA, DA, MPA, and LPA, which should be taken into consideration in clinical trials and treatments for the elasticity-related cardiovascular diseases.

**Abbreviations:** AA = ascending aorta, BMI = body mass index, BP = blood pressure, CCTA = coronary computed tomographic angiography, DA = descending aorta, DBP = Diastolic blood pressure, LPA = left pulmonary artery, MPA = main pulmonary artery, PA = pulmonary artery, PH = pulmonary hypertension, RPA = right pulmonary artery, SBP = systolic blood pressure.

**Keywords:** aorta, coronary computed tomography Angiography, correlation, ECG-gating, elasticity, pulmonary artery, volume CT

## 1. Introduction

As we know, artery elasticity is an important functional property of vessel and is increasingly used as an important clinical marker in cardiovascular disease prediction and medication therapy evaluation.[1,2] In particular, the artery elasticity indexes aortic distensibility (AD) has been reported to be the best index to reflect different levels of atherosclerosis.[3] The decrease of arterial elasticity is a manifestation of abnormal function.

Similarly, pulmonary artery (PA) is also elastic, which determines pulse pressure and directly affects myocardial workload and ventricular function.[4,5] In addition, acute elevation of PA pressure could reduce the PA elasticity.[6,7] It was found that in the early course of pulmonary hypertension (PH), the PA elasticity decreased, which had considerable pathophysiological implications in PH.[3] Some scholars found that the decreased PA elasticity correlated with mortality in PH patients, which could be used as a strong predictor of mortality in PH.[8–10] Therefore, we can see the important value of PA elasticity in the occurrence and development of the PA-related diseases.

At present, many studies focus on the noninvasive evaluation of arterial elasticity of aorta, carotid artery, and other large arteries, and the main research methods utilized are magnetic resonance imaging (MRI) and ultrasonography.[4,6,7,11,12] Some studies concentrate on PA elasticity using ultrasound and MR,[4,6,7] but the use of computed tomography (CT) on PA elasticity is rarely reported. In our study, retrospective electrocardiograph (ECG)-gated coronary computed tomographic angiography (CCTA) was used to evaluate the functional change of large artery, not just the aorta, but also the PA. According to

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[a] Department of Medical Imaging, The Second Hospital of Hebei Medical University, Shijiazhuang, [b] Department of Medical Imaging, [c] Department of Cardiac Surgery, The First Affiliated Hospital of Hebei North University, Zhangjiakou, [d] Department of CT, Toshiba Medical Systems (China) Co. Ltd., Beijing, China.

[*] Correspondence: Huaijun Liu, Department of Medical Imaging, The Second Hospital of Hebei Medical University, Shijiazhuang 050000, China (e-mail: hiliuhuaijun@126.com).



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literature review, this is the first time for CCTA image data to be applied to evaluating the PA elasticity characteristics and its correlation with aorta, which was a noninvasive assessment of PA elasticity without increasing the patient's radiation dose and the contrast agent dosage. Our hypothesis was that the elasticity characteristics of PA, ascending aorta (AA), and descending aorta (DA) could be well shown by CT, and which were also related to age.

## 2. Materials and methods

### 2.1. Subjects

This study was approved by the hospital ethics committee for scientific research and all patients had signed informed consent of participation.

From October 2015 to April 2016, hundreds of people who were suspected of coronary artery disease or other heart diseases underwent CCTA on 640 slice-volume CT in our institution. We excluded patients with any known disease that may influence or enlarge the aorta and PA including patients with hypertension, diabetes mellitus, known coronary heart disease, lung disease, renal disease, abnormal electrocardiogram, CTA-diagnosed coronary artery disease, pulmonary embolism, PA tumor, received thoracotomy or stent, bypass surgery patients, difficult to cooperate with the examination, allergic to iodine, hyperthyroidism, or history of any known systemic illness. Subjects were excluded if CCTA image quality was poor for the detection because of motion artifacts. Finally, 42 subjects were enrolled in this study, with an age range of 19 to 69 years (mean $46.1 \pm 12.3$), 25 males (mean $42.1 \pm 10.7$; range 19–65), and 17 females (mean $52.1 \pm 12.3$; range 20–69). The height, weight, and body mass index (BMI) of these patients were $166.0 \pm 7.8$ (150–180) cm, 67 $\pm 10.6$ (50–88) kg, and $24.3 \pm 3.2$ (17.7–31.3) kg/m$^2$, respectively. Three cases of left PA (LPA) were not measured because of incomplete scanning range.

The blood pressure (BP) was measured twice before examination and the mean value of the measurements were recorded: systolic blood pressure (SBP) (mean $124.4 \pm 10.1$, range 104–139); diastolic blood pressure (DBP) (mean $79.0 \pm 7.0$, range 65–89); heart rate during scanning (mean $70.98 \pm 10.47$, range 52–101).

According to the research results of relevant domestic literature and national conditions[13,14], the subjects were divided into 2 groups according to their age: Group 1, age <46 (22 cases); Group 2, age ≥46 (20 cases). (With the improvement of people's living standard and the change of lifestyle and diet structure, the incidence of atherosclerosis is becoming younger in China. Previous study had shown that the incidence of acute coronary heart disease in men was increasing rapidly from the age of 35, whereas in women was from the age of 45 in China.[13] The number of acute coronary syndrome patients was the highest in the 65- to 74-year-old group, followed by the 55- to 64-year-old group, the 45- to 54-year-old group, the >75-0year-old group, and the <45-year-old group was the least in China.[14] So this study was grouped at age 45.)

### 2.2. Scanning protocol

CT scanning was performed using a 640 slice-volume CT (Aquilion ONE, Toshiba Medical Systems Corporation, Tokyo, Japan). Patients with a pre-scan heart rate of ≥75 beats per minute were given 20 to 60 mg of metoprolol tartrate tablets orally 1 hour before scanning.

The volume of contrast material was adapted to the patient's body weight. All the patients received 0.7 mL/kg of isotonic contrast medium (iodixanol, 320 mgI/mL; Yangtze River Pharmaceutical Group, China) injected at a fixed duration of 10 seconds, 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, MallinckrodtTyco Healthcare), the contrast material and saline solution were injected through a 18-gauge intravenous injection catheter inserted into the antecubual vein. As soon as the single density level in the descending aorta was enhanced by 150 Hounsfield units (HU) over the baseline, the patient was instructed to take a deep breath and hold it. Five seconds after being triggered, the contrast-enhanced CT scan with retrospective ECG gated technology was undertaken.

The tube current was determined with the help of automatic exposure control (SUREExposure3D, Toshiba Medical Systems) on the basis of x-ray attenuation on anterior-posterior and lateral scout images and the reconstruction kernel. Tube voltage was manually set by the operator with the default of 100 kVp, and adjusted to 120 kVp when the automatic tube current was selected the maximum. The rotation time was 0.35 seconds and z-coverage value was 140 to 160 mm when the entire heart was scanned in a single rotation.

### 2.3. Reconstruction and measurements

**2.3.1. CT Image postprocessing.** Raw data reconstruction was performed using 0.5-mm slices in 0.25-mm intervals, by using kernel FC43, with adaptive iterative dose reduction (AIDR3D, Toshiba Medical Systems) standard. Retrospective trigger reconstruction was completed, in 5% to 95% phases and 10% intervals. The 10 sets of images were sent to an image post-processing workstation (Vitrea, Version 6.7.2).

**2.3.2. Area measurement process PA.** On the first set of images reconstructed, a cross-section of the main pulmonary artery (MPA), right pulmonary artery (RPA), or LPA was obtained midway between the origin and its first anterior branch, and was adjusted to be perpendicular to the long axis on both axial and coronal views (Figs. 1–3).This plane of reformation was then automatically displayed on the other 9 image sets, allowing cross-sections to be manually drawn at every 10% of the cardiac cycle, by using the electronic calipers available on the workstation. ***AA and DA***. The AA and DA were measured on the cross-section of MPA's measurements level (Fig. 4). To ensure the objectivity of this study, the data were measured by 2 physicians who were skilled in using the software and did not know the information of the subjects.

### 2.4. Vascular elasticity evaluation

In this study, 2 different parameters were chosen to evaluate the elastic properties of AA, DA, and PA, including AD ($\times 10^{-3}$ mm/Hg) and aortic compliance (AC, mm$^2$/mmHg), which were reported by previous publications[15]:

$$AD = ([Ss - Sd]/Sd)/(SBP - DBP)$$
$$AC = (Ss - Sd)/(SBP - DBP)$$

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

### 2.5. Statistical analysis

Data analysis was performed with SPSS17.0 statistical software package (SPSS Inc, Chicago, IL). Quantitative

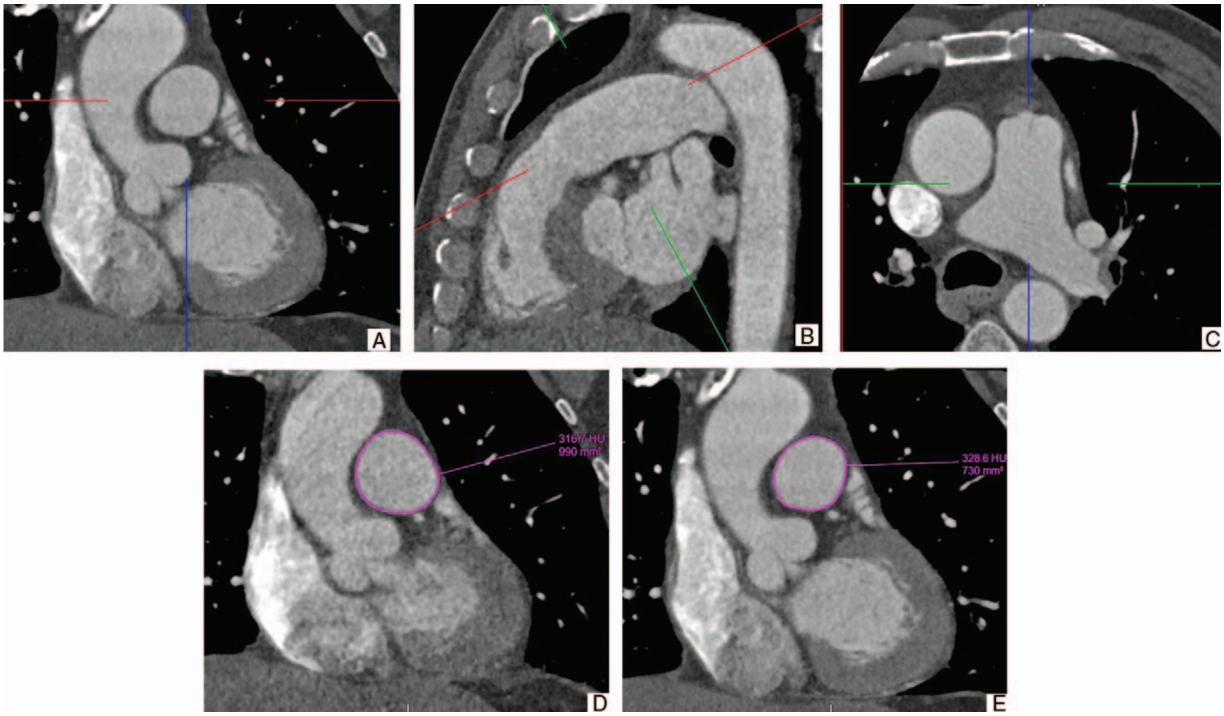


**Figure 1.** Computed tomography reconstruction plane for main pulmonary artery (MPA) cross-sectional area. (A) Coronal reconstruction of MPA cross-section after correction for its double obliquity. The plane of reconstruction used for cross-sectional area measurement was adjusted to be perpendicular to the MPA on both (B) sagittal and (C) axial views. The manual measurement method of MPA at (D) systolic and (E) diastolic.

data were expressed as the mean ± standard deviation (SD) and categorical variables as frequencies or percentage. Differences among groups were tested using independent test. The correlation analysis was performed on the basis of Pearson correlation analysis. Intraclass correlation coefficient was adopted to identify the interobserver differences. Significance was assessed with 2-tailed testing, with $P < .05$ indicating significant difference.

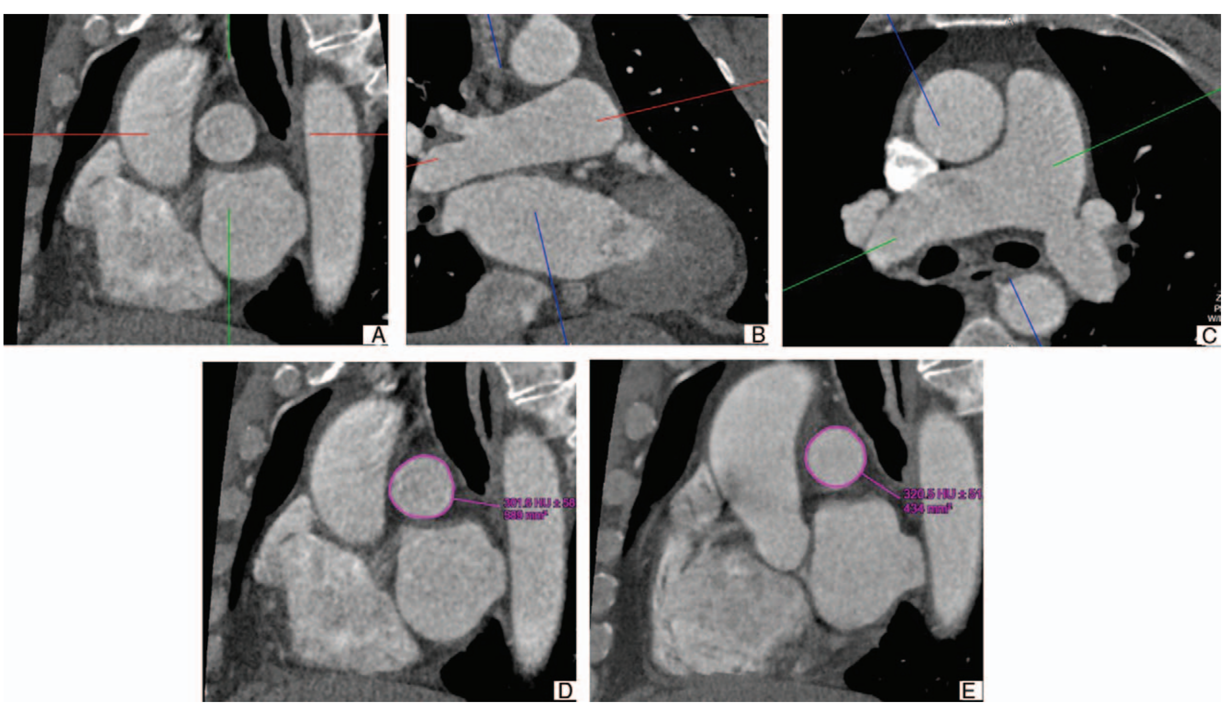


**Figure 2.** Computed tomography reconstruction plane for right pulmonary artery (RPA) cross-sectional area. (A) Sagittal reconstruction of RPA cross-section after correction for its double obliquity. The plane of reconstruction used for cross-sectional area measurement was adjusted to be perpendicular to the RPA on both (B) coronal and (C) axial views. The manual measurement method of RPA at (D) systolic and (E) diastolic.

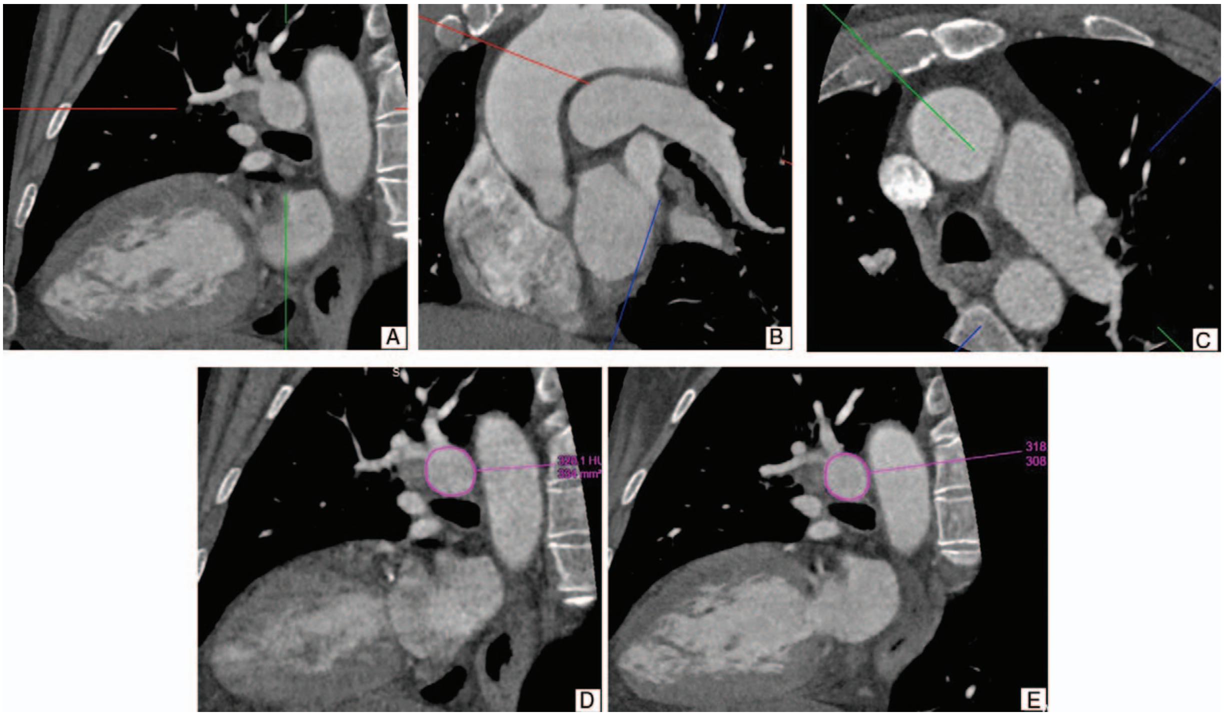


Figure 3. Computed tomography reconstruction plane for left pulmonary artery (LPA) cross-sectional area. (A) Sagittal reconstruction of LPA cross-section after correction for its double obliquity. The plane of reconstruction used for cross-sectional area measurement was adjusted to be perpendicular to the LPA on both (B) coronal and (C) axial views. The manual measurement method of LPA at (D) systolic and (E) diastolic.

## 3. Results

### 3.1. Reproducibility of CT measurements

Interobserver agreement was good (intraclass correlation coefficient >0.75) for measurements of all CT parameters (Table 1). For all parameters *P* was .000.

### 3.2. Elasticity characteristics and association of AA, DA, MPA, LPA, and RPA

The AD and AC of AA, DA, MPA, LPA, and RPA were shown in Table 2.

The AD and AC of pulmonary artery decreased in the following order: MPA, RPA, and LPA.

The correlation coefficients of different elastic parameters between different vessels were found to be different.

**3.2.1. AD.** The correlation coefficient of AA and DA, AA and MPA, DA and MPA, RPA and MPA, LPA and MPA, RPA and LPA, were 0.689 ($P$=.000), 0.520 ($P$=.000), 0.393 ($P$=.010), 0.329 ($P$=.033), 0.579 ($P$=.000), 0.534 ($P$=.000) respectively, which is shown in Table 3.

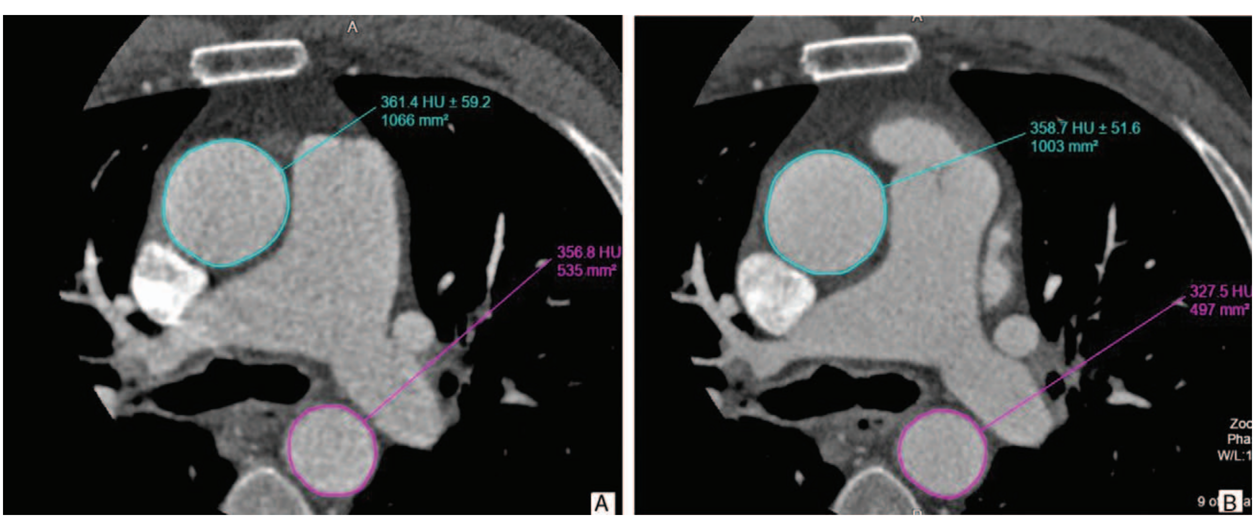


Figure 4. Selection and methods of measurement of AA and DA. The cross-sectional areas of AA and DA were manually measured on the cross section of main pulmonary artery's measurements level at (A) systolic and (B) diastolic.

**Table 1**

**Intraclass Correlation Coefficient (ICC).**

| Parameter | AA | DA | MPA | RPA | LPA |
|---|---|---|---|---|---|
| ICC (AD) | 0.891 | 0.871 | 0.770 | 0.804 | 0.861 |
| *P* (AD) | .000 | .000 | .000 | .000 | .000 |
| ICC (AC) | 0.752 | 0.794 | 0.834 | 0.904 | 0.926 |
| *P* (AC) | .000 | .000 | .000 | .000 | .000 |

AA = ascending aorta, AC = aortic compliance, AD = aortic distensibility, DA = descending aorta, LPA = left pulmonary artery, MPA = main pulmonary artery, RPA = right pulmonary artery.

**Table 2**

**The mean AD of AA, DA, MPA, LPA, and RPA.**

| | AA | DA | MPA | LPA | RPA |
|---|---|---|---|---|---|
| AD | 4.02 ± 2.16 | 3.23 ± 1.46 | 7.94 ± 3.04 | 5.89 ± 3.61 | 7.37 ± 2.77 |
| AC | 2.34 ± 0.78 | 1.09 ± 0.35 | 3.66 ± 1.28 | 1.45 ± 0.97 | 1.94 ± 0.80 |

AA = ascending aorta, AC = aortic compliance, AD = aortic distensibility, DA = descending aorta, LPA = left pulmonary artery, MPA = main pulmonary artery, RPA = right pulmonary artery.

Among them, AA and DA, AA and MPA, LPA and MPA, RPA and LPA, had significant correlation. DA and MPA, RPA and MPA had low correlation.

*3.2.2. AC.* The correlation coefficient of AA and DA, AA and MPA, DA and MPA, RPA and MPA, LPA and MPA, RPA and LPA were 0.351 ($P = .023$), 0.470 ($P = .002$), 0.249 ($P = .112$), 0.190 ($P = .228$), 0.441 ($P = .005$), 0.409 ($P = .010$), respectively. (Table 4).

Among them, AA and DA, AA and MPA, LPA and MPA, RPA and LPA had low correlation. DA and MPA, RPA and MPA, were not linearly related ($P > 0.05$).

### 3.3. Association between age and vascular elasticity

The mean AD and AC of AA, DA, MPA, LPA, RPA in Group 1 and Group 2 were shown in Table 5 and Table 6.

There was an age-dependent decrease of AD in AA ($t = 4.546$, $P = .000$), DA ($t = 3.478$, $P = .001$), MPA ($t = 2.458$, $P = .018$), LPA ($t = 3.038$, $P = .004$), but no difference in RPA ($t = 1.586$, $P = .121$). (Table 5)

There was an age-dependent decrease of AC in AA ($t = 3.467$, $P = .001$), DA ($t = 2.721$, $P = .010$), MPA ($t = 2.029$, $P = .049$), LPA ($t = 2.250$, $P = .030$), but no difference in RPA ($t = -1.038$, $P = .306$). (Table 6)

## 4. Discussion

To the best of our knowledge, this is the first study to assess the ability of 640-slice volume CT to evaluate elasticity of each PA in normal subjects. This study has 3 main findings. First, the elasticity characteristics of AA, DA, MPA, LPA, and RPA could be well shown by ECG-gated 640 slice-volume CT without increasing the patient's radiation dose and the contrast agent dosage. Second, the elasticity relativity was observed between AA and DA, AA and MPA, LPA and MPA, LPA and RPA, which had positive correlation. Third, an obvious age-related decrease in vascular elasticity was found in AA, DA, MPA, and LPA.

Direct assessment of PA elasticity requires pressure measurements, which could only be achieved by invasive right heart catheterization currently. For evaluations of clinically frequent follow-up, screening tests, or treatment responses, it would be desirable to look for an alternative noninvasive method. As a simple and convenient method, ultrasound was firstly chosen in aortic elasticity evaluation. However, the measurement result was influenced by adjacent structures, the operators' experience, and other factors.[15,16] As for MR, measurements are unreliable in situations with complex flow patterns, limited by the long scan time and low spatial resolution and unavailable for patients with unstable situation.[15,17]

Currently, CCTA is now widely used in clinical practice, and many studies have demonstrated that CCTA could not only acquire structural information of cardiovascular system, but also provide functional information, such as the aortic elasticity.[18–22] With 16 cm of craniocaudal coverage per gantry rotation, 640 slice-Volume CT enables scanning of the whole heart in a single heartbeat, thereby eliminates the "stair-step" artifact,[23] and gets a really complete cardiac cycle data which can be reconstructed at any time and the dynamic systolic and diastolic images can be obtained. Therefore, this study adopted retrospective ECG-gated CCTA performed on 640 slice-Volume CT to evaluate the functional information of large arteries without additional contrast doses and radiation doses, not only the aorta, but also the PA, which could be described as "do both."

As we all know, the size of the arterial lumen including AA and DA changes regularly with the heartbeat. In our study, we discovered that PA lumen also changed in the cardiac cycle, so we believed that the PA was also elastic. This is consistent with previous research reports, including echocardiography, MRI, and CT. [4,5,9,24,25] However, the factors of pulse pressure were not taken into account in previous studies on PA elasticity.[25,26] In our research, pulmonary arterial elasticity was defined by the change in cross-sectional area between diastole and systole and

**Table 3**

**The correlation coefficient of AA, DA, and MPA of AD.**

| | AA and DA | AA and MPA | DA and MPA | RPA and MPA | LPA and MPA | LPA and RPA |
|---|---|---|---|---|---|---|
| Correlation coefficient | $r = 0.689$, $P = .000$ | $r = 0.520$, $P = .000$ | $r = 0.393$, $P = .010$ | $r = 0.329$, $P = .033$ | $r = 0.579$, $P = .000$ | $r = 0.534$, $P = .000$ |

AA = ascending aorta, DA = descending aorta, LPA = left pulmonary artery, MPA = main pulmonary artery, RPA = right pulmonary artery.

**Table 4**

**The correlation coefficient of AA, DA, and MPA of AC.**

| | AA and DA | AA and MPA | DA and MPA | RPA and MPA | LPA and MPA | LPA and RPA |
|---|---|---|---|---|---|---|
| Correlation coefficient | $r = 0.351$, $P = .023$ | $r = 0.470$, $P = .002$ | $r = 0.249$, $P = .112$ | $r = 0.190$, $P = .228$ | $r = 0.441$, $P = .005$ | $r = 0.409$, $P = .010$ |

AA = ascending aorta, AC = aortic compliance, DA = descending aorta, LPA = left pulmonary artery, MPA = main pulmonary artery, RPA = right pulmonary artery.

**Table 5**

**The comparison of mean AD of Group 1 and Group 2.**

| | Group 1 | Group 2 | *T* | *P* |
|---|---|---|---|---|
| AA | 5.21±2.32 | 2.71±0.85 | 4.546 | .000 |
| DA | 3.89±1.60 | 2.50±0.85 | 3.478 | .001 |
| MPA | 8.98±3.02 | 6.80±2.69 | 2.458 | .018 |
| RPA | 8.00±3.06 | 6.67±2.28 | 1.586 | .121 |
| LPA | 7.29±3.65 | 4.07±2.71 | 3.038 | .004 |

AA=ascending aorta, DA=descending aorta, LPA=left pulmonary artery, MPA=main pulmonary artery, RPA=right pulmonary artery.

**Table 6**

**The comparison of mean AC of Group 1 and Group 2.**

| | Group 1 | Group 2 | *t* | *P* |
|---|---|---|---|---|
| AA | 2.69±0.81 | 1.95±0.54 | 3.467 | .001 |
| DA | 1.22±0.32 | 0.95±0.34 | 2.721 | .010 |
| MPA | 4.03±1.37 | 3.26±1.06 | 2.029 | .049 |
| RPA | 1.83±0.83 | 2.09±0.76 | -1.038 | .306 |
| LPA | 1.80±1.07 | 1.13±0.76 | 2.250 | .030 |

AA=ascending aorta, DA=descending aorta, LPA=left pulmonary artery, MPA=main pulmonary artery, RPA=right pulmonary artery.

then divided by pulse pressure difference. Our method was more comprehensive, and more consistent with the definition of arterial elasticity.

Our study found that the AD and AC of PA decreased in the following order: MPA, RPA, and LPA, which was consistent with the previous studies.[26] We also found that the elasticity relativity existed between AA and DA, AA and MPA, LPA and MPA, LPA and RPA, which were positively correlated. No similar research had been reported before. The correlation coefficients of different elastic parameters between different vessels were found to be different. Among them, AA and DA, AA and MPA, LPA and MPA, RPA and LPA had correlation. DA and MPA, RPA and MPA, had low correlation in AD, and were not linearly related in AC ($P>.05$). We found no correlation or low correlation between MPA and DA in elasticity. This may suggest that the vascular elasticity of MPA is probably more similar to AA, compared to DA.

In this study, we showed that the aorta and PA elasticity was substantially lower in elderly patients without known vascular disease. This is consistent with Dawes et al's[5] report using cardiac MRI in a large cohort of healthy adults. These studies indicate that PA also degrades with age, which is similar to the systemic circulation.

As we all know, the arteries age gradually, leading to a decrease in elasticity, which is a normal physiological process. In previous studies, different assessment methods were used to evaluate the relationship between age and aortic elasticity, and the aortic elasticity was found to decrease with age.[15,21,27] Some scholars believe that the reason for this effect is the structural reconstruction of arterial wall in pace with age. It was found that the elastic fibers decreased, the collagen increased, intimal calcified and lipid material deposited with the aging process, which resulted in decreased arterial elasticity.[21,28] Thus, that may be the reason why the stiffness of aorta and pulmonary arteries in the older was significantly higher than that in the younger in AA, DA,MPA, LPA in our study ($P<.05$). In addition, there was no age difference in RPA in this study, which may be related to the small sample size or the choice of measurement site.

This study still has several limitations. First, the primary purpose of our study was to put forward a new method for assessing the aortic and pulmonary arterial elasticity in people who do not suffer from aortic and pulmonary arterial disease. However, the subjects of our study were suspected of cardiovascular disease, who were not really a healthy crowd. In addition, the number of subjects who met the inclusion criteria and younger than 30 years or older than 60 years was pretty small. Furthermore, the measuring method could only reflect the elastic characteristics of a certain segment of arteries, but not the entire arteries. Therefore, the results of this study could not be used as a standard of vascular elasticity for healthy population, but the results obtained by this study were quite obvious and reasonable in terms of age dependence and elastic correlation.

Second, this study has used brachial pulse pressure to assess elasticity instead of central blood pressure. However, it was reported that peak systolic and bottom diastolic pressures in the AA can be directly estimated from systolic and diastolic pressures obtained from the upper arm in the senior, which showed no significant difference.[29]

Furthermore, this cohort was exclusively subjects living in plain areas, which limits its applicability to other subjects of different races, living in different regions, and so on, which may influence the elasticity. Sex is not recorded in the study.

In the future, a larger population will be assessed to achieve a better understanding of vascular pathophysiology in healthy and related disease patients.

In conclusion, this study establishes the feasibility and reproducibility of measuring pulmonary arterial and aortic elasticity using retrospective ECG-gated CCTA as a potentially useful noninvasive method. The age-dependent decrease in pulmonary arterial and aortic elasticity and positive correlation relationship were significant and should be taken into account in clinical trials and treatments for the elasticity-related cardiovascular diseases. The ability of ECG-gated CCTA to acquire both structural and functional information in patients suspected of CAD enhances the clinical application of this approach. In addition, the improvements of CT technology and post-processing software will be beneficial to develop this method in the future.

## Author contributions

**Conceptualization:** Fei Yang, Dawei Wang, Huaijun Liu.
**Data curation:** Dawei Wang, Xiaolong Zhu, Dianjun Zou, Xiaocan Wang.
**Investigation:** Xiaolong Zhu, Xiaocan Wang, Mengmeng Ji.
**Methodology:** Huaijun Liu.
**Project administration:** Shujun Cui.
**Software:** Zhenshun Hu.
**Supervision:** Yuexiang Zhu.
**Writing – original draft:** Fei Yang.
**Writing – review & editing:** Jing Wen.

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