Preliminary study of carotid variables under ultrasound analysis as predictors for the risk of coronary arterial atherosclerosis

Wen-Bin Cai MD1,2 | Yi Wang MS1,3 | Jia Wang MD1 | Wan-Gang Guo MD4 | Yun-You Duan MD1 | Li Zhang MD1

1Department of Ultrasound Diagnostics, Tangdu Hospital, The Fourth Military Medical University, Xi’an, China
2Department of Ultrasound Diagnostics, General Hospital of Tibet Military Region, Lhasa, China
3Disease Surveillance Division, Jiangsu International Travel Healthcare Center, Nanjing, China
4Department of Cardiology, Tangdu Hospital, the Fourth Military Medical University, Xi’an, China

Correspondence
Li Zhang, Department of Ultrasound Diagnostics, Tangdu Hospital, The Fourth Military Medical University, 569# Xinsi Road, Baqiao District, Xi’an, China. Email: lilyzhang319_20@hotmail.com

Wen-Bin Cai and Yi Wang contributed equally to this work.

Abstract

Background: Carotid atherosclerosis by ultrasound scanning can be considered as an ideal window to reflect systemic artery atherosclerosis, which has aroused wide concern for predicting the severity of coronary artery atherosclerosis clinically. Ultrasound radio frequency (RF) data technology has enabled us to evaluate the carotid structure and elastic function precisely, for predicting the severity of coronary artery atherosclerosis.

Methods: Patients with suspected coronary artery disease (CAD) underwent coronary angiography and were assigned to four groups according to whether atherosclerotic plaque was found or not and it caused stenosis. Carotid artery intima-media thickness (IMT) and arterial stiffness were investigated by quality intima-media thickness (QIMT) and quality arterial stiffness (QAS) techniques during ultrasound scanning. Univariable and multivariable modeling were used to investigate correlations of carotid parameters to coronary artery atherosclerosis. Receive operating characteristic (ROC) curves were used to evaluate diagnostic performance of these ultrasound variables.

Results: Carotid IMT and stiffness variables pulse wave velocity (PWV), α, β and compliance coefficient (CC) were statistically different between every two-group’s comparisons. IMT correlated with stiffness variables significantly with $r = 0.70, 0.77, 0.63,$ and $−0.39$, respectively. All variables correlated with the severity of coronary atherosclerosis with the odd ratio (OR) of $1.73, 1.67, 1.23,$ and $0.56$ accordingly as IMT, PWV, α, β and CC were concerned. The AUC of IMT, PWV, α, β and CC were $0.9257, 0.8910, 0.8016, 0.9383, 0.8581$ with correctly classified rate of $88.16\%$, $83.77\%$, $78.07\%$, $86.84\%$, and $81.58\%$, respectively.

Conclusions: Carotid artery IMT and stiffness variable PWV, α, β and CC presented favorable predicting and differentiating values for patients with coronary atherosclerosis of different severity.

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1 | INTRODUCTION

Coronary atherosclerosis is the leading cause of CAD, while confined to the professional requirement of coronary angiography, it is hard to evaluate coronary artery through an easy and fast way for routine screening. Many studies and clinical cases have shown that atherosclerosis is a systemic disease; coronary atherosclerosis and carotid atherosclerosis have the same risk factors and pathological basis, and are closely related to each other in occurrence and development. The clinical evaluation of carotid IMT and stiffness is the preferred means for predicting coronary atherosclerotic lesions.1–4

Ultrasound RF data technology is a newly developed method for quantitative evaluating IMT and arterial stiffness structurally and functionally based on the monitoring of RF signals transmitted by ultrasound with good reproducibility and much higher accuracy.5–8 Reports on the relationship between large arterial structures and elastic indexes in cardiovascular (CV) events indicate the possibility of early detection of CAD noninvasively.5,9,10 In the present study, we adapted this method for analyzing carotid artery with the aim of assessing the relationship of carotid arterial wall changes with coronary atherosclerotic severity in patients with CAD who were verified by coronary angiography. The diagnostic performance of the carotid variables in predicting coronary atherosclerosis was validated preliminarily.

2 | METHODS

2.1 | Patients and grouping

From April 2018 to September 2020, 228 consecutive patients with suspected CAD (146 men and 72 women; mean age, 55.30 ± 10.73 years) who had the symptom of chest tightness or chest pain, ST-T changes of ECG and positive exercise treadmill test were assigned to take coronary angiography for assessing coronary atherosclerosis were enrolled as study subjects in the study. Those presenting with diabetes, nephropathy and carotid stenosis ≥50% were excluded from the study for the consideration of keeping a comparative independence for each disease. The subjects were divided into four groups according to the results of coronary angiography: patients without atherosclerotic plaque in coronary artery were considered as normal ones (n = 54); patients with coronary atherosclerotic plaques but arterial stenosis <50% were grouped as atherosclerotic group (n = 41); patients with atherosclerotic plaques, which caused arterial stenosis ≥50% in one major coronary artery were named as single-vessel lesion group (n = 55); patients with more than one coronary arteries stenosis ≥50% caused by atherosclerotic plaques were called as multivessel lesion group (n = 78).

Prior to ultrasonography, patients underwent a physical examination, and the following physical and laboratory parameters were assessed: body mass index (BMI), body surface area (BSA), smoking status, low density lipoprotein (LDL), high density lipoprotein (HDL) and clinical blood pressure, which was determined by performing three measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as SBP > 140mmHg and DBP > 90mmHg. The investigation conforms to the principles outlined in the Declaration of Helsinki. All subjects included in the study provided written informed consent. The study protocol was approved by the ethics committee of the Fourth Military Medical University Tangdu Hospital (Xi’an, China) and all the methods were performed in accordance with the relevant guidelines and regulations.

2.2 | Coronary angiography

All patients had previously undergone a coronary angiography by an experienced physician with a Digital Subtraction Angiography System (GE INOVA3100, GE Healthcare) due to a suspicion of CAD. The narrowing caused by the most severe lesion in each coronary artery was recorded. Significant stenosis of the major coronary arteries was used to classify the patients as having single vessel or multivessel lesions.

2.3 | Ultrasound examination

Ultrasound examinations were conducted with a Mylab Twice color Doppler ultrasound diagnostic system (Esaote, Firenze, Italy), using a 5–13 MHz vascular probe, LA523, with built-in QIMT and QAS analysis software. Each patient was placed in the supine position, and the common carotid artery (CCA), carotid bulb and portions of the internal carotid arteries on both sides were scanned. The region of interest (ROI) was defined as 30 mm proximal to the beginning of the dilation of the bifurcation bulb.

Examination of the CCA was performed by two experienced ultrasound physicians who had been trained in vascular screening. The physicians were blinded to any clinical information about the subjects.

2.3.1 | QIMT analysis

Similar to our previous study,11 subjects were placed in the correct position, so that the CCA was shown in longitudinal view. The ultrasonographic imaging was focused on the QIMT measurement site, ensuring that the anterior and posterior walls of the CCA were clearly shown. The IMT was measured at ROIs, which were plaque-free sites of the CCA. Atherosclerotic plaque was defined as a lesion with a focal...
FIGURE 1  QIMT analysis of CCA. The red line represents the RF signal tracking the leading edge of the lumen-intima boundary; the green line represents the RF signal tracking the leading edge of the media-adventitia interface. IMT and vascular diameter were calculated automatically for six cardiac cycles shown on the left side of the picture.

IMT ≥1.5 mm, with localized protrusion of the vessel wall into the lumen. The QIMT function was started, and a radiofrequency signal tracked the leading edge of the lumen-intima boundary to the leading edge of the media-adventitia interface at the posterior wall of the selected vascular segment. The software automatically acquired six cardiac cycle measurements of QIMT (Figure 1). When the standard deviation (SD) value became less than 15, the image was frozen and stored for further analysis.

2.3.2 QAS analysis

QAS measurements were carried out at the same time as QIMT measurements.11 A RF signal tracked the vascular wall (the red line), and another signal tracked the motion of the vascular wall (the green line) for at least six cardiac cycles. The mean and SD values were calculated automatically; again, images were frozen when the SD value became less than 15 (Figure 2). A derived carotid pressure waveform was calibrated by brachial end diastolic and mean arterial pressure, which allowed the calculation of the arterial stiffness, including pulse wave velocity (PWV, m/s), compliance coefficient (CC, mm²/kPa), α and β. Variable β was normalized on the carotid artery diameters.

2.4 Statistical analysis

All continuous variables were expressed as mean ± SD. The χ² test was used to compare the distributions of the studied variables between two groups for categorical data. One-way ANOVA was used to calculate the difference among groups for continuous variables with normal distribution. The Wilcoxon rank-sum test was used to determine the difference between the two groups for continuous variables with non-normal distribution. The reproducibility of the arterial stiffness measurements was tested in the younger subjects of normal group, and the intra- and inter-observer variability was assessed by linear correlation analysis and Bland-Altman plots. Smoking was stratified into two categories: never smoker and ever smoker, which included former smoker and current smoker. A Spearman correlation coefficient was used to examine the correlation among all vascular stiffness variables. Linear regression analysis was performed to assess correlations among all variables. The ORs and corresponding 95% CI were calculated to evaluate the association of risk of severity of coronary atherosclerosis and various risk factors using univariate and multivariate regression analyses. Performance of the carotid variables as predictive factors was tested using ROC curve analysis as expressed in terms of area under ROC curve (AUC), sensitivity, specificity. The optional cutoff threshold values were determined at the point on the ROC curve at which Youden’s index (YI, sensitivity + [100%-specificity]) was maximal. The level of significance was set at P < 0.05. Statistical analyses were carried out using the Stata 11.0 statistical software package (StataCorp LP, College Station, TX).

3 RESULTS

3.1 Clinical characteristics of the study subjects

The clinical and laboratory data for study participants are summarized in Table 1. No significant differences were found between two-group
FIGURE 2  QAS analysis of CCA. The red line represents the RF signal tracking the vascular wall; the green line represents the RF signal tracking the motion of the vascular wall. A derived carotid pressure waveform was calibrated by brachial end diastolic and mean arterial pressure after six cardiac cycles. Then the arterial stiffness was calculated automatically.

TABLE 1  Clinical characteristics of the study participants

| Characteristic        | Normal group (n = 54) | Atherosclerotic group (n = 41) | Single-vessel lesion group (n = 55) | Multivessel lesion group (n = 78) |
|-----------------------|-----------------------|-------------------------------|------------------------------------|----------------------------------|
| Gender                |                       |                               |                                    |                                  |
| Male, n (%            | 34 (63)               | 28 (68)                       | 35 (64)                            | 49 (63)                          |
| Age (y)               | 54.17 ± 12.50         | 55.56 ± 10.53                | 53.45 ± 11.59                      | 57.26 ± 8.55*                    |
| BMI (kg/m²)           | 25.21 ± 4.04          | 24.89 ± 3.48                 | 24.54 ± 3.71                       | 24.82 ± 3.84                     |
| BSA (m²)              | 1.82 ± 0.1485         | 1.82 ± 0.13                  | 1.79 ± 0.13                        | 1.79 ± 0.12                      |
| SBP (mmHg)            | 117.24 ± 10.33        | 115.54 ± 9.81                | 122.47 ± 11.30*                    | 121.46 ± 12.07*                  |
| DBP (mmHg)            | 82.41 ± 6.299         | 83.63 ± 10.32                | 85.80 ± 10.64                      | 86.19 ± 7.82*                    |
| HP, n (%)             | 9 (17)                | 16 (39)*                     | 26 (47)*                           | 37 (47)*                         |
| Smoking status        |                       |                               |                                    |                                  |
| Ever, n (%)           | 16 (30)               | 15 (36)                      | 25 (45)                            | 43 (55)*                         |
| HDL (mmol/L)          | 1.41 ± 0.17           | 1.34 ± 0.16*                 | 1.22 ± 0.22*                       | 1.21 ± 0.22*                     |
| LDL (mmol/L)          | 2.93 ± 0.46           | 2.96 ± 0.33                  | 3.08 ± 0.36*                       | 3.12 ± 0.36*                     |

Abbreviations: BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood; HP, hypertensive (was defined as SBP > 140 mmHg and DBP > 90mmHg); HDL, high density lipoprotein; LDL, low density lipoprotein; IMT, intima-media thickness; PWV, pulse wave velocity; CC, compliance coefficient. Value are presented as mean ± SD or number of subjects.

*Significantly different from Normal group (P < 0.05).

#Significantly different from the Single-vessel lesion group (P < 0.05).

comparison of gender, BMI, and BSA. Patients in the multivessel lesion group were older than single-vessel lesion patients (57.265 ± 8.550 vs. 53.454 ± 11.593, P = 0.0313). The percentage of smoker was much higher in multivessel lesion group compared with normal (55% vs. 30%, P = 0.004). Meanwhile, patients with coronary atherosclerosis were more likely to be hypertensive than normal subjects (P = 0.014, P = 0.001, P < 0.0001 for atherosclerotic, single-vessel lesion and multivessel lesion group, accordingly). Laboratory test indicated that patients with coronary atherosclerosis had much lower HDL profiles compared with normal subjects with all P < 0.05. Patients in single-vessel lesion
group and multivessel lesion group had a higher profile LDL than that in other group.

3.2 | Comparison of ultrasound variables among groups

Ultrasound variables IMT and $\beta$ presented significant difference among intergroup comparisons. There is no significant difference for $\alpha$ and PWV as compared between normal and atherosclerotic group; no significant difference was found for $\alpha$ and CC as compared between atherosclerotic and single-vessel lesion group ($5.658 \pm 2.052$ vs. $6.968 \pm 2.811; 0.867 \pm 0.319$ mm$^2$/Kpa vs. $0.801 \pm 0.385$ mm$^2$/Kpa, $P = 0.2055$); neither for CC as compared between single-vessel lesion group and multivessel lesion group ($0.801 \pm 0.385$ mm$^2$/Kpa vs. $0.654 \pm 0.297$ mm$^2$/Kpa, $P = 0.055$). The data and comparison results were shown in Figure 3. IMT was found to correlate with stiffness variables significantly such as IMT positively correlated with PWV, $\alpha$ and $\beta$ with $r = 0.7001, 0.7718, 0.6292$ ($P < 0.0001$), while negatively related to CC with $r = -0.3855$ ($P < 0.0001$) as Figure 4 showed.
### TABLE 2  Adjusted relative risk of coronary artery disease in relation to carotid ultrasound parameters

|       | OR (95%CI)         | P      | ORa (95%CI)          | P      | ORb (95%CI)          | P      |
|-------|--------------------|--------|----------------------|--------|----------------------|--------|
| IMT   | 1.73 (1.57–1.90)   | <0.0001| 1.78 (1.60–1.97)     | <0.0001| 1.78 (1.60–1.99)     | <0.0001|
| PWV   | 1.67 (1.51–1.85)   | <0.0001| 1.72 (1.54–1.92)     | <0.0001| 1.69 (1.52–1.89)     | <0.0001|
| α     | 1.19 (1.13–1.25)   | <0.0001| 1.19 (1.14–1.26)     | <0.0001| 1.17 (1.11–1.23)     | <0.0001|
| β     | 1.23 (1.18–1.29)   | <0.0001| 1.24 (1.19–1.30)     | <0.0001| 1.22 (1.16–1.28)     | <0.0001|
| CC    | 0.56 (0.49–0.65)   | <0.0001| 0.54 (0.47–0.63)     | <0.0001| 0.56 (0.47–0.65)     | <0.0001|

*aAdjusted by age, gender, BSA, BMI.

*bAdjusted by age, gender, BSA, BMI, hypertensive status, smoking status, LDL, and HDL.

### 3.3 Risk association of carotid variables

Table 2 presents the risk estimates of carotid variable. The OR for IMT, PWV, α, and β, without adjustment, was 1.73, 1.67, 1.19, and 1.23, respectively, which meant that every 20 μm increment in IMT, 0.5 m/s increment in PWV, 1.5 increment in α, 1.0 increment in β measurements and 0.2 mm²/kPa reduction in CC increased the risk of coronary atherosclerotic severity by 73%, 67%, 68%, 51%, and 44%. After being adjusted by gender, age, BSA, BMI, smoking status, blood pressure, HDL, and LDL, all the carotid vascular variables exhibited similar OR values to that of without adjustment.

Taking normal group as reference, OR value of IMT, PWV, α, β and CC was 1.44 (95% CI: 1.21–1.72; P < 0.0001), 1.40 (95% CI: 1.15–1.71; P < 0.0001), 1.25 (95% CI: 1.09–1.45; P = 0.001), 1.45 (95% CI: 1.21–1.67; P < 0.0001), and 0.51 (95% CI: 0.37–0.70; P < 0.0001) respectively for the atherosclerotic group with clinical characteristics’ adjustment. Similarly, the relationships were also evident for single-vessel lesion and multivessel lesion group, with the OR of 3.88 (95% CI: 1.89–7.98) and 4.27 (95% CI: 1.46–12.39) for IMT, 2.79 (95% CI: 1.73–4.51) and 3.70 (95% CI: 1.85–7.37) for PWV. However, the OR values decreased to 1.41 (95% CI: 1.20–1.65), 2.45 (95% CI: 1.56–3.83), 0.28 (95% CI: 0.17–0.47) for multivessel lesion group compared with 1.45 (95% CI: 1.21–1.67) for single-vessel lesion group.
TABLE 3 Risk estimates of IMT, PWV, α, β, and CC for coronary atherosclerosis in multivariate analysis

| Variables          | N  | ORa (95% CI) | P   |
|--------------------|----|--------------|-----|
| **IMT**            |    |              |     |
| Normal             | 54 | 1.00         | Refb |
| Atherosclerotic    | 41 | 1.44 (1.21–1.72) | <0.0001 |
| Single-vessel lesion | 55 | 3.88 (1.89–7.98) | <0.0001 |
| Multivessel lesion | 78 | 4.27 (1.46–12.39) | 0.008 |
| **PWV**            |    |              |     |
| Normal             | 54 | 1.00         | Refb |
| Atherosclerotic    | 41 | 1.40 (1.15–1.71) | 0.001 |
| Single-vessel lesion | 55 | 2.79 (1.73–4.51) | <0.0001 |
| Multivessel lesion | 78 | 3.70 (1.85–7.37) | <0.0001 |
| α                  |    |              |     |
| Normal             | 54 | 1.00         | Refb |
| Atherosclerotic    | 41 | 1.25 (1.09–1.45) | 0.001 |
| Single-vessel lesion | 55 | 1.45 (1.22–1.74) | <0.0001 |
| Multivessel lesion | 78 | 1.41 (1.20–1.65) | <0.0001 |
| β                  |    |              |     |
| Normal             | 54 | 1.00         | Refb |
| Atherosclerotic    | 41 | 1.45 (1.21–1.67) | <0.0001 |
| Single-vessel lesion | 55 | 3.29 (1.58–6.85) | <0.001 |
| Multivessel lesion | 78 | 2.45 (1.56–3.83) | <0.0001 |
| CC                 |    |              |     |
| Normal             | 54 | 1.00         | Refb |
| Atherosclerotic    | 41 | 0.51 (0.37–0.70) | <0.0001 |
| Single-vessel lesion | 55 | 0.57 (0.43–0.77) | <0.0001 |
| Multivessel lesion | 78 | 0.28 (0.17–0.47) | <0.0001 |

aAdjusted by age, hypertensive status, gender, smoking status, BSA, BMI, LDL, and HDL. 
bReference group.

1.22–1.74), 3.29 (95% CI: 1.58–6.85), 0.57 (95% CI: 0.43–0.77) for single-vessel lesion group as α, β and CC indicated (Table 3).

3.4 | Diagnostic performance analysis

The predictive performance of these variables for different coronary atherosclerosis as independent factor, which compared with normal group, including the AUC, sensitivity, specificity and corresponding cutoff values were further evaluated as Table 4 indicated. IMT showed the highest predictive performance for patients with multivessel lesion (AUC = 0.9909, P < 0.0001). When the cut-off value of IMT was set as 905.5 μm, the diagnostic sensitivity and specificity was 96.15% and 96.3%. The AUC for β values was higher than other variables in both atherosclerotic group and single-vessel lesion group with AUC of 0.8042 and 0.9689 (P < 0.0001), especially for patients with single-vessel lesion, the diagnostic sensitivity and specificity was 90.91% and 92.59% as cutoff value was set at 8.91.

Furthermore, the diagnostic capability of the variables in differentiating was also analyzed, such as the multivessel lesion group from the atherosclerotic, single-vessel lesion group and single-lesion group from atherosclerotic group as Figure 5 showed. Compared with other variables, IMT had a much higher accuracy in discriminating multivessel lesion from atherosclerotic ones (AUC = 0.9742; 95% CI, 0.9501–0.9982), single-vessel lesion (AUC = 0.8735; 95% CI, 0.7706–0.9044), and also single-vessel lesion from atherosclerotic lesion (AUC = 0.8561; 95% CI, 0.7836–0.9286).

3.5 | Repeatability comparison

Good agreement was found in the intragroup and intergroup comparisons for IMT (intragroup mean bias: 10.32 ± 33.06 μm; intergroup mean bias: 8.15 ± 26.11 μm) and PWV values (intragroup mean bias: 0.0126 ± 0.643 m/s; intergroup mean bias: 0.007 ± 0.194 m/s). Bland-Altman analysis showed a consistent trend in the difference and mean values of IMT and PWV by repeated measurements.

4 | DISCUSSION

The guidelines for assessment of CV risk published in 2010 recommended some vascular imaging parameters should be used as the biomarkers.12,13 Extra-cranial carotid artery is the most widely accepted window to predict CV disease, especially when IMT measurement and arterial stiffness evaluation by ultrasonographic method became available.14,15 Carotid IMT has long been measured in routine clinical examinations, current guidelines stating that a common carotid IMT > 900 μm can be regarded as a conservative estimate of existing abnormalities,16 is considered as a good indicator of any future CV disease. An increase in carotid IMT has been reported to be associated with an increased risk of ischemic heart disease and cerebrovascular disease independent of all other major risk factors.17,18 Hodis HN, et al.19 have shown that each 0.03 mm increase per year in carotid IMT there was an increase in the relative risk of coronary event of 3.1. Another study by a meta-analysis of 8 large, prospective studies found that each 0.1 mm increment in carotid IMT was associated with a 10%–15% to increase the risk of myocardial infarction.20 Similar results were found in our study that thickened carotid IMT increased the risk of coronary atherosclerotic severity; every 20 μm increment in IMT increased the severity of atherosclerosis in coronary artery by 78% after adjustment by all clinical characteristics. The cut-off value of carotid IMT for presenting the existence of coronary atherosclerotic plaque in our study was 702 μm and when the IMT increased to about 900 μm, the patients were fund to have multiple coronary stenosis caused by atherosclerotic plaque. While, still other studies disagreed.21-23 One study showed that using a cut-off of 0.050 cm, 28.9% (66/228) of healthy individuals showed a thickened IMT and 30.9% of (144/466) of atherosclerosis risk patients showed a non-thickened IMT. Moreover, the progression of a thickened IMT measurement was proved not to indicate cardiovascular risk in a
TABLE 4  Predictive performance of the carotid variables as independent factor for the assessment of coronary atherosclerosis taking Normal group as reference

| Variables | AUC   | 95% CI        | P value  | Cut off | Sensitivity (%) | Specificity (%) |
|-----------|-------|---------------|----------|---------|-----------------|-----------------|
| **For atherosclerotic** |       |               |          |         |                 |                 |
| IMT       | 0.783 | 0.6894–0.8766 | <0.0001  | 702.0   | 97.56           | 59.26           |
| PWV       | 0.7157| 0.6114–0.8200  | =0.0003  | 5.980   | 87.8            | 40.74           |
| α         | 0.7161| 0.6091–0.8231  | <0.0001  | 6.935   | 87.8            | 55.56           |
| β         | 0.8042| 0.7147–0.8937  | <0.0001  | 4.150   | 78.05           | 57.41           |
| CC        | 0.7995| 0.7118–0.8872  | <0.0001  | 0.895   | 58.45           | 83.33           |
| **For single-vessel lesion** |       |               |          |         |                 |                 |
| IMT       | 0.9408| 0.8991–0.9820  | <0.0001  | 821.5   | 98.18           | 81.40           |
| PWV       | 0.9187| 0.8695–0.9679  | <0.0001  | 7.465   | 85.05           | 81.48           |
| α         | 0.8131| 0.7345–0.8917  | <0.0001  | 5.885   | 64.45           | 85.19           |
| β         | 0.9689| 0.9420–0.9958  | <0.0001  | 8.91    | 90.91           | 92.59           |
| CC        | 0.8359| 0.7611–0.9107  | <0.0001  | 0.885   | 67.27           | 85.19           |
| **For multivessel lesion** |       |               |          |         |                 |                 |
| IMT       | 0.9909| 0.9793–1.001   | <0.0001  | 905.5   | 96.15           | 96.3            |
| PWV       | 0.9637| 0.9367–0.9906  | <0.0001  | 8.165   | 87.18           | 90.74           |
| α         | 0.8517| 0.7885–0.9150  | <0.0001  | 6.980   | 60.26           | 98.15           |
| β         | 0.8517| 0.9711–1.003   | <0.0001  | 9.18    | 96.15           | 96.3            |
| CC        | 0.9046| 0.8566–0.9525  | <0.0001  | 0.8050  | 73.08           | 90.74           |

FIGURE 5  ROC curves of IMT, PWV, α, β, and CC as the independent variables for differential diagnosis

large-scale study (n = 36,984).24 As discussed before, the technique of measuring carotid IMT could be sufficiently standardized before widespread clinical screening, particularly when the sub-millimeter difference in IMT will be treated as an important factor to separate low-risk and high-risk groups.25 Meanwhile, it seemed that measuring the carotid IMT precisely may be a reliable way to qualify atherosclerosis, but not sufficient.

A large number of clinical studies have demonstrated a good association of carotid stiffness with atherosclerotic burden as well as with incident cardiovascular events. Carotid arterial stiffness is an independent predictor.26–28 Carotid-femoral PWV is the gold standard for measuring large artery stiffness. A PWV more than 10 m/s is considered a conservative estimate of significant alterations of aortic function in middle-aged hypertensive patients.29 Studies also found that PWV had a strong positive association with carotid IMT30 and coronary atherosclerosis31 as our study showed likewise. Carotid PWV correlated positively with IMT change (r = 0.70) and every 0.5 m/s increment in PWV increased the risk of coronary atherosclerotic severity by 67% as indicated in our study. Another ultrasound stiffness index β of alive patients showed a high correlation with carotid...
atherosclerotic grade ($r = 0.68$), vessel wall area and mean wall thickness ($r = 0.61$ and $0.53$, respectively) verified by postmortem, suggesting that $\beta$ reflects not only elastic properties of the artery but also its atherosclerotic damage. Results in our study that $\beta$ normalized by carotid artery diameters automatically as QAS measuring had the strongest correlation with IMT ($r = 0.77$) and a preferred performance of predicting value especially for patients in atherosclerotic group and single-vessel lesion group (AUC: 0.8042 and 0.9689) agreed with previous study.

Some reports indicated that functional impairment of the arterial wall may occur early in the atherosclerotic process and arterial stiffening may be a process independent of arterial thickening. Although the relationship between carotid structural and functional changes was obvious in our and other studied, the mechanism of the interaction still remained to be elucidated. One recent study supports the postulate that arterial stiffening and atherosclerosis share some common pathophysiological mechanisms, like endothelial dysfunction and insulin resistance, and could be viewed as two synergistic processes that may potentiate each other in the development of vascular changes underlying cardiovascular disease. Besides PWV and $\beta$, $\alpha$ and CC showed significant correlation with IMT, although the $r$ value of CC was much lower, which might be the reason that CC is the fractional change in cross-sectional area more likely relative to the arterial pressure. Each 1.5 increment in $\alpha$ and $0.2$ mmHg/KPa reduction in CC increased the risk of coronary atherosclerotic severity by $68\%$ and $44\%$. An interesting finding was that at an earlier stage, for the patients with only coronary atherosclerosis, $\beta$ presented the highest diagnostic accuracy, even higher than that of IMT, which might be a support that functional impairment of the arterial wall may occur early in the atherosclerotic process. Furthermore, $\beta$ also exhibited excellent diagnostic accuracy of single-lesion with sensitivity of 90.91% and specificity of 92.59%. Functional arterial changes such as stiffness may be a marker for the onset of vascular stenosis for the detection of preclinical atherosclerotic lesions. The results, for the first time, raised the concern that different stage during coronary atherosclerotic changes might need different biomarkers to predict or diagnose.

There were some limitations of our study. Firstly, our study was a retrospective, cross-sectional and observational study, the diagnostic value we concluded in the present study was a preliminary testing result, less of convincing; the number of patients in each group was relatively small, resulting in low statistical power. A large sample of subjects need to recruited for further validation. Secondly, the IMT measurement site in the study was plaque-free, we did not account the presence of plaques and the value of plaque scores, which has been considered as a strong predictor for both stroke and myocardial infarction independently, and own a superior prognostic accuracy for future myocardial infarction compared with IMT. Thirdly, this study excluded patients with diabetes, which has been shown to be high risk population for CV events. There should be some changes of the results after including diabetic patients but the general trend of these ultrasound variables would keep unchanged, we proposing. Further research with quantitative analysis of carotid plaques should be carried out to verify the present results and validate the predictive value of CCA morphological and functional variables in diagnosing CAD through a full-scaled study design.

Ultrasoundographic modalities provide great opportunity to non-invasive imaging both vascular structural and functional changes in large-scale population study. The changes were closely related with detectable coronary lesions. Both QIMT and QAS techniques applied in carotid artery are likely to play a role in CV risk screening of patients with CAD.

**COMPETING INTERESTS**
The authors declare that they have no competing interests.

**ORCID**
Li Zhang MD  
https://orcid.org/0000-0001-8719-4407

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