

# Increased carotid stiffness detected by ultrafast ultrasound imaging is associated with the Gensini score

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## Abstract

**Aim:** To test the ability of carotid stiffness evaluated by using ultrafast ultrasound imaging to indicate coronary atherosclerosis and its association with the severity of coronary artery disease (CAD). **Material and methods:** This cross-sectional study included 131 patients with CAD and 60 normal controls. Carotid intima-media thickness (cIMT) was measured by two-dimensional ultrasound. Carotid stiffness was determined by ultrafast ultrasound imaging, with which the carotid pulse wave velocity at the beginning (PWV<sub>BS</sub>) and end (PWV<sub>ES</sub>) of systole were calculated. Gensini scores based on coronary angiography were used to estimate the severity of CAD. **Results:** Compared with normal controls, the CAD patients had higher carotid diameters, cIMT, PWV<sub>BS</sub> and PWV<sub>ES</sub> ( $p < 0.05$ ). In the CAD group, Gensini scores correlated significantly with cIMT, PWV<sub>BS</sub> and PWV<sub>ES</sub> ( $r = 0.279$ ,  $p = 0.001$ ;  $r = 0.661$ ,  $p < 0.001$ ;  $r = 0.620$ ,  $p < 0.001$ ; respectively). The multivariate analysis further indicated that PWV<sub>BS</sub>, PWV<sub>ES</sub> and body mass index were independently associated with the Gensini score ( $\beta = 0.466$ ,  $p < 0.001$ ;  $\beta = 0.308$ ,  $p < 0.001$ ; and  $\beta = 0.209$ ,  $p = 0.001$ ; respectively). In addition, the sensitivity and specificity were 54% and 83%, respectively, for PWV<sub>BS</sub> (cutoff value, 6.9 m/s; area under the receiver operating characteristic curve, 0.70) and 64% and 83%, respectively, for PWV<sub>ES</sub> (cutoff value, 8.0 m/s; area under the curve, 0.73). **Conclusions:** Increased carotid PWV<sub>BS</sub> and PWV<sub>ES</sub> detected by ultrafast ultrasound imaging as indices of carotid stiffness might serve as promising indicators for CAD and its severity.

**Keywords:** coronary artery disease; carotid intima-media thickness; pulse wave velocity; arterial stiffness

## Introduction

Coronary artery disease (CAD) ranks as the most common cause of human death worldwide and early detection or screening for CAD is of clinical value in primary prevention, as well as for patient survival [1]. Since atherosclerosis is characterized by the pathologi-

cal feature of systemic inflammation that frequently affects multiple vascular regions in the same patient, the predictive value of carotid atherosclerosis in coronary atherosclerosis has been investigated [2,3]. Previous studies have demonstrated that the carotid intima-media thickness (cIMT), a well-established index for assessing the morphological changes of the arterial wall, was associated with the severity of CAD based on angiography [2,4]. However, increased cIMT is an intermediate stage in the continuum of atherosclerosis and appears more slowly than functional alterations such as vessel stiffening in the early stage of atherosclerosis [5,6]. Hence, precise assessment of the changes in arterial stiffness might be more useful for prediction of coronary atherosclerosis.

Carotid-femoral pulse wave velocity (PWV) is generally accepted as the gold standard for non-invasively

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assessing arterial stiffness [6]. Evidence shows that increased carotid-femoral PWV is independently associated with cardiovascular events that arise from atherosclerosis [7]. Nevertheless, measurement of the carotid-femoral PWV relies on a high level of skill and exposure of the inguinal region, which leads to its limited application in clinical settings [8]. Moreover, its inaccuracy derived from distance measurement and pulse transit time estimation has also been questioned [9,10]. Recently, a new ultrasound technique for arterial stiffness assessment, called ultrafast imaging, has emerged with the technological breakthrough of a significant increase in the imaging frame rate that can reach 10,000 images/s [9,11,12]. Ultrafast imaging enables direct measurement of the local arterial PWV at both the beginning and the end of systole [9,11,12].

The value of ultrafast PWV for evaluating carotid stiffness and its association with atherosclerosis risk have been validated [9,10,12,13]. However, there have been no reports on the evaluation of carotid stiffness using ultrafast PWV in patients with CAD. We therefore performed this cross-sectional study to test the ability of carotid ultrafast PWV to indicate coronary atherosclerosis and to examine its association with the severity of CAD.

## Material and methods

### Study population

The study protocol was approved by the institutional ethics board and written informed consent was obtained from each subject. A total of 150 consecutive patients with clinically suspected CAD, without the presence of the carotid plaque or thickened cIMT ( $>1.0$  mm) [14] by using conventional carotid ultrasound, were admitted to our hospital for coronary angiography between January 2018 and June 2019. All patients underwent carotid ultrafast ultrasound imaging before coronary angiography. Exclusion criteria included negative angiography findings, acute myocardial infarction, history of myocardial infarction, cardiac surgery, stroke, chronic liver and kidney disease or autoimmune diseases. Individuals without evidence of cardiovascular disease, dyslipidemia, diabetes mellitus and smoking and normal physical examination, laboratory testing, electrocardiogram, chest X-ray, echocardiography and coronary computed tomography angiography served as controls.

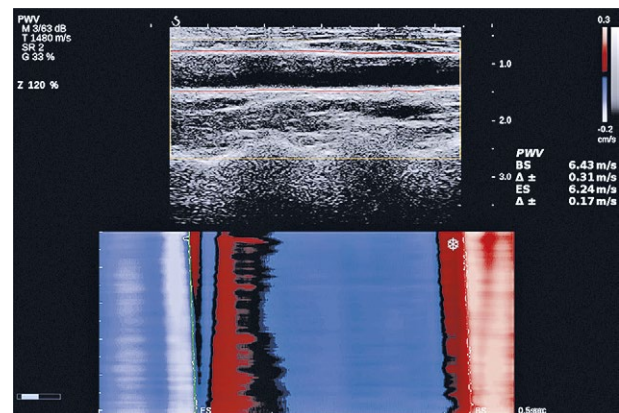
### Ultrafast ultrasound imaging

Consistent with previous studies [9,11], the carotid ultrafast PWV was measured by an Aixplorer ultrafast imaging system (Supersonic Imaging Company, Aixen Provence, France) equipped with a 4- to 15-MHz SL15-4 linear array probe.

Patients were studied in a supine position with their neck fully exposed. The common carotid artery was scanned longitudinally to obtain an ultrasound view of the intima-media layer in B-mode imaging. When the image was optimized, the patients were instructed to hold their breath and the ultrafast imaging acquisition was activated and finished within 2 seconds. After a stable gram of ultrafast PWV formed, a region of interest that was adjusted to cover the whole sonographic view of the common carotid artery was selected. Then, the software automatically tracked and calculated the PWV at the beginning of systole ( $PWV_{BS}$ ) and at the end of systole ( $PWV_{ES}$ ) and their standard deviations (expressed as  $\Delta\pm$ ; fig 1). A  $\Delta\pm$  less than 20% was considered a valid ultrafast PWV acquisition [9]. Three valid measurements of  $PWV_{BS}$  and  $PWV_{ES}$  from each side of the common carotid artery were averaged and the mean value of the two sides was adopted in the final data analysis.

### Coronary angiography

Coronary angiography was applied with each patient using the Judkins approach and standard techniques. Quantitative coronary angiography software (Artis, Siemens AG, Berlin, Germany) was used to assess coronary artery stenosis. Quantitative analysis was performed independently by an experienced cardiologist blind to the results of the ultrasound studies. Atherosclerotic vessel was localized manually and a contour automated detection algorithm detected the edge of lumen. After the detecting quality was verified, the degree of stenosis was



**Fig 1.** The measurement of carotid  $PWV_{BS}$  and  $PWV_{ES}$  using ultrafast ultrasound imaging. The upper panel shows a two-dimensional image of the common carotid artery. The lower panel shows a colour-coded map of relative displacement and relative velocity between the artery anterior wall and the probe within a certain period (red represents the motion towards the probe, blue represents the motion away from probe, and the colour shade represents the velocity magnitude).  $PWV_{BS}$ : PWV at the beginning of systole;  $PWV_{ES}$ : PWV at the end of systole;  $\Delta\pm$ : standard deviation.

automatically analyzed. When coronary atherosclerosis was identified, the Gensini scoring system was used for estimating the severity of coronary atherosclerosis [15,16]. First, the severity of stenosis for each coronary artery was quantified (stenosis of 0 to 25%, 26% to 50%, 51% to 75%, 76% to 90%, 91% to 99% and 100% corresponded to 1, 2, 4, 8, 16, and 32 points, respectively). Then, each lesion score was multiplied by a weighted coefficient representing the importance of the lesion's localization in the coronary circulation (5 for the left main coronary artery; 2.5 for the proximal segments of the left anterior descending artery and the left circumflex artery; 1.5 for the mid-segment of the left anterior descending artery; 1 for the distal segment of the left anterior descending artery, the first obtuse marginal branch, the right coronary artery, and the posterior descending artery; and 0.5 for the other segments). Finally, the Gensini scores were calculated by summation of the individual coronary segment scores.

**Laboratory tests**

For blood biochemical analysis, serum glucose, total cholesterol, triglycerides, low-density and high-density lipoprotein cholesterol, alanine transaminase and creatinine were measured with the Cobas 8000 automatic biochemical analyser (Roche Diagnostics, Mannheim, Germany) after 10 h of overnight fasting.

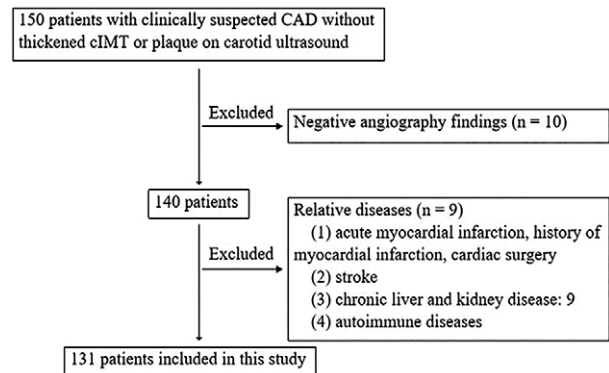
**Statistical analysis**

The Kolmogorov–Smirnov test was used to confirm the normal distribution of continuous variables. Continuous data are presented as the mean ± standard deviation. A two-sample t-test was used to compare continuous data between the study group and the control group. Pearson linear correlation was utilized to assess the association between carotid parameters and Gensini scores. Multivariate linear regression was utilized to identify the independent associates of Gensini scores, and variance inflation factors were used to assess the multicollinearity. The sensitivity and specificity of PWV<sub>BS</sub> and PWV<sub>ES</sub> for predicting CAD were determined by using receiver operating characteristic curve analysis. The cutoff values for diagnostic indexes were determined when the Youden index attained its maximum. The data were analysed using SPSS Statistics 23.0 (IBM, Armonk, NY, USA). p values <0.05 were considered statistically significant.

**Results**

**Characteristics of the study population**

According to the exclusion criteria, 10 patients with negative angiography, 5 patients with chronic kidney dysfunction and 4 patients with chronic liver dysfunction were excluded and the final study group consisted



**Fig 2.** Flow diagram of the patient identification process. CAD: coronary artery disease; cIMT: carotid intima-media thickness.

**Table I.** Characteristics of the study population

	<b>CAD</b>	<b>Controls</b>	<b>p value</b>
Age (y)	58±13	55±10	0.080
HR (bpm)	72±11	69±10	0.088
Height (mm)	166.3±6.9	166.7±6.3	0.691
Weight (kg)	67.6±12.7	59.0±7.4	<0.001
BMI	24.3±3.7	21.1±1.9	<0.001
SBP (mm Hg)	137.1±14.0	115.3±7.6	<0.001
DBP (mm Hg)	81.4±11.6	78.1±7.3	0.018
GLU (mmol/L)	6.4±2.7	4.8±0.6	<0.001
TC (mmol/L)	4.3±1.9	3.9±0.7	0.036
LDL (mmol/L)	2.2±0.9	2.0±0.6	0.016
HDL (mmol/L)	0.9±0.2	1.3±0.3	<0.001
TG (mmol/L)	1.9±2.6	1.0±0.2	0.001
ALT (U/L)	22.28±18.2	16.4±6.3	0.001
Cr (umol/L)	72.5±17.1	54.5±9.2	<0.001

Data are presented as the mean±standard deviation. CAD: coronary artery disease; HR: heart rate; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GLU: serum glucose; TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglycerides; ALT: alanine transaminase; Cr: creatinine.

of 131 patients (85 males, mean age: 58±13 y, range: 35-80 y). The screening process was detailed in Figure 2. Sixty normal subjects (41 males; mean age 55±10 y; range 40-77 y) were recruited as the controls. The clinical characteristics of CAD patients and controls are listed in Table I. No statistically significant differences were found with respect to age, heart rate or height between the two groups. The weight, body mass index, blood pressure, serum glucose, serum cholesterol, low-density lipoprotein cholesterol, triglycerides, alanine transaminase and creatinine were higher in CAD patients than in controls. High-density lipoprotein cholesterol was lower in CAD patients than in controls.

### Carotid parameters and the Gensini score

The carotid parameters of the two groups are outlined in Table II. Carotid diameter, cIMT, PWV<sub>BS</sub> and PWV<sub>ES</sub> were higher in CAD patients than in controls. The Gensini score in CAD patients ranged from 2 to 180 and the mean score was 29±29. After controlling for systolic blood pressure, serum glucose, total cholesterol, low-density lipoprotein cholesterol, creatinine, PWV<sub>BS</sub> and PWV<sub>ES</sub>, the results indicated that PWV<sub>BS</sub> and PWV<sub>ES</sub> were independently associated with CAD ( $\beta=0.607$ ,  $p=0.045$ ;  $\beta=0.440$ ,  $p=0.015$ ; respectively).

### Correlation between ultrafast PWV and the severity of CAD

The correlation coefficients between ultrafast PWV and Gensini score in CAD patients are shown in Table III. A significant correlation was found between PWV<sub>BS</sub> and PWV<sub>ES</sub> and Gensini score. There was a significant but weak association between cIMT and Gensini score. No significant relationship was found between carotid diameter and Gensini score. After controlling for age, body mass index, systolic blood pressure, serum glucose, serum cholesterol, PWV<sub>BS</sub> and PWV<sub>ES</sub>, the results indicated that PWV<sub>BS</sub>, PWV<sub>ES</sub> and body mass index were independently associated with the Gensini score ( $\beta=0.466$ ,  $p<0.001$ ;  $\beta=0.308$ ,  $p<0.001$ ; and  $\beta=0.209$ ,  $p=0.001$ ; respectively).

### Receiver operating characteristic curve analysis

The sensitivity and specificity were 54% and 83%, respectively, for PWV<sub>BS</sub> (cutoff value, 6.9 m/s; area under the receiver operating characteristic curve, 0.70) and 64% and 83%, respectively, for PWV<sub>ES</sub> (cutoff value, 8.0 m/s; area under the curve, 0.73).

## Discussion

Our study showed that the increased carotid PWV<sub>BS</sub> and PWV<sub>ES</sub> detected by ultrafast ultrasound imaging could be used as indices of carotid stiffness in CAD patients. We also found that carotid PWV<sub>BS</sub> and PWV<sub>ES</sub> were independent determinants of the Gensini score, indicating the diagnostic value of carotid ultrafast PWV for predicting CAD severity.

PWV is defined as the velocity with which the pressure wave, generated by cardiac ejection, propagates along the arterial wall [11]. PWV is directly linked to the elasticity of the artery along which it propagates and serves as a classic indicator of arterial stiffness [11]. Since PWV is calculated as the distance propagated between the two recording sites divided by the propagation time, it can be measured at different sites of the arterial tree [17,18]. The PWV measured between the carotid and the femoral site is presently considered the gold standard

Table II. Carotid parameters in patients with coronary artery disease and controls

	CAD	Controls	p value
Dist (mm)	6.7±0.8	5.3±0.6	<0.001
cIMT (mm)	0.8±0.2	0.6±0.1	<0.001
PWV <sub>BS</sub> (m/s)	7.3±2.3	5.9±1.4	<0.001
PWV <sub>ES</sub> (m/s)	8.7±2.9	6.7±1.9	<0.001

Data are presented as the mean±standard deviation. CAD: coronary artery disease; Dist: systolic carotid diameter; cIMT: carotid intima-media thickness; PWV<sub>BS</sub>: the pulse wave velocity at the beginning of systole; PWV<sub>ES</sub>: the pulse wave velocity at the end of systole

Table III. Correlation coefficient between ultrafast pulse wave velocity and Gensini score in patients with coronary artery disease

	Gensini score	p value
Dist (mm)	0.082	0.359
cIMT (mm)	0.279	0.001
PWV <sub>BS</sub> (m/s)	0.661	<0.001
PWV <sub>ES</sub> (m/s)	0.620	<0.001

Data are presented as the mean±standard deviation. Dist: systolic carotid diameter; cIMT: carotid intima-media thickness; PWV<sub>BS</sub>: the pulse wave velocity at the beginning of systole; PWV<sub>ES</sub>: the pulse wave velocity at the end of systole.

for non-invasive assessment of aortic stiffness [19]. The independent value of PWV for predicting cardiovascular events, including primary coronary events, has also been demonstrated in various studies [13,19]. Although well accepted in clinical situations, the measurement of carotid-femoral PWV is still limited by imprecision and complexity caused by the arterial path and pressure dependency [20].

With the development of temporal resolution in new ultrasound techniques, ultrafast ultrasound imaging has recently emerged and become a promising modality to assess regional PWV [20,21]. Ultrafast ultrasound imaging captures the pulse wave propagation time from the beginning to the end of systole, using a sampling rate of over 10,000 frames/s [9,11,12]. The feasibility of ultrafast ultrasound imaging for assessing carotid stiffness, as well as the clinical value of carotid ultrafast PWV in pathological situations such as carotid atherosclerosis, hypertension, diabetes, and vascular Ehlers-Danlos syndrome, have been validated in previous studies [9,10,12,13,22]. To our knowledge, this is the first study to evaluate the role of carotid ultrafast PWV in prediction of coronary atherosclerosis and its association with the severity of CAD.

With the concept that atherosclerosis is a systemic condition, the relationship between coronary and carot-

id arterial diseases is commonly accepted [23]. CIMT, the traditional screening index for atherosclerotic cardiovascular disease, is useful for predicting the risk of CAD and its degree [4,14]. This concept is consistent with part of our results, which showed that cIMT was significantly correlated with the Gensini score. Furthermore, we found that the carotid ultrafast PWV was significantly related to the Gensini score in patients with CAD without a thickened cIMT. Moreover, the relationship between cIMT and Gensini score was weaker than that between carotid ultrafast PWV and Gensini score. Therefore, our results likely suggest that carotid ultrafast PWV might be more sensitive than cIMT for indicating CAD and of clinical value in identifying CAD patients without thickened cIMT. Recently, by comparing the differences in carotid ultrafast PWV between the thickened and non-thickened cIMT subgroups in individuals with atherosclerosis risk, Zhu et al found that carotid ultrafast PWV levels increased in the two groups, which indicated that the carotid ultrafast PWV, representing the vessel stiffness, was possibly altered earlier than cIMT during the process of atherosclerosis development [10]. The above evidence implicates the incremental diagnostic value of ultrafast PWV in atherosclerotic cardiovascular risk stratification.

According to the principle of the largest Youden exponent, we further obtained diagnostic cutoff values of 6.9 m/s and 8.0 m/s for  $PWV_{BS}$  and  $PWV_{ES}$  to predict CAD, respectively. We found that the sensitivity and diagnostic accuracy of  $PWV_{ES}$  were higher than those of  $PWV_{BS}$ . Previous studies have suggested that early wave reflections could interfere with the local  $PWV_{BS}$  measurement, leading to a lower reproducibility than that of  $PWV_{ES}$  [20,24,25]. Therefore, the finding might be partly explained by the fact that regional  $PWV_{ES}$  is more accurately estimated than  $PWV_{BS}$  [10]. Hence, our results likely indicate that  $PWV_{ES}$  is a stronger predictor of artery stiffness than  $PWV_{BS}$  and could probably be used to screen populations at a high risk of CAD.

The study has limitations. First, the retrospective nature and relatively small sample size of the study may lead to selection bias. In addition, the ultrafast PWV was not compared with the traditional carotid-femoral PWV for measuring local carotid stiffness in this study. Although the ultrafast PWV seems technically superior to the carotid-femoral PWV, more studies that compare the two modalities within different diseases are still expected to confirm the practicability and efficacy of ultrafast ultrasound imaging. Finally, coronary angiography is considered the “gold standard” for the diagnosis of CAD, but the normal controls in our study were classified as no CAD by using clinical materials and non-invasive testing rather than coronary angiography, since they could

not reach the indication to receive the invasive coronary angiography. According to ESC guidelines [26], subjects without clinical manifestation and positive non-invasive testing could be considered as individuals with no CAD. Based on these above, although without coronary angiograms, subjects without clinical manifestation and positive non-invasive testing were included in our normal control group. Therefore, the cutoffs for PWV to differentiate between CAD and no CAD subjects in our study may be of relatively high validity.

## Conclusions

Increased carotid  $PWV_{BS}$  and  $PWV_{ES}$  detected by ultrafast ultrasound imaging as indices of carotid stiffness might serve as promising indicators for CAD and its severity.

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**Conflict of interest:** None.

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