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# The value of coronary computed tomography angiography in assessing the cardiac circulation of an outpatient-based population

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**Abstract**

To evaluate the perfusion of coronary circulation and its related factors and the difference in the peak filling times in aortic sinus and coronary sinus by coronary computed tomography angiography (CCTA).

From January 1 to August 1, 2018, 61 outpatients with angina pectoris were recruited, completed a questionnaire about risk factors and underwent CCTA, which was also used to assess the stenosis of different coronary artery segments.

The duration of circulation was 9.50±2.43 seconds in patients with flat T wave, which was shorter than the duration in normal subjects ($P=.021$). However, other cardiovascular risk factors showed no effect on the duration of circulation. In addition, the duration of circulation was closely related to the peak filling time of coronary sinus [$r(s)=0.681$]. We further divided the circulation time difference (delta) values into 3 levels (<6, 6–12, and ≥12 seconds).

It showed that the circulation duration (Y) was associated with:

a. the status of 1st diagonal left anterior descending artery;

b. the status of proximal left coronary artery (LCA);

c. the peak filling time of the coronary sinus;

d. Y=0.597–0.166a–0.045b+0.064c.

Therefore, the cardiac circulation duration was negatively related to the degree of stenosis in the 1st diagonal and proximal LCA.

It compensates for the inability of CCTA to assess circulation at rest simply by determining the peak filling time in the aortic sinus and the coronary sinus. Moderate cardiac microcirculation duration was related to a low incidence of clinical symptoms and electrocardiogram disorders, which was determined mainly by the diagonal and left circumflex branch 1 of LCA.

**Abbreviations:** CAD = coronary atherosclerotic heart disease, CCTA = coronary computed tomography angiography, CMD = coronary microvascular dysfunction, CT-MPI = computed tomography-myocardial perfusion imaging, LCA = left coronary artery, LCA = left coronary artery, LM = left main, PET = positron emission tomography, RCA = right coronary artery.

**Keywords:** computed tomography angiography, coronary circulation, risk factors

## 1. Introduction

The incidence of coronary atherosclerotic heart disease (CAD) is underestimated due to the low sensitivity of coronary computed tomography angiography (CCTA) for the estimation of non-obstructive CAD and coronary microvascular dysfunction (CMD). CMD is present in 50% to 65% of angina pectoris patients with nonobstructive CAD (i.e., patients with >20% but <50% narrowing).[1] At 10 years of follow-up, cardiovascular death or myocardial infarction occurred in 6.7% of women with minimal CAD (i.e., ≤20% diameter reduction) and in 12.8% of women with nonobstructive CAD, which may be a result of CMD.[2] Due to the relatively high occurrence and severity of events in patients with nonobstructive CAD, the incorporation of a noninvasive imaging examination into clinical decision-making can be of great importance for improved identification of CMD.

Myocardial perfusion reserve can be measured noninvasively by coronary sinus flow velocity-encoded cine cardiovascular magnetic resonance, which quantifies the maximal possible increase in myocardial blood flow (above baseline conditions) in response to exercise or pharmacological stimuli and integrates perfusion through both the large epicardial coronary arteries and the microcirculation.[3] In addition, 15O-H2O positron emission

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tomography (PET) can be used to assess the coronary microvascular flow and function of the free diffusion of 15O-H2O.[4,5] Myocardial PET is the gold standard for ischemia assessment and quantification (it also serves as the standard of reference for the fractional flow reserve). However, its use is mainly limited to research because it requires an on-site cyclotron due to the short half-life of the tracer.

Moreover, Williams et al evaluated the diagnostic performance of "snapshot" adenosine stress computed tomography-myocardial perfusion imaging (CT-MPI) and demonstrated its diagnostic value for microvascular dysfunction.[6] Unfortunately, the radiation exposure of subjects increases accordingly[7] and can reach levels of 5.9 mSv (range 1.9–15.7 mSv) in snapshot CT-MPI and 9.2 mSv (range 3.8–12.8 mSv) in dynamic CT-MPI. Furthermore, adenosine administration, which is used for CT-MPI, is still of concern for patients with advanced heart block or asthma, although it has been used in clinical practice.[8] Additionally, CCTA is an excellent noninvasive a priori anatomical imaging assessment for ruling out obstructive CAD.[9] Nevertheless, the detection of functional coronary artery stenosis with CCTA is suboptimal.

In our study, we estimated the perfusion state of the coronary vasculature by determining the duration from the peak of filling of the aortic sinus to that of the coronary sinus by CCTA, and we also explored the supplementary value of CCTA analysis. We aimed to noninvasively quantify myocardial perfusion and microcirculation in addition to traditional parameters via CCTA and to investigate the relationship between these parameters and clinical symptoms as well as the risk factors for atherosclerotic lesions. The evaluation of myocardial perfusion represents an additional clinical application of CCTA, especially in the work-up of suspected nonobstructive CAD.

## 2. Materials and methods

### 2.1. Patient selection and data acquisition

The Ethics Committee at our institution approved this prospective study, and all patients provided written informed consent. Between January and August 2018, 61 outpatients with angina pectoris, regardless of prior history of CAD, were recruited. All patients completed a questionnaire and underwent CCTA. The following exclusion criteria were applied: atrial fibrillation, severe heart rate variations, myocardial infarction history within the last 6 months, liver or renal insufficiency, known allergy to iodinated contrast media, potential pregnancy or currently breastfeeding, and inability to hold one's breath for 10 seconds.

### 2.2. CCTA scan protocol

All patients underwent breath-holding training and were able to maintain their heart rates at less than 70 bpm. CCTA scans were performed on an HD Discovery 750 CT scanner (GE Healthcare, Waukesha, WI). Prior to each CCTA scan, a calcium-scoring scan was first used to determine the minimal z-axis coverage, with the goal of minimizing radiation exposure. Then, test-bolus scans were performed after the application of 15 mL of the iodinated contrast agent IOVERSOL 350 (Optiray$^{TM}$ 350, Guerbet) through a double-cylinder power injector. The infusion rate of the median cubital vein was controlled at 5 mL/s.

The volume helical shuttle unique scan mode was used for scanning with the following parameters: 120 kV and 64x0.625 mm as the scan field-of-view. The tube voltage and current were 100 to 120 kVp and 480 to 550 mA, respectively, according to the patient's body mass index. During data acquisition, the CT scanning bed was continuously shuttled and reciprocated. The z-axis coverage was increased to 312.5 mm, resulting in a z-axis range of 120 mm in 15 seconds. The scanning time in the central region was 1.5 seconds, which is also the upper limit recommended for accurate perfusion studies.

### 2.3. Image analysis

The data from the thin layer of the volume helical shuttle scans were reconstructed. To ensure appropriate density resolution, the image was reconstructed with a layer thickness of 2.5 mm. The reconstructed data generated an image of the corresponding array according to the number of shuttle reciprocations, and each set of images was called a set of passes. Images were transferred to a GE AW4.7 workstation. The volume viewer function of the workstation was selected, the region of interest was drawn, and the CT values in the aortic sinus and coronary sinus of each group of passes were measured. After all, passes of all groups were similarly measured, the scan time corresponding to the group with the highest aortic sinus CT value was recorded on the AW workstation, and the peak time of coronary sinus filling was recorded. The delta values were calculated by subtracting the duration to peak filling in the coronary sinus from that in the aortic sinus, which was used to estimate the cycle time in the cardiac vasculature.

Coronary artery images were divided into 15 segments by 2 experienced readers, who were blinded to the clinical and angiographic characteristics, according to the guidelines of the American Heart Association as follows S1 to S4, proximal, mid and distal right coronary artery (RCA), and posterior descending artery; S5, left main (LM) coronary artery; S6 to S8, proximal, mid and distal left anterior descending artery; S9 to S10, 1$^{st}$ and 2$^{nd}$ diagonal; S11, S13, S15, and S16, proximal, mid, 1$^{st}$ and 2$^{nd}$ distal left coronary artery (LCA); S12 and S14, 1$^{st}$ and 2$^{nd}$ obtuse marginal branch; and S17, intermediate branch.

### 2.4. Radiation dosimetry

The CT dose index (mGy) and dose-length-product (mGy-cm) were recorded automatically by the scanner for the CCTA scans of every patient. The radiation dose was converted to millisieverts by multiplying by the conversion factor of 0.014

**Table 1**

**Patients characteristics in relation to myocardial microcirculation.**

| Parameter | Group N = 61 | Delta values (Δ) | *P* value |
|---|---|---|---|
| Gender, n (%) | Male: 39 (63.9) | 10.00 ± 3.61 | .760[a] |
| | Female: 22 (36.1) | 10.13 ± 3.87 | |
| Age, n (%) | ≤50: 16 (26.2) | 10.63 ± 3.53 | .770[b] |
| | 51–60: 26 (42.6) | 9.52 ± 3.95 | |
| | 61–70: 15 (24.6) | 10.46 ± 3.87 | |
| | 71–: 4 (6.6) | 9.67 ± 1.49 | |
| BMI, kg/m2 | ≤23: 17 | 8.69 ± 2.92 | .311[b] |
| 24.51 ± 2.54 | 23.1–24.9: 23 | 10.88 ± 3.68 | |
| | 25–27.9: 14 | 10.13 ± 4.46 | |
| | 28–: 7 | 10.46 ± 3.35 | |

[a] independent *t* test.
[b] one-way ANOVA.
BMI = body mass index.

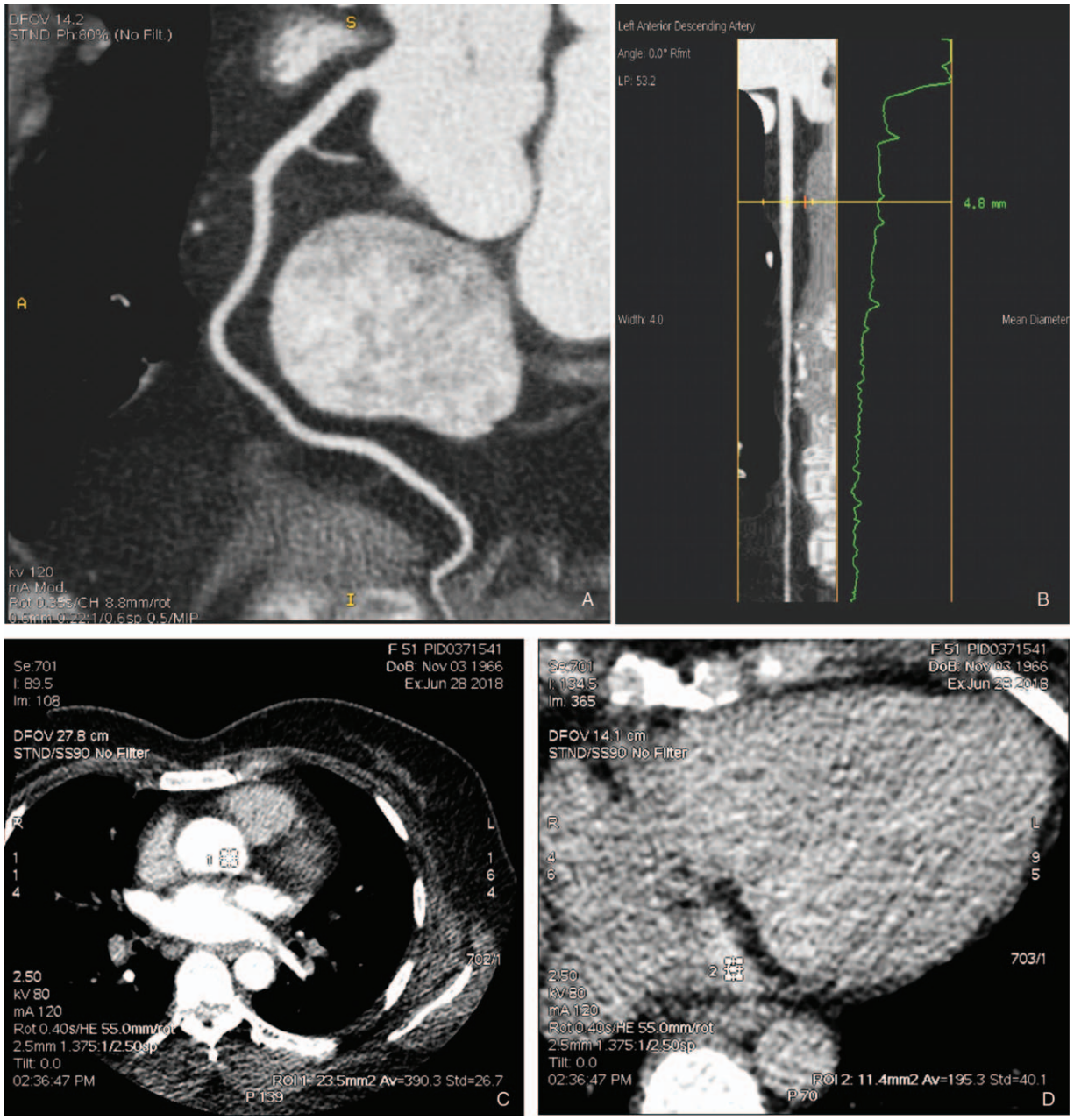


**Figure 1.** Example of coronary artery stenosis and circulation duration assessment. (A) and (B) Surface reconstruction (CPR) images of coronary artery show the semiautomatic measurement of the vascular diameter by the software, which could reveal the coronary artery stenosis and its degree. (C) shows the peak filling time of the aortic sinus. (D) shows the peak filling time of the coronary sinus. The region of interest was selected, and the computed tomography values in the aortic sinus and coronary sinus in each group of passes were measured. After all passes were similarly measured in the groups, the scan times corresponding to the group with the highest computed tomography value of the aortic sinus (C) and the coronary sinus (D) were recorded on the AW workstation. The value of circulation duration was defined as the difference between the peak filling time of the aortic sinus (C) and the coronary sinus (D).

$mSv*mGy^{-1}*cm^{-1}$, as described by the European Working Group for Guidelines on Quality Criteria in Computed Tomography.[10] The average radiation dose was $9.40 \pm 1.22$ mGy (min 7.55, max 11.71).

### 2.5. Quantitative evaluation of coronary artery stenosis

All subjects also underwent coronary artery CT imaging at the same time with the CCTA, so the degree of coronary artery stenosis could be evaluated while measuring the duration of coronary microcirculation. The normal vascular diameter of the proximal point was set as 100%. The degree of stenosis was divided into the following 6 grades according to the percentage of vascular reduction: Grade 0: normal, no coronary artery stenosis; Grade 1: stenosis <25%, often manifested as an irregular lumen; Grade 2: stenosis of 25% to 50%, mild stenosis; Grade 3: stenosis of 50% to 70%, moderate stenosis; Grade 4: stenosis of <99%, nearly full occlusion; and Grade 5: lumen completely occluded with no blood flow observed.

**Table 2**

**Cardiovascular risk factors information of the patients.**

| Cardiovascular risk factors | Yes | No | Uncertain | *P* value[a] |
|---|---|---|---|---|
| Angina pectoris | 11.46 ± 4.45 [7 (11.5)] | 9.93 ± 3.63 [48 (78.7)] | [6 (9.8)] | .592 |
| Electrocardiogram disorder | 9.50 ± 2.43 [12 (19.7)] | 10.57 ± 4.09 [37 (60.7)] | [12 (19.7)] | .021 |
| CAD family history | 10.97 ± 3.65 [14 (23.0)] | 10.16 ± 3.56 [33 (54.1)] | [14 (23.0)] | .907 |
| Hyperlipidemia | 9.21 ± 3.27 [20 (32.8)] | 10.04 ± 3.78 [34 (55.7)] | [7 (11.5)] | .439 |
| Hypertension | 10.25 ± 3.68 [29 (47.5)] | 9.79 ± 3.70 [30 (49.2)] | [2 (3.3)] | .763 |
| Diabetes | 9.95 ± 3.05 [11 (18.0)] | 10.15 ± 3.88 [48 (78.7)] | [2 (3.3)] | .443 |
| Smoking | 9.96 ± 3.17 [18 (29.5)] | 10.42 ± 3.92 [39 (63.9)] | [4 (6.6)] | .606 |

[a] independent *t* test for the value between "Yes" and "No" group.

### 2.6. Statistical analysis

Statistical analysis was performed using SPSS 16.0 software for Windows (Chicago, IL). Continuous variables are expressed as the mean ± SD. One-way ANOVA was used for comparisons of normally distributed variables among different groups. The effects of stenosis in different artery segments on the peak filling time of the aortic sinus (coronary sinus) and the circulation duration were investigated, and a mathematic model was generated by multiple linear regression analysis. A *P*-value $<.05$ was considered statistically significant.

## 3. Results

### 3.1. Study population

Patient characteristics for the study group are shown in Table 1. The mean age was 57.02 ± 9.43 years, and 63.9% (n = 39) of patients were male. There were no significant differences in the delta values of the peak filling times according to the gender, age or body mass index of the groups. The average radiation dose was 9.40 ± 1.22 mGy (min 7.55, max 11.71).

### 3.2. Effect of cardiovascular risk factors on circulation duration

The circulation duration was calculated by the peak filling time in the aortic sinus and the coronary sinus detected through CCTA, which was also used to assess the stenosis of different coronary artery segments (Fig. 1). The circulation duration was 9.50 ± 2.43 seconds in patients with abnormal electrocardiogram (ECG) of coronary insufficiency (Flat T wave, upright T wave is less than 0.2 mV, or less than 1/10 of the same lead R wave) according to the guidelines from European society of cardiology,[11] which was shorter than that of normal subjects ($P = .021$). In addition, other cardiovascular risk factors, such as angina pectoris, family history of CAD, hyperlipidemia, hypertension, diabetes, and smoking, did not significantly affect the delta values of the peak filling times. The details are shown in Table 2 and Figure 1.

### 3.3. The relationship among stenosis of different segments of the coronary artery, the peak filling time of the aortic sinus (coronary sinus) and the circulation duration

The circulation duration was related to the peak filling time of the coronary sinus [r(s) = 0.681 ($P < .001$)], which may be closely associated with the LM coronary artery (S6) [r(s) = −0.251 ($P = .052$)] and the first diagonal branch (S10) [r(s) = 0.248 ($P = .054$)]. The circulation duration was independent of the peak filling time of the aortic sinus, although the latter was significantly associated with the distal RCA (S3) [r(s) = 0.306 ($P = .017$)] (Table 3). Further regression analysis showed that the circulation duration and the peak filling time of the coronary sinus were not affected by vascular status of each segment. However, the peak filling time of the aortic sinus (Y) was associated with the status of S1, S2, S3, S5, and S12 (Table 4). The regression equation was as follows: peak filling time of the aortic sinus (Y) = 16.058+0.854 (S1)–1.421 (S2)+2.251 (S3)+0.606 (S5)–1.013(S12). Therefore, the peak filling time of the aortic sinus was positively related to the degree of stenosis in the proximal RCA (S1), distal RCA (S3) and LM coronary artery (S5). Meanwhile, the peak filling time of the aortic sinus was negatively related to the degree of stenosis in the mid RCA (S2) and 1st OM branch (S12). The peak filling time of the aortic sinus in patients with 25% to 50% arterial stenosis (n = 8) was 20.49 ± 4.39 seconds, which was significantly higher than the value of 17.10 ± 2.18 seconds observed in normal patients ($P = .001$). The peak filling time of the aortic sinus in patients with 50% to 70% arterial stenosis (n = 4) was 16.63 ± 1.87 seconds, which may have contributed to coronary stenting.

We further divided the delta values into 3 levels (<6, 6–12, and ≥12 seconds). Repeated linear regression analysis showed that the circulation duration (Y) was associated with the status of S9 and S11 and the peak filling time of the coronary sinus. The regression equation was updated as follows: circulation duration (Y) = 0.597–0.166(S9)–0.045(S11)+0.064 (peak filling time of the coronary sinus). Therefore, the cardiac circulation duration was negatively related to the degree of stenosis in the 1st diagonal (S9) and proximal (S11) LCA, which are major branches of the LCA.

## 4. Discussion

Human microcirculation is unique due to its capacity to balance the supply of oxygen or nutrients and the metabolic demands of cells through adjusting vascular tone and regulating vasoactive molecules.[12] In recent years, the importance of assessing microvascular function has become evident in research on the pathophysiology of CAD and its risk stratification.[13] Even in the absence of obstructive CAD, patients with angina pectoris usually have a poor prognosis possibly due to CMD occurring at the level of the coronary microcirculation, resulting in vessel diameters <500 μm.[14] The presence of regional ischemia in the microcirculation perfusion area is described as an additional mechanism of myocardial ischemia, especially in patients with ischemia without severe stenosis or without ischemia in the presence of significant stenosis.[15]

**Table 3**

**The correlation analysis on stenosis of different segments of coronary artery, the peak time of artery (vein) and the microcirculation duration.**

| | Peak time of aortic sinus | Peak time of vein | Microcirculation duration | S1 | S2 | S3 | S4S | S5 | S6 | S7 | S8 | S9 | S10 | S11 | S12 | S13 | S14 | S15 | S16 | S17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Peak time of aortic sinus | | 0.037 (0.777) | −0.040 (0.757) | 0.169 (0.192) | 0.152 (0.242) | 0.306 (0.017) | −0.176 (0.175) | 0.000 (0.999) | −0.049 (0.710) | −0.014 (0.913) | −0.097 (0.455) | 0.032 (0.804) | 0.065 (0.618) | 0.0190 (0.142) | 0.101 (0.437) | 0.155 (0.233) | 0.134 (0.302) | −0.005 (0.969) | −0.077 (0.555) | 0.030 (0.818) |
| Peak time of vein | 0.037 (0.777) | | 0.681 (<0.001) | 0.000 (0.994) | 0.109 (0.405) | −0.025 (0.848) | −0.147 (0.259) | 0.021 (0.874) | −0.251 (0.052) | −0.159 (0.220) | 0.106 (0.417) | 0.146 (0.263) | 0.248 (0.054) | −0.061 (0.640) | −0.073 (0.576) | −0.050 (0.702) | 0.033 (0.800) | 0.120 (0.358) | 0.154 (0.236) | 0.113 (0.386) |
| Microcirculation duration | −0.040 (0.757) | 0.681 (<0.001) | | 0.000 (0.999) | 0.037 (0.774) | −0.085 (0.517) | −0.220 (0.088) | −0.121 (0.353) | −0.154 (0.237) | −0.180 (0.164) | 0.025 (0.847) | 0.007 (0.959) | 0.155 (0.232) | −0.126 (0.332) | −0.035 (0.788) | −0.099 (0.450) | 0.048 (0.713) | 0.090 (0.491) | 0.087 (0.503) | −0.038 (0.773) |

The prognostic importance of myocardial microvascular dysfunction has been acknowledged, which has increased studies on the subject, although vessel diameters <300 μm cannot be directly imaged in vivo and can only be assessed by imaging techniques.[3,16] The assessment of myocardial microcirculation was initially performed using invasive techniques, such as coronary angiography[17]; however, the rapid evolution and technological advances in image reconstruction technology have allowed diagnosis of microcirculatory abnormalities in CAD patients using noninvasive methods.[18] These methods range from stress ECGs and myocardial perfusion scintigraphy[19] to PET,[20,21] cardiac magnetic resonance imaging[21,22] and Myocardial contrast echocardiography.[23] Although previous studies have indicated the ultimate potential for CT coronary imaging, they also revealed numerous limitations, such as low spatial and temporal resolutions, longer scan times, and higher radiation doses. Additionally, the need for noninvasive physiological assessment of CMD has facilitated the incorporation of CT and other technologies, such as CT-MPI and multidetector computed tomography (mDCT).[24,25] Due to the key role of the coronary microcirculation in the assessment of myocardial perfusion or ischemia, improvements in technology and methodology are being urgently sought.

The blood supply to the heart passes through the following structures in order: the aorta, aortic sinus, left and right coronary artery, cardiac capillaries, cardiac vein, coronary sinus, and right atrium. To some extent, the aortic sinus and coronary sinus are the beginning and end of the cardiac circulation process. In our study, we analyzed the delta values between the peak filling times of the aortic sinus and coronary sinus in patients using CCTA and their relationship with cardiovascular risk factors or vascular segments, aiming to explore the supplementary application of traditional methods in the field of coronary microcirculation perfusion. Unexpectedly, the delta values were affected by both the macrovascular circulation and capillary microcirculation.

The results showed a relationship between the delta values and the peak filling time of the coronary sinus prior to the aortic sinus, which supported that cardiac circulation was also important in coronary circulation. The underlying mechanism may be complicated. Not surprisingly, the peak filling time of the coronary sinus may not be affected by the status of different segments in the artery. However, the *P*-values found for the LM coronary artery and first diagonal branch (S10) were close to .05. In contrast, the peak filling time of the aortic sinus was positively associated with the degree of coronary artery stenosis in segments with higher diameter, such as S1 and S5, which was negatively related to the stenosis of the main artery branch. This suggests that the peak filling time of the aortic sinus is due to not only the left ventricular dynamics but also the elastic resistance of the posterior vasculature. In addition, if the cardiac perfusion time is determined solely by the peak filling time of the aortic sinus, it may not be possible to distinguish patients with branch stenosis from normal patients, both of whom have a lower peak filling time of the aortic sinus.

Linear regression analysis showed that circulation duration systematics were associated with the status of S9 and S11 and the peak filling time of the coronary sinus. The results suggested that the cardiac circulation duration was negatively related to the degree of stenosis in the major branch of the LCA. As shown in Figure 2, diagonal branch 1 and left circumflex branch 1 were important factors for the cardiac perfusion time. In addition, we attempted to merge and group different durations, which showed

**Table 4**

**A. The status of S1, S2, S3, S5, and S12 were associated with peak time of aortic sinus.**

| | | e | S2 (n) | S12 (n) | S5 (n) | S1 (n) |
|---|---|---|---|---|---|---|
| No stenosis | I | 17.10±2.18[III] (42) | 17.65±3.03 (45) | 17.69±2.90 (49) | 17.75±2.72 (55) | 17.61±3.17 (37) |
| Artery stenosis (%) | II: <25 | 18.83±1.64 (5) | 18.00±0.28 (2) | 18.16±0.81 (2) | 20.74 (1) | 17.13±1.54 (6) |
| | III: 25-50 | 20.49±4.39[I,IV] (8) | 18.46±1.89 (5) | 18.31±2.00 (6) | 14.63 (1) | 18.77±1.87 (8) |
| | IV: 50-70 | 16.63±1.87[III,a] (4) | 17.63±1.33 (5) | 17.73±4.38 (2) | | 17.64±2.59 (7) |
| | V: 70-99 | | | 15.57 (1) | | |
| | VI: >99 | | 14.63 (1) | | | |

[a] Three patients in 4 had been implanted with a coronary stent.

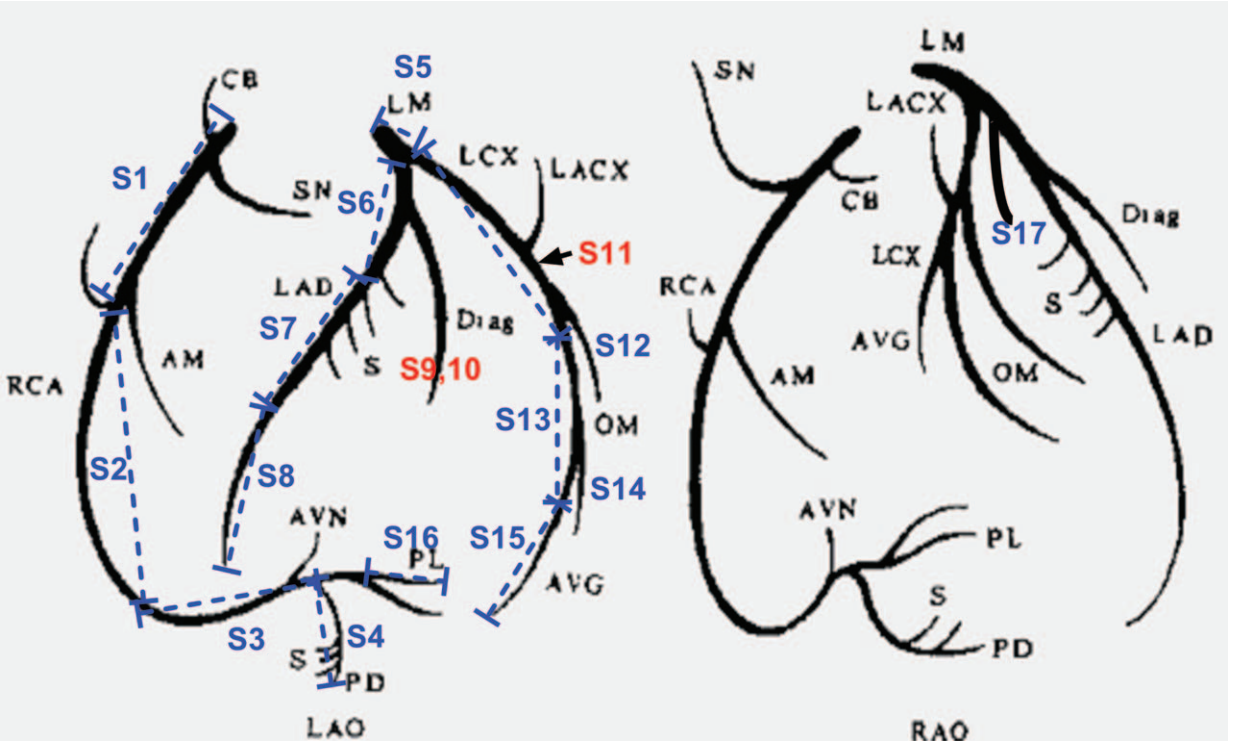


**Figure 2.** The coronary artery segments. The arteries listed in red were associated with the microcirculation duration.

that the group with circulation times of 6 to 12 seconds had a lower incidence of angina pectoris and flat T wave (Supplementary Table, http://links.lww.com/MD/F192); therefore, this seems to be an appropriate range.

Traditionally, CMD is defined as an inadequate adaptation of the microcirculation to increased demand. However, in this study, CCTA was performed at rest and revealed that the flow at rest might indicate the hemodynamic relevance of coronary lesions, which was consistent with the findings of other scholars.[26,27] These views suggest that measurement of the flow at rest may indicate possible pathological changes following inadequate adaptation.

An advantage of this study is that it compensates for the inability of CCTA to assess circulation simply by determining the peak filling time of the aortic sinus. The use of CCTA for the assessment of coronary perfusion has provided novel insights into the pathophysiological role of CAD and CMD in the development of myocardial ischemia. There are still some deficiencies in this study. Due to the limited sample size and possible sampling error, the measured coronary circulation time in this study cannot be considered as generally representative, especially in the patients with coronary microcirculation dysfunction caused by different causes, which need further studies with larger samples and more accurate classification. In addition, the selection of region of interest in image post-processing is also affected by the reliability of human factors, although the data acquisition is determined by the same skilled technician. With the development of large sample population research and the application of artificial intelligence technology in imaging, the above shortcomings are expected to be improved, which will also be our future research direction.

## 5. Conclusion

Moderate cardiac circulation duration, including microcirculation perfusion, calculated by subtracting the peak filling time of

the aortic sinus and from that of coronary sinus, was related to a low incidence of clinical symptoms and ECG disorders. The flow at rest detected by CCTA might indicate the hemodynamic relevance of coronary lesions. The crucial role of diagonal branch 1 and left circumflex branch 1 attracted our attention when assessing the perfusion and function of the coronary circulation. Furthermore, clinical research efforts aimed at a better characterization of the underlying mechanisms could allow development of targeted treatment options.

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## Author contributions

Guisheng Wang conceived and designed the research; Xiaoxia Chen analyzed the data and wrote the paper; Lin Zhao, Jingwei Zhao, Ting Liu, Guoquan Zhao and Wenjuan Han collected the data of patients.

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