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Carotid artery stiffness in rural adult Chinese: a cross-sectional analysis of the community-based China stroke cohort study

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ABSTRACT

Objectives To derive normative carotid artery stiffness data in rural adult Chinese population-based study of ultrasound measurements of carotid elasticity by using quality arterial stiffness (QAS), and to assess the changes of relevant parameters in Chinese adults 40 years of age and older.

Design A China stroke cohort study (total number: 1586) in the northern countryside were carried out between June 2013 and April 2016, designed to investigate the risk factors of cardiovascular and age-related diseases.

Setting The present study was a cross-sectional analysis of an ongoing community-based Shunyi cohort study in China.

Participants A total of 583 participants (227 men and 356 women; aged 40–80 years) with ultrasound carotid QAS examination were retrieved from the study to analyse.

Primary and secondary outcome measures Arterial stiffness parameters included diastolic diameter (Dd), pulse wave velocity (PWV), stiffness indices α and β were calculated by QAS. Other clinical indicators included physical measurements, medical histories and blood biochemical test.

Results In the entire study sample, mean Dd was 7.93±0.88 mm, mean PWV was 9.4±2.4 m/s, mean α was 7.65±5.13 and mean β was 15.53±10.29. PWV was significant higher in participants with hypertension (9.9 m/s vs 9.2 m/s in those without, p=0.002), and with diabetes (10.3 m/s vs 9.2 m/s in those without, p=0.003). PWV were significantly higher in participants with HbA1c at 5.8%–6.4% versus <5.8%, but no difference was found between subjects with glycohaemoglobin (HbA1c) at 5.8%–6.4% versus >6.4% (p=0.005, p=0.955, respectively). Age increase by every 10 years was associated with Dd increased by 0.27 mm, PWV increased by 1.2 m/s, α increased by 1.34 and β increased by 2.71. Systolic blood pressure (SBP) increase by every 10 mm Hg was associated with Dd increased by 0.15 mm, PWV increased by 0.35 m/s, α increased by 0.13 and β increased by 0.15.

Conclusion Among the participants older than 40 years, stiffness of the carotid artery had differences between hypertension and non-hypertension adults, as well as between diabetes and non-diabetes adults. Stiffness of the carotid artery also have differences between adults with HbA1c at 5.8%–6.4% versus <5.8%. Stiffness of the

Strengths and limitations of this study

► The ultrasound automated quality arterial stiffness (QAS) technique, which possesses favourable reliability and feasibility, can be used for assessing local arterial elasticity non-invasively and comprehensively.
► The ultrasound automated QAS technique, which was economical and practical, can be used for large sample screening.
► The ultrasound automated QAS was limited by some special conditions such as arrhythmia, carotid multiple atherosclerosis plaques, carotid with excessive bending, carotid with excessive pulsatility and excessive superficial carotid.

carotid artery increases with increasing age and increasing SBP at a range from 40 and up.

INTRODUCTION

The stiffening of arteries is the most important cause for the increase in both systolic and pulse pressures as well as the decrease in diastolic blood pressure (DBP) in people 40 years of age and older. These changes lead to cardiovascular complications, such as left ventricular hypertrophy, aneurysm formation and rupture. Arterial stiffness is an independent predictor of cardiovascular, cerebrovascular and all-cause mortality.[1 2] Hence, non-invasive determination of arterial stiffness during routine ultrasound examination of the carotid arteries is a powerful clinical tool in cardiovascular disease (CVD) prevention. Carotid ultrasound is one of the several imaging modalities that allow non-invasive assessment of vascular anatomy and function.[3 4] Recently, high resolution ultrasound acquisitions based on radio frequency (RF) signal have given the opportunity to assess precisely local arterial wall properties,[5] which may be performed by using automatic quality

arterial stiffness (QAS). QAS provides a list of standard arterial stiffness parameters including diastolic diameter (Dd), pulse wave velocity (PWV), the stiffness indices α and β, which are calculated by combining the measured values with the brachial blood pressure measured externally through an automated system or standard cuff. In the present study, we used QAS with the aim of determining carotid arterial stiffness in a population defined by age and blood pressure in the northern countryside of China.

METHODS
Study population
The present study was a cross-sectional analysis of an ongoing community-based Shunyi cohort study in China, designed to investigate the risk factors of cardiovascular and age-related diseases. The study design has been described elsewhere.[6] Briefly, 1586 inhabitants were recruited between June 2013 and April 2016. In each village, temporary assessment clinics were set up in residential centres. All participants attending the study underwent an interview and had their physical measurements recorded. The participants also provided blood and urine samples and underwent carotid ultrasound. In our study, the exclusion criteria included adults under

40 years old, stroke, cerebral haemorrhage, myocardial infarction, arrhythmia, carotid multiple atherosclerosis plaques, carotid with excessive bending, carotid with excessive pulsatility and excessive superficial carotid. People who could not obtain satisfactory QAS waveforms in 5 min were also excluded. Finally, among the inhabitants, 583 participants (227 men and 356 women; aged 40–80 years) completed carotid artery stiffness examination (figure 1).

Carotid QAS
Participants were in a supine position. Common carotid arterial ultrasound parameters were measured using a Mylab Twice Color Doppler ultrasound diagnostic system (Esaote, Genova, Italy) using a linear 5–13 MHz transducer (LA523) with built in a previously validated RF-based QAS module. This module used a complex algorithm that could process all data coming from the region of interest (ROI) as RF signals offline. It can be used for quantitative evaluation of the properties of the vessel wall.

The left common carotid artery (LCCA), carotid bulb and portions of the internal carotid arteries were scanned twice by one trained sonographer for each participant. The reproducibility of QAS technique varied in different indicators and methods has been discussed elsewhere.[7] The ROI was a 15 mm long segment, about 10 mm proximal
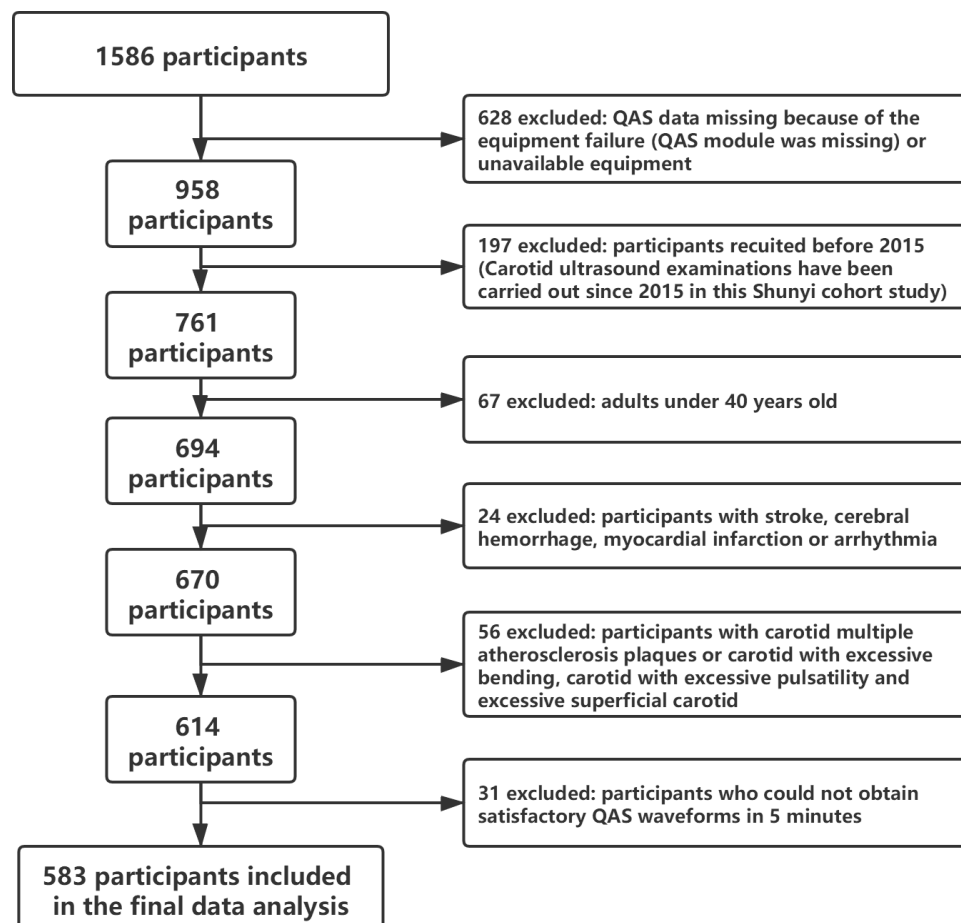

Figure 1 Participant selection flowchart. QAS, quality arterial stiffness.
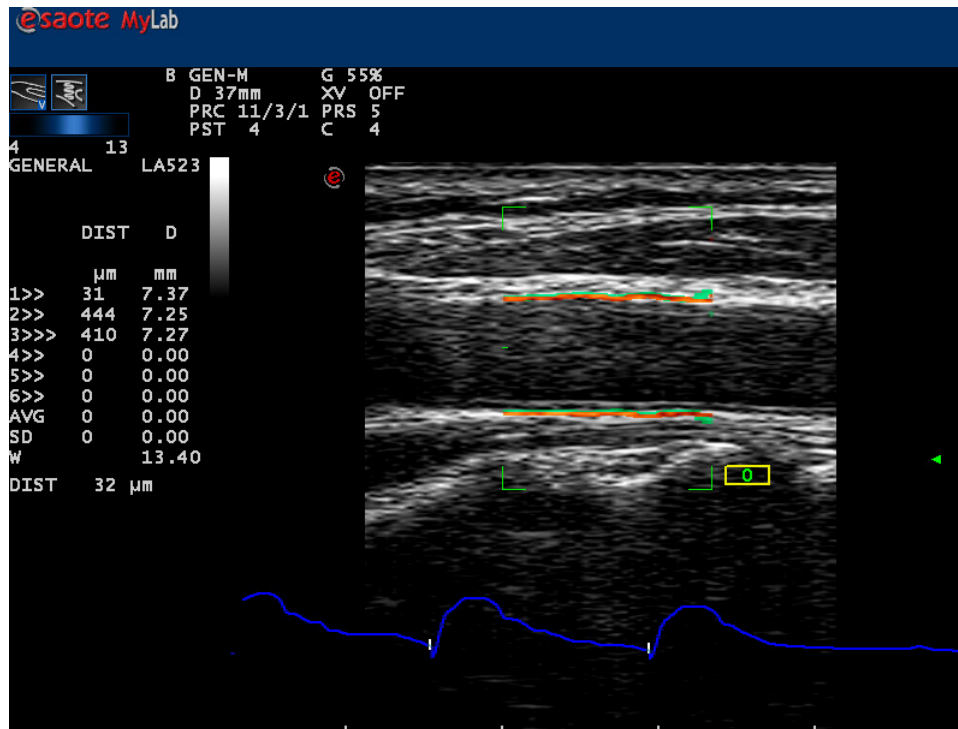
Figure 2 Quality arterial stiffness analysis of the common carotid artery. The red line represents the radio frequency (RF) signal tracking the leading edge of the lumen intima; the green line represents the RF signal tracking the leading edge of medial adventitial interface.

to the carotid bifurcation, where is free of plaque. QAS measurements automatically measured the changes in the arterial diameter between the systolic and diastolic phases on the LCCA segments. A RF signal tracked the vascular wall, while another signal tracked the motion of the vascular wall for at least six cardiac cycles and the mean and SD values were calculated automatically. The SD value was controlled with a cut-off value 15 (figure 2). The QAS data analysis software also calculated the Dd (mm), the PWV (m/s) and the stiffness indices α and β (figure 3). One-point carotid PWV was calculated applying the Bramwell-Hill equation[8]: $PWV = \frac{1}{\sqrt{\rho \cdot DC}} = \sqrt{\frac{Dd^2 \cdot \Delta p}{\rho \cdot (2 \cdot Dd \cdot \Delta D + \Delta D^2)}}$, where Dd: diastolic diameter, ΔD: change in diameter in systole, DC: distensibility coefficient, Δp: local pulse pressure and ρ: blood density. PWV is a functional parameter directly affected by arterial wall stiffness. The stiffness index α was expressed as: $\ln\left(\frac{Ps}{Pd}\right) \times Ad/(As - Ad)$, where Ps and Pd are carotid systolic and DBP, respectively; As: systolic area and Ad: diastolic area. The stiffness index β was expressed as: $\ln\left(\frac{Ps}{Pd}\right) \times Dd/\Delta D$.
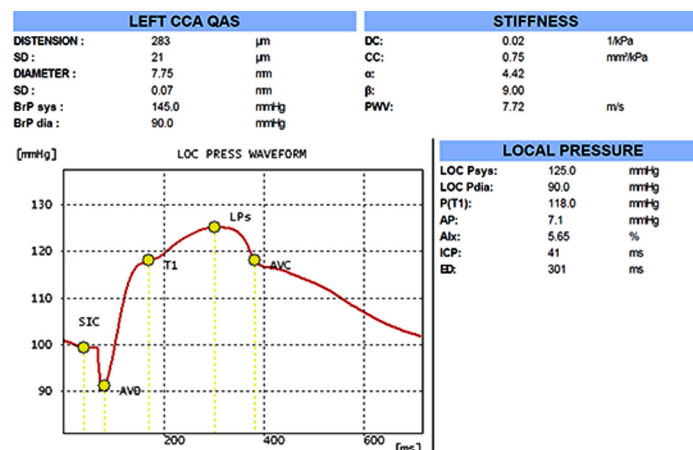

Figure 3 Quality arterial stiffness analysis of the common carotid artery. The stiffness value was calculated automatically for six cardiac cycles.

Statistical methods

All data are expressed as the mean±SD for continuous variables. General linear regression analysis, independent sample t-test and analysis of variance (ANOVA, Bonferroni t-test) were used to assess the correlations among all the parameters. The results were considered significant at p<0.05. The statistical software package SPSS V.19.0 (IBM Corporation) was used for all data analyses.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS
Population characteristics

Among the 583 participants with carotid ultrasound measurements, the mean±SD age at measurement was 54.6±7.8 years, 38.9% were men, and 61.1% were women. The mean systolic blood pressure (SBP) was 132±20 mm Hg, the mean DBP was 79±11 mm Hg, the mean body mass index (BMI) was 26.4±3.8, the mean blood glucose (Glu) was 6.0±1.7 mmol/L, the mean glycohemoglobin (HbA1c) was 5.8%±0.9%, the mean total aldehyde was 4.91±0.94 mmol/L, the mean low density lipoprotein cholesterol was 2.91±0.77 mmol/L and the mean triglyceride was 1.84±2.38 mmol/L (table 1). Overall, 33.3% of the participants had hypertension, and 17.2% had diabetes (table 1).

Quality assurance of carotid measurements

Among the 583 participants with carotid ultrasound measurements, arterial stiffness parameters calculated by QAS were listed in table 2. The values of Dd, PWV, α and β were not different between men and women (p=0.304, p=0.087, p=0.182, p=0.177, respectively, table 2).

Comparison of arterial stiffness parameters in medical histories and HbA1c

The results of the QAS analysis in table 3 show that PWV was much higher in participants with hypertension (p=0.002). The Dd, stiffness indices α and β were also slightly higher in participants with hypertension, but they were not significantly different (p=0.105, p=0.623, p=0.615, respectively). The PWV, stiffness indices α and β were much higher in participants with diabetes (p=0.003, p=0.029, p=0.030, respectively). The Dd was slightly higher in participants with diabetes, but no significant difference was found (p=0.160).

The HbA1c concentration represents a continuum: values <5.8% indicate a lower risk for diabetes, whereas those >6.4% indicate the presence of diabetes. HbA1c concentrations of 5.8%–6.4% are associated with an increasing risk of diabetes.[9] Considering the medical

Table 1 Distribution of demographic information, medical history and physical measurements in the study

All participants (n=583)	Mean±SD or n (%)
Demographic/medical history	
Age, years	54.6±7.8
Sex, % male	227 (38.9)
Hypertension, n (%)	194 (33.3)
Prior diabetes, n (%)	100 (17.2)
Physical measurements	
Height, cm	159.6±8.0
Weight, kg	67.2±11.3
BMI, kg/m^2	26.4±3.8
SBP, mm Hg	132±20
DBP, mm Hg	79±11
Blood tests	
Glu, mmol/L	6.0±1.7
HbA1c, %	5.8±0.9
TCHO, mmol/L	4.91±0.94
LDL-C, mmol/L	2.91±0.77
TG, mmol/L	1.84±2.38

BMI, body mass index; DBP, diastolic blood pressure; Glu, glucose; HbA1c, glycohemoglobin; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TCHO, total aldehyde; TG, triglyceride.

treatment influence to the participants with prior diabetes, we divided all participants into lower risk for diabetes (without diabetes), increasing risk of diabetes (without diabetes) and prior diabetes. The results of the QAS analysis in table 4 show that both of PWV and Dd increased with the lower, increasing risk of diabetes and diabetes group. PWV had a significant difference between lower risk and increasing risk of diabetes (p=0.005). But there was no significant difference between increasing risk of diabetes and diabetes group (p=0.955). Dd had no significant difference among lower risk, increasing risk of diabetes and diabetes group (p=0.363, p=0.810, p=0.908, respectively).

Associations with all the parameters

Age, SBP and HbA1c had a significant linear correlation with the Dd (p<0.001, p<0.001, p=0.010, respectively). Age, SBP had a significant linear correlation with the PWV (p<0.001, p=0.012, respectively).

Associations with age and SBP

In the entire study sample, mean Dd was 7.93±0.88 mm, mean PWV was 9.4±2.4 m/s, mean α was 7.65±5.13 and mean β was 15.53±10.29 (table 2).

Age increase by every 10 years was associated with Dd increased by 0.27 mm, PWV increased by 1.2 m/s, α increased by 1.34 and β increased by 2.71 (table 2, figure 4).

Table 2 Common carotid arterial characteristics of participants and distribution of mean±SD values of arterial stiffness parameters by sex, age and SBP

	N	Dd, mm Mean±SD	PWV, m/s Mean±SD	α Mean±SD	β Mean±SD
All	583	7.93±0.88	9.4±2.4	7.65±5.13	15.53±10.29
Sex					
Male	227	8.00±0.88	9.2±2.6	7.30±6.40	14.81±12.84
Female	356	7.90±0.88	9.6±2.3	7.88±4.11	16.00±8.24
		p=0.304	p=0.087	p=0.182	p=0.177
Age, years					
40–49	170	7.61±0.80	8.4±1.8	6.04±2.60	12.30±5.22
50–59	252	7.97±0.86	9.4±2.0	7.52±3.43	15.25±6.89
60–69	135	8.21±0.89	10.1±2.7	8.91±7.73	18.07±15.48
≥70	26	8.33±0.83	12.2±3.5	12.88±8.54	26.16±17.12
SBP, mm Hg					
<100	10	7.09±0.71	7.8±2.2	6.67±4.61	13.58±9.32
100–109	51	7.30±0.79	8.4±1.9	6.75±3.10	13.71±6.22
110–119	105	7.70±0.85	8.9±2.8	6.51±2.78	13.23±5.59
120–129	128	7.95±0.85	9.2±2.1	6.93±3.07	14.07±6.22
130–139	109	8.04±0.78	9.6±2.5	7.34±4.11	14.9±8.24
140–149	87	8.16±0.82	9.5±2.0	7.18±2.56	14.58±5.15
150–159	43	8.21±0.82	10.0±2.2	7.56±3.18	13.35±6.36
≥160	50	8.25±0.88	10.5±2.4	7.33±2.41	14.9±4.85

Dd, diastolic diameter; PWV, pulse wave velocity; SBP, systolic blood pressure.

SBP increase by every 10 mm Hg was associated with Dd increased by 0.15 mm, PWV increased by 0.35 m/s, α increased by 0.13 and β increased by 0.15 (table 2, figure 5).

DISCUSSION
The Chinese CVD report of 2015 showed that the incidence of CVD is continuously increasing and will maintain an upward trend in the next decade in China. CVD was still the leading cause of death in 2014.[10] The mortality of CVD is significantly higher in China than in other developed countries. Both structural and functional changes of arteries have been a research focus for several years, as they are considered risk factors for cardiovascular events.[11–13]

Many studies showed that arterial stiffness is correlated with the presence and severity of arterial atherosclerosis and is also associated with myocardial dysfunction.[14–16] Various risk factors such as hypertension, diabetes and metabolic syndrome (METS) cause the progression of

Table 3 Comparison between participants with and without hypertension by quality arterial stiffness (QAS) measurements after adjustment for age. Comparison between participants with and without diabetes by QAS after adjustment for age

	Hypertension			Diabetes		
	No	Yes	P value	No	Yes	P value
N	389	194		483	100	
Dd, mm Mean±SD	7.89±0.90	8.02±0.84	0.105	7.91±0.88	8.05±0.87	0.161
PWV, m/s Mean±SD	9.2±2.5	9.9±2.1	0.002	9.2±2.1	10.3±3.3	0.003
α Mean±SD	7.58±5.65	7.80±3.87	0.623	7.29±3.67	9.37±9.23	0.029
β Mean±SD	15.38±11.34	15.83±7.77	0.615	14.82±7.38	18.96±18.51	0.030

Dd, diastolic diameter; PWV, pulse wave velocity.

Table 4 Comparison between participants in different risk levels of diabetes by Dd and PWV after adjustment for age

		N	Dd, mm Mean±SD	PWV, m/s Mean±SD
All		583	7.93±0.88	9.4±2.4
HbA1c, %	Lower risk (participants without diabetes) <5.8	405	7.82±0.85	9.2±2.1
	Increasing risk of diabetes (participants without diabetes) 5.8–6.4	78	8.06±0.84	10.1±2.4
	Prior diabetes or >6.4	100	8.58±0.88	10.2±3.2

Dd, diastolic diameter; HbA1c, glycohemoglobin; PWV, pulse wave velocity.

arteriosclerosis. These factors may cause macrovascular and microvascular complications, leading to arterial wall thickening, endothelial dysfunction and calcification, finally resulting in arterial stiffness. Many studies showed that arterial stiffness is a strong predictor of future cardiovascular events. In addition, it is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall.[17 18] Both the Danish population study[19] and Baltimore Longitudinal Study of Aging (BLSA) study[20] have shown the predictive role of arterial stiffness for cardiovascular outcomes beyond traditional cardiovascular risk factors.

In our study, large population samples were collected. We focused on carotid wall changes by evaluating arterial stiffness using the ultrasound QAS technique, which is a rapid and specific manner to measure the stiffness parameters. For functional changes, we obtained the arterial stiffness parameters calculated by QAS, such as Dd, PWV, the stiffness indices α and β to explore the baseline of the parameters. In our study, the value of Dd, PWV, α and β increased with age (by approximately 0.27 mm, 1.2 m/s, 1.34 and 2.71, respectively, per 10-year increase in age); they also increased with SBP (by approximately 0.15 mm, 0.35 m/s, 0.13 and 0.15, respectively, for every 10 mm Hg increase in SBP). According to the Chinese CVD report of 2015, hypertension and diabetes are two of the most common chronic non-infectious diseases and the most important risk factors for CVDs. As the most useful and robust index of arterial stiffness,[21] PWV measured by QAS likely provides accurate information regarding the local alterations in the vascular characteristics. In our study, we found that PWV provide some information related with hypertension and diabetes.

Arterial dysfunction is the pathophysiological change occurring in CVD. If we could identify the damage in arterial function early, it may be possible to intervene early
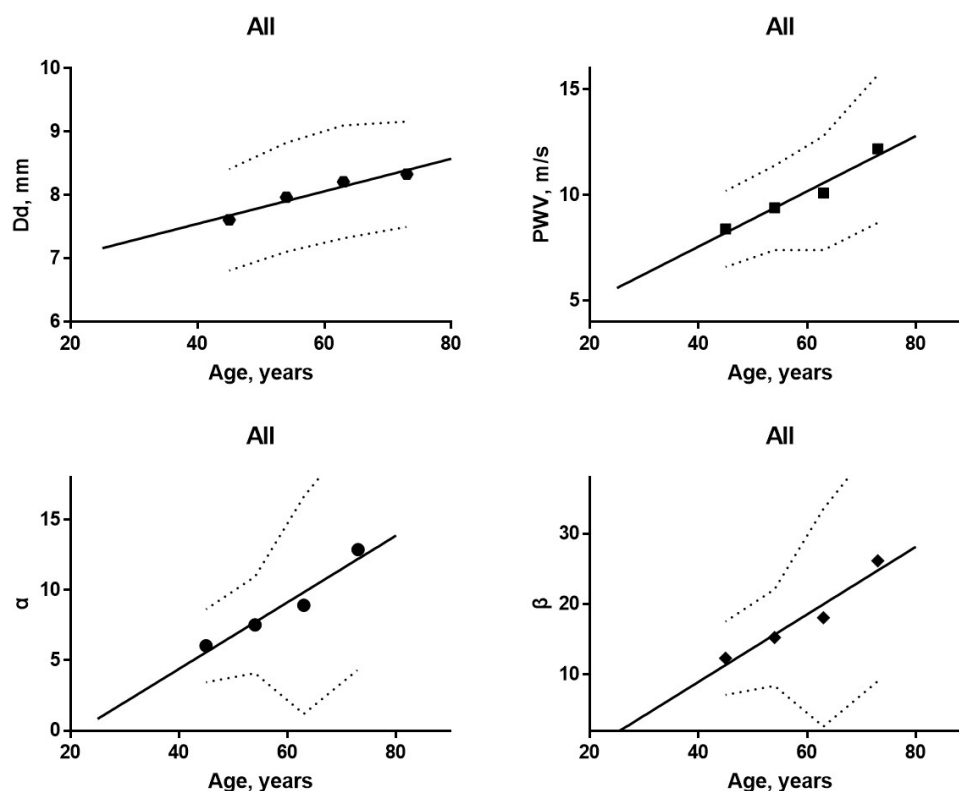

Figure 4 The increase in the mean Dd, PWV, α and β with increasing age in the participants of the study. Dd, diastolic diameter; PWV, pulse wave velocity.
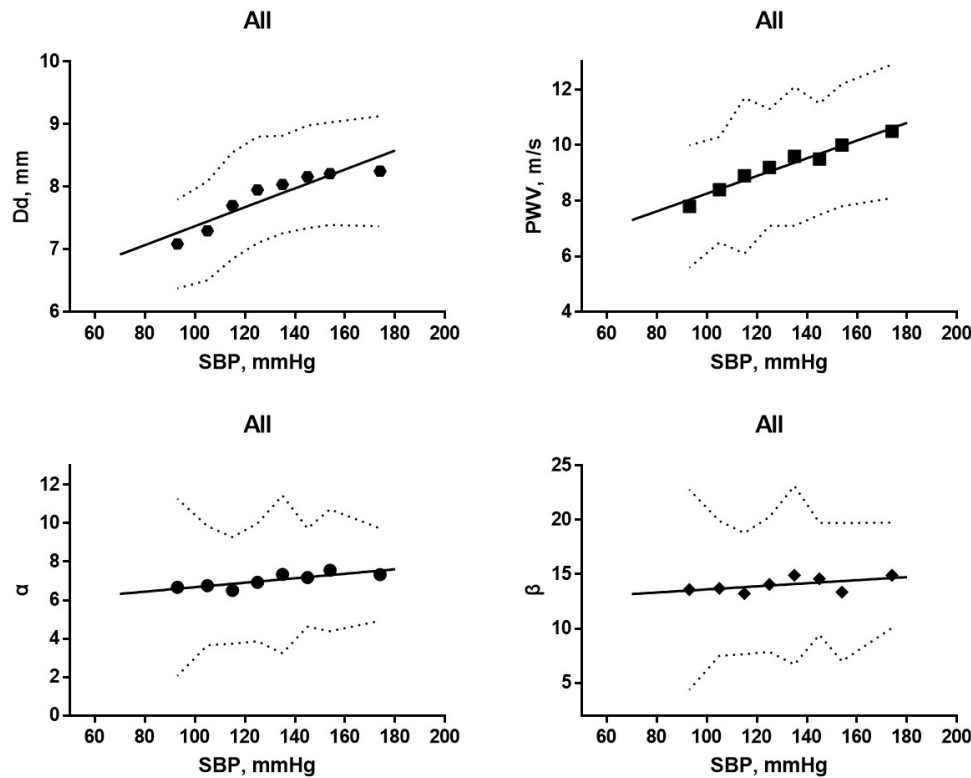
Figure 5 The increase in the mean Dd, PWV, α and β with increasing SBP in the participants of the study. Dd, diastolic diameter; PWV, pulse wave velocity; SBP, systolic blood pressure.

before the occurrence of CVD events such as myocardial infarction.[22] It is becoming clear that arterial stiffness may be increased even in pre-diabetic populations with impaired glucose tolerance and in those with METS well before the onset of overt diabetic mellitus (DM). A study with 91 patients demonstrated that patients with type 2 diabetes have significantly increased arterial stiffness as assessed by QAS.[23] Our study also supported the conclusion. Some other data suggest that arterial stiffness can predict the DM. Arterial stiffness is irreversible in DM although HbA1c influenced by medical treatment in several patients. Several studies have shown that quantitative carotid stiffness as a functional index is influenced mainly by the quality of blood glucose control and a high-normal HbA1c level was independently associated with arterial stiffness, but not with carotid atherosclerotic parameters (such as intima-media thickness (IMT) and Dd), in the general population without diabetes.[24–26] The functional atherosclerotic process may already be accelerated according to HbA1c level, even at a level below the diagnostic threshold for diabetes. There are many risk predictive models with great importance in primary practice. However, these models predicted the traditional risk factors instead of the vascular function itself due to a lack in recent vascular health assessment methods. In our study, the carotid arterial stiffness parameters Dd, PWV, α and β we measured were much higher in the population with diabetes. Our study also showed the relationship between Dd, PWV and HbA1c. According to the HbA1c risk level mentioned before, in the lower risk of diabetes

group, the value of PWV was significantly lower than the increasing risk of diabetes and presence of diabetes groups. These results validate the hypothesis that arterial remodelling occurring in local and elastic arteries increases the risk for future CVD, because the carotid artery can be considered as a model reflecting the conditions common to all involved arteries.

In our study, we focused on the population older than 40 years in the northern countryside of China. The healthcare development in rural areas is relatively backward compared with urban areas in China. People lived in rural areas usually neglect personal health management and have bad living habits such as smoking, high salt and high-carbonhydrate diet. All of these can cause a bad health condition leading to some severe chronic disease such CVD. The Chinese CVD report of 2015 also showed that CVD mortality in rural areas has exceeded that of urban areas since 2009.[10] Thus, we make our efforts to explore some simple inspection methods which can be easily carried out in both rural and urban areas and find some new indicators such as non-invasive carotid arterial functional indices combined with traditional risk factors to comprehensively assess arterial structural and functional changes.

Strengths and limitations of this study

According to our study, the ultrasound automated QAS technique, which possesses favourable reliability and feasibility, can be used for assessing local arterial elasticity non-invasively and comprehensively. The technique can

be used for large sample screening because it is economical and practical. However, the technique still has its limitations. QAS technique is based on RF technique. The RF signal tracked the vascular wall, while another signal tracked the motion of the vascular wall for at least six cardiac cycles and the mean and SD values were calculated automatically. In that case, anything that affects the cardiac cycle or vascular wall recognition will affect the measurement of QAS. The QAS data cannot be obtain satisfactorily in some conditions such as arrhythmia, carotid multiple atherosclerosis plaques, carotid with excessive bending, carotid with excessive pulsatility and excessive superficial carotid.

CONCLUSION

Arterial function evaluation is becoming more important than structural evaluation in recent studies. The ultrasound automated QAS technique, which possesses favourable reliability and feasibility, can be used for assessing local arterial elasticity non-invasively and comprehensively.

A total of 583 people in the northern countryside in China were enrolled into our present study at baseline. Stiffness of the carotid artery have differences between hypertension and non-hypertension adults, as well as between diabetes and non-diabetes adults. Stiffness of the carotid artery have differences between adults with HbA1c at 5.8%–6.4% versus <5.8%. Stiffness of the carotid artery increases with increasing age and increasing SBP at a range from 40 and up. The present study provides important information regarding the association between arterial function and the risk factors of CVD.

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