Reference values of carotid intima-media thickness and arterial stiffness in Chinese adults based on ultrasound radio frequency signal: A nationwide, multicenter study

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Abstract

Background: Carotid intima-media thickness (IMT) and diameter, stiffness, and wave reflections, are independent and important clinical biomarkers and risk predictors for cardiovascular diseases. The purpose of the present study was to establish nationwide reference values of carotid properties for healthy Chinese adults and to explore potential clinical determinants.

Methods: A total of 3053 healthy Han Chinese adults (1922 women) aged 18–79 years were enrolled at 28 collaborating tertiary centers throughout China between April 2021 and July 2022. The real-time tracking of common carotid artery walls was achieved by the radio frequency (RF) ultrasound system. The IMT, diameter, compliance coefficient, β stiffness, local pulse wave velocity (PWV), local systolic blood pressure, augmented pressure (AP), and augmentation index (AIx) were then automatically measured and reported. Data were stratified by age groups and sex. The relationships between age and carotid property parameters were analyzed by Jonckheere–Terpstra test and simple linear regressions. The major clinical determinants of carotid properties were identified by Pearson's correlation, multiple linear regression, and analyses of covariance.

Results: All the parameters of carotid properties demonstrated significantly age-related trajectories. Women showed thinner IMT, smaller carotid diameter, larger AP, and AIx than men. The β stiffness and PWV were significantly higher in men than women before forties, but the differences reversed after that. The increase rate of carotid IMT (5.5 μm/year in women and 5.8 μm/year in men) and diameter (0.03 mm/year in both men and women) were similar between men and women. For the stiffness and wave reflections, women showed significantly larger age-related variations than men as demonstrated by steeper regression slopes (all *P* for age by sex interaction <0.05). The blood pressures, body mass index (BMI), and triglyceride levels were identified as major clinical determinants of carotid properties with adjustment of age and sex.

Conclusions: The age- and sex-specific reference values of carotid properties measured by RF ultrasound for healthy Chinese adults were established. The blood pressures, BMI, and triglyceride levels should be considered for clinical application of corresponding reference values.

Keywords: Intima-media thickness; Arterial stiffness; Reference values; Ultrasound radio frequency signal; Wave reflections

Introduction

The carotid artery serves as a window of the whole arterial system for cardio- and cerebrovascular assessment.[1–3] Numerous studies have proven the important value of carotid properties, including intima-media thickness (IMT), stiffness, and wave reflections, as clinical biomarkers and risk predictors for cardio- and cerebrovascular diseases.[4–6] The measurements and progression of carotid properties showed significant and independent associations with cardiovascular events in clinical and epidemiological studies.[7–10] However, the comprehensive evaluation of the carotid properties usually needs different devices, e.g., tonometry for pulse wave velocity (PWV) or wave analysis, ultrasound for IMT and diameter, which is time-consuming and inconvenient, impeding the integrative evaluation of carotid properties in clinical practice.[1,11] The ultrasound radio frequency (RF) signal can be used to determine the wall thickness and diameter changes of the artery precisely with a high spatial and temporal resolution.[12] In combination with brachial blood pressure (BP), the arterial stiffness and wave reflection analysis can also be achieved automatically in the meantime by the advanced analysis function,[13] which is very quick without repeated evaluation or patient transfer. Furthermore, the RF ultrasound system provides real-time feedback for quality control,[14] which makes the measurement more reliable and operator-independent. Therefore, the RF ultrasound is very suitable for the integrative assessment of carotid properties, and ideal for routine clinical application.

Normal reference values are indispensable for the discrimination of normality and abnormality. Previous studies suggested non-negligible ethnic differences in carotid properties.[15–17] However, most of the current widely used references for carotid properties were derived from European and North American populations with various selection criteria and methods.[18–21] The nationwide reference values of carotid properties for the healthy Chinese adults are still lack of results from multicenter study with large sample size. Moreover, several biological factors besides age and sex, such as BP and body mass index (BMI), may need to be taken into account during the clinical use of carotid reference values.[18–20,22]

This study aimed to establish age- and sex-specific reference values of carotid properties by RF ultrasound in a nationwide, multicenter population of healthy Chinese adults, and to explore potential influencing factors.

Methods

Ethical approval

The study complied with the *Declaration of Helsinki*, and the research protocol was approved by the ethical committees of all collaborating hospitals (Approval Number of the Heading Hospital: Independent Ethics Committee of Institution of Clinical Trials, Tangdu Hospital, No. K202104-04). Informed consent was obtained from all the participants. The study was registered at the ClinicalTrials.gov (No. NCT04881292) and the Chinese Clinical Trial Registry (https://www.chictr.org.cn, No. ChiCTR2100045419).

Study population

This nationwide, multicenter study was headed by Tangdu Hospital, and was conducted in 28 tertiary hospitals throughout China between April 2021 and July 2022 (Supplemental Table 1, http://links.lww.com/CM9/C16). Healthy Chinese adult volunteers aged 18–79 years were recruited from hospital staff members, health examination centers, and adjacent communities, and divided into six age groups: 18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, and 70–79 years. The initial number of eligible participants was 3599; 546 volunteers were then excluded for reasons as follows: withdrawal from the study, not fulfill the inclusion criteria at the appointed examination, and unsatisfied image quality for carotid property analysis. The final number of participants was 3053.

The inclusion criteria were: (1) 18–79 years old; (2) Han ethnicity; (3) normal BP (systolic BP <140 mmHg, diastolic BP <90 mmHg); (4) normal results of physical examination (normal vital signs, no malformations of the head, limbs or trunk, no disability of speaking, listening or visual acuity, no neurological or psychiatric issues by general physical examination) and electrocardiography. The exclusion criteria were as follows: (1) IMT of the common carotid artery (CCA) ≥1.0 mm by conventional B-mode ultrasound screen[23]; (2) previous cardiovascular disease history and medication history, including coronary heart disease, congenital heart disease, heart failure, hypertension, stroke, hyperlipidemia (total cholesterol [TC] >6.2 mmol/L),[18,24] diabetes (fasting blood glucose [FBG] >7.0 mmol/L), aortic arteritis, and other diseases that may impair the carotid structure or function; (3) history of endocrine, rheumatism, chronic respiratory disease, liver, and kidney diseases; (4) obesity (BMI ≥28.0 kg/m^2),[25] professional athletes, pregnant, and lactating women; (5) alcohol or drug addicts and current smokers.

BPs were measured on the upper arm using the electronic BP monitors (YE666CR, Yuwell, Jiangsu, China) just before the ultrasound examinations. The blood specimen for the examinations of TC, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and FBG was collected within 24 h before or after the ultrasound examinations. The heart rate (HR) was determined by the ultrasound system based on the carotid distension waves during the examinations. The height and weight were measured and the smoking and drinking histories were collected on the day of ultrasound examinations. For potential subgroup analysis, BP, BMI, TC, and TG were categorized using the following established clinical criteria: BP, optimal (<120/80 mmHg), normal (≥120/80 mmHg and <130/85 mmHg), and high normal (≥130/85 mmHg and <140/90 mmHg); BMI, underweight (<18.5 kg/m^2), normal (≥18.5 kg/m^2 and <24.0 kg/m^2), and overweight (≥24.0 kg/m^2 and <28.0 kg/m^2); TC, appropriate level (<5.2 mmol/L), and marginal increase (≥5.2 mmol/L and <6.2 mmol/L); TG, appropriate level (<1.7 mmol/L), and marginal increase (≥1.7 mmol/L and <2.3 mmol/L).[24]

RF ultrasound examination of the carotid arteries

For the quality control of the study, each collaborating center appointed two certificated and experienced ultrasound doctors to receive centralized and strict training for standardized image acquisition and measurement with a uniform protocol in advance.

The carotid properties determined by RF ultrasound were performed using Esaote ultrasound systems (MyLab^{TM}9, MyLab^{TM}X7 or MyLab^{TM}Alpha, Esaote, Genova, Italy), equipped with L4-15 (4–15 MHz) or SL1543 (3–13 MHz) probe. The volunteers were examined in supine position. Bilateral CCA were clearly imaged under B-mode at first. Then, the real-time measurement of carotid far-wall IMT, diameter, and distension were achieved by the advanced RF tracking programs (quality intima-media thickness [QIMT] and quality arterial stiffness [QAS], Esaote, Genoa, Italy).[26] The region of interest was a 10–15 mm segment that was about 10–15 mm proximal to the carotid bifurcation in the longitudinal view, which is perpendicular to the direction of probe. Average values over six consecutive heartbeats of the RF-derived measures were reported in real-time, and the corresponding standard deviations (SDs) were used for quality control feedback (≤20 μm for IMT and distension, ≤0.2 mm for diameter) [Figure 1]. The local pressure waveform is obtained by transforming the last six cycles of the distension curve over time into one pressure curve with calibration by brachial BPs.[27,28] The arterial stiffness parameters, including compliance coefficient (CC), β stiffness, and local PWV, were automatically calculated using the following formulas: $CC = \pi \times (2 \times D \times \Delta D + \Delta D^2) / (4 \times \Delta P)$; $\beta \text{ stiffness} = D \times \ln(Ps/Pd) / \Delta D$; $PWV = [D^2 \times \Delta P / (2 \times \rho \times D \times \Delta D + \rho \times \Delta D^2)]^{1/2}$, where D is the diastolic diameter, ΔD is the distention (difference between the diastolic and systolic diameters), Ps is the local systolic BP, Pd is the local diastolic BP, $\Delta P = Ps - Pd$, ρ is the blood density.[27,29] Greater PWV, β stiffness, and lower CC represent worse arterial stiffness. The augmented pressure (AP) and augmentation index (AIx) were also determined through the wave analysis of the transformed local pressure waveform automatically. The mean values of right and left carotid property parameters were used for analyses.

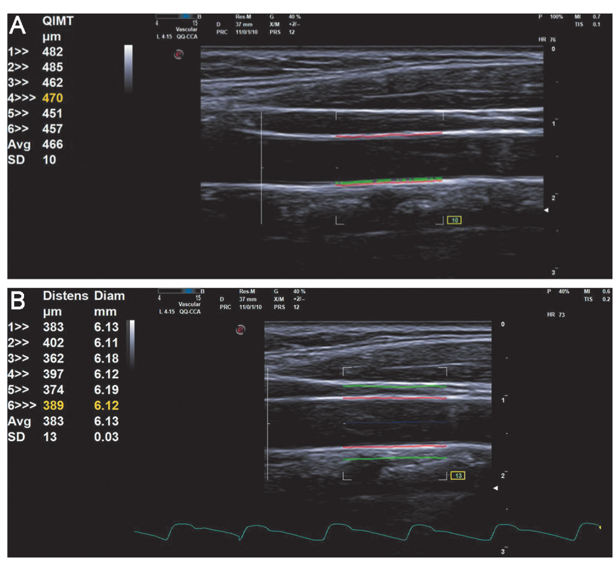

Figure 1: Measurement of the IMT, diameter, and distension of the CCA based on ultrasound RF signal. The ROI was a 10–15 mm segment that was about 10–15 mm proximal to the carotid bifurcation in the longitudinal view. (A) The white-thin square box is the ROI, and the number beside the ROI is the SD of the successive measurements of six consecutive heartbeats, which is continuously updated in real time. The green line inside the ROI represents the intima-media and the red line represents the adventitia. The beat-to-beat values and the average value of six consecutive heartbeats of IMT were reported in real time by the QIMT function (QIMT, Esaote, Genova, Italy). (B) Within the ROI, the red lines represent the wall diameter tracking, the green lines represent the amplified wall distension, and the blue line is the reference line for the location of the center of CCA. The cyan curve represents the distension curve over time. The beat-to-beat values and the average value of six consecutive heartbeats of distension and diameter were reported in real-time by the QAS function (QAS, Esaote). CCA: Common carotid artery; IMT: Intima-media thickness; QAS: Quality arterial stiffness; QIMT: Quality intima-media thickness; RF: Radio frequency; ROI: Region of interest; SD: Standard deviation.

Statistical analyses

All the statistical analyses were performed using SPSS 27.0 (IBM SPSS Statistics, Armonk, NY, USA). Data were stratified by age groups and sex, and were expressed as the mean ± standard deviation (SD) for normally distributed continuous variables, medians (inter-quartile ranges) for non-normally distributed continuous variables and number (%) for categorical variables. Independent Student's *t*-test or Mann–Whitney *U* test for continuous variables and χ^2 test for categorical variables were used to compare differences between women and men. Jonckheere–Terpstra test was used for the trend analyses of age groups. Simple linear regressions were conducted between age and carotid property parameters to establish the corresponding regression equations for women and men, separately. Pearson's correlation was used to examine simple correlations between the clinical characteristics and carotid properties. Multiple linear regression was further performed to determine the relationship between significant correlated variables and carotid properties with adjustment of age and sex. The analyses of covariance (ANCOVA) with age and sex as covariates were subsequently used to reveal the effects of the still significant clinical correlates on carotid properties, where the clinical characteristics were treated as categorical variables according to established criteria. A two-tailed P <0.05 was considered statistically significant.

Table 1: Clinical characteristics of the included healthy Chinese adults for the establishment of reference values of carotid intima-media thickness and arterial stiffness.

Variables	Women (*n* = 1922)	Men (*n* = 1131)	*P*-value
Age (years)	39.6 ± 12.4	37.5 ± 13.6	<0.001
Height (cm)	161 ± 5	173 ± 6	<0.001
Weight (kg)	56.4 ± 7.0	68.8 ± 8.9	<0.001
BMI (kg/m^2)	21.7 ± 2.5	23.0 ± 2.5	<0.001
SBP (mmHg)	114 ± 12	120 ± 10	<0.001
DBP (mmHg)	72 ± 8	75 ± 8	<0.001
MAP (mmHg)	86 ± 9	90 ± 8	<0.001
PP (mmHg)	42 ± 9	45 ± 9	<0.001
HR (bpm)	72.3 ± 10.1	71.0 ± 10.3	<0.001
TC (mmol/L)	4.36 ± 0.71	4.27 ± 0.75	<0.001
HDL-C (mmol/L)	1.41 ± 0.33	1.25 ± 0.27	<0.001
LDL-C (mmol/L)	2.44 ± 0.61	2.56 ± 0.62	<0.001
TG (mmol/L)	0.93 (0.70–1.27)	1.15 (0.86–1.49)	<0.001
FBG (mmol/L)	4.94 ± 0.52	4.92 ± 0.58	0.220
Smoking history	22 (1.14)	276 (24.40)	<0.001
Drinking history	47 (2.45)	274 (24.23)	<0.001

Data are presented as the means ± SDs, medians (inter-quartile ranges), or numbers (%). BMI: Body mass index; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; HR: Heart rate; LDL-C: Low-density lipoprotein cholesterol; MAP: Mean arterial pressure; PP: Pulse pressure; SBP: Systolic blood pressure; SDs: Standard deviations; TC: Total cholesterol; TG: Triglyceride.

Results

Study population

A total of 3053 healthy subjects were ultimately enrolled, including 1922 women (39.6 ± 12.4 years) and 1131 men (37.5 ± 13.6 years). As shown in Table 1, the height, weight, BMI, BPs, LDL-C level, and TG level were significantly higher in men than women (all P <0.05), while HR, TC, and HDL-C levels were lower in men. No significant difference of FBG were found between sex groups. Men showed a significantly higher percentage of smoking and drinking history than women (all P <0.05).

Age- and sex-specific reference values for carotid properties

The reference values for carotid properties stratified by sex and age group are shown in Table 2. All of the structure (IMT and diameter), stiffness (CC, β stiffness, and PWV), and wave reflections (Ps, AP, and AIx) parameters of CCA demonstrated age-related trajectories in both men and women. Overall, women had thinner IMT and smaller diameter of CCA than men. There was no significant sex difference of CC before forties, and women showed lower CC than men after that. The β stiffness was significantly higher in men than women in age groups of 18–29 years and 30–39 years, but the differences were inverse in the following age groups. PWV was higher in age groups of 18–29 years and 30–39 years, but lower in age group of 60–69 years in men than women. Men demonstrated higher Ps than women before fifties. Women showed larger AP than men across the adult lifespan except in age group of 18–29 years. The AIx was consistently higher in women than men.

Sex-specific simple linear regression for carotid properties and age

The sex-specific simple linear regression equations for each carotid property parameters and age are summarized in Table 3. All of the carotid property parameters showed significant linear regression relationship with age for both men and women [Figure 2]. The increase rates of IMT and diameter of CCA were similar between men and women (5.5 μm/year in women and 5.8 μm/year in men for IMT; 0.03 mm/year for diameter in both men and women; all P for age by sex interaction >0.05). For the stiffness and wave reflections, women showed larger age-related variations than men as demonstrated by steeper slopes (all P-values for age by sex interaction <0.05).

Associations between clinical characteristics and carotid properties

Most of the clinical characteristics and the carotid properties were correlated, except for the following pairs: diastolic BP and β stiffness; HR and β stiffness, PWV; HDL-C and CC, β stiffness, AP, AIx [Supplementary Table 2, http://links.lww.com/CM9/C16]. With further multiple linear regression with adjustment of age and sex, significant clinical determinants of carotid properties were identified using stepwise method [Supplementary Table 3, http://links.lww.com/CM9/C16]. BP, BMI, TC, and TG were then

Table 2: Age- and sex-specific reference values for carotid properties of the study population.

Age group (years)	n	IMT (μm)		CCA diameter (mm)		CC (mm^2/kPa)		β stiffness		PWV (m/s)		Ps (mmHg)		AP (mmHg)		AIx (%)	
		Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
18–29	793	492 ± 65	498 ± 72	6.61 ± 0.42	6.89 ± 0.43*	1.432 ± 0.494	1.378 ± 0.402	4.93 ± 1.61	5.16 ± 1.57*	4.98 ± 0.83	5.23 ± 0.80*	101 ± 9	111 ± 10*	1.25 ± 1.19	2.31 ± 1.71*	0.003 ± 5.479	−0.944 ± 2.972*
30–39	1049	521 ± 68	550 ± 82*	6.77 ± 0.42	7.26 ± 0.50*	1.153 ± 0.377	1.185 ± 0.391	6.27 ± 1.89	6.59 ± 2.19*	5.66 ± 0.89	5.98 ± 0.99*	102 ± 10	110 ± 9*	1.81 ± 1.99	1.50 ± 1.35*	3.467 ± 6.223	−0.049 ± 2.936*
40–49	572	575 ± 80	595 ± 83*	6.99 ± 0.46	7.48 ± 0.59*	0.914 ± 0.290	1.081 ± 0.357*	8.20 ± 2.50	7.55 ± 2.41*	6.58 ± 1.06	6.47 ± 1.05	105 ± 12	110 ± 10*	3.85 ± 3.34	2.17 ± 1.93*	7.262 ± 6.540	2.892 ± 4.475*
50–59	383	645 ± 91	660 ± 88	7.42 ± 0.60	7.61 ± 0.69*	0.805 ± 0.285	0.931 ± 0.384*	10.23 ± 3.58	9.39 ± 3.60*	7.51 ± 1.31	7.25 ± 1.44	111 ± 11	112 ± 12	6.44 ± 4.12	3.30 ± 3.04*	11.835 ± 7.395	5.491 ± 6.035*
60–69	192	700 ± 92	747 ± 120*	7.85 ± 0.71	8.05 ± 0.72	0.748 ± 0.246	0.895 ± 0.323*	11.86 ± 3.99	10.42 ± 3.31*	8.15 ± 1.24	7.73 ± 1.25*	115 ± 11	115 ± 11	7.87 ± 3.84	4.98 ± 3.98*	13.909 ± 6.850	9.090 ± 7.117*
70–79	64	744 ± 97	820 ± 98*	8.20 ± 0.74	8.64 ± 1.04	0.776 ± 0.320	0.879 ± 0.234	12.89 ± 4.29	11.47 ± 4.20	8.50 ± 1.48	8.41 ± 1.94	117 ± 10	120 ± 9	8.49 ± 5.07	6.68 ± 6.92*	15.243 ± 9.502	10.485 ± 9.994
P for trend		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.003	<0.001	<0.001

Data are presented as the means ± SDs. *P <0.05 *vs.* women. AIx: Augmentation index; AP: Augmented pressure; CC: Compliance coefficient; CCA: Common carotid artery; IMT: Intima-media thickness; Ps: Local systolic blood pressure; PWV: Pulse wave velocity; SDs: Standard deviations.

Table 3: Simple linear regression equations for carotid properties and age of the study population.

Variables	Sex	Equations	R^2	*P*-value
IMT (μm)	Women	5.475 × age + 340.629	0.449	<0.001
	Men	5.845 × age + 352.501	0.481	<0.001
CCA diameter (mm)	Women	0.031 × age + 5.740	0.376	<0.001
	Men	0.029 × age + 6.226	0.331	<0.001
CC (mm^2/kPa)	Women	−0.018 × age + 1.816	0.267	<0.001
	Men	−0.012 × age + 1.645	0.165	<0.001
β stiffness	Women	0.182 × age + 0.165	0.457	<0.001
	Men	0.130 × age + 2.072	0.355	<0.001
PWV (m/s)	Women	0.084 × age + 2.829	0.520	<0.001
	Men	0.063 × age + 3.761	0.407	<0.001
Ps (mmHg)	Women	0.369 × age + 89.843	0.169	<0.001
	Men	0.099 × age + 107.299	0.019	<0.001
AP (mmHg)	Women	0.180 × age – 3.915	0.391	<0.001
	Men	0.054 × age + 0.366	0.084	<0.001
AIx (%)	Women	0.376 × age – 9.423	0.345	<0.001
	Men	0.228 × age – 6.971	0.334	<0.001

AIx: Augmentation index; AP: Augmented pressure; CC: Compliance coefficient; CCA: Common carotid artery; IMT: Intima-media thickness; Ps: Local systolic blood pressure; PWV: Pulse wave velocity.

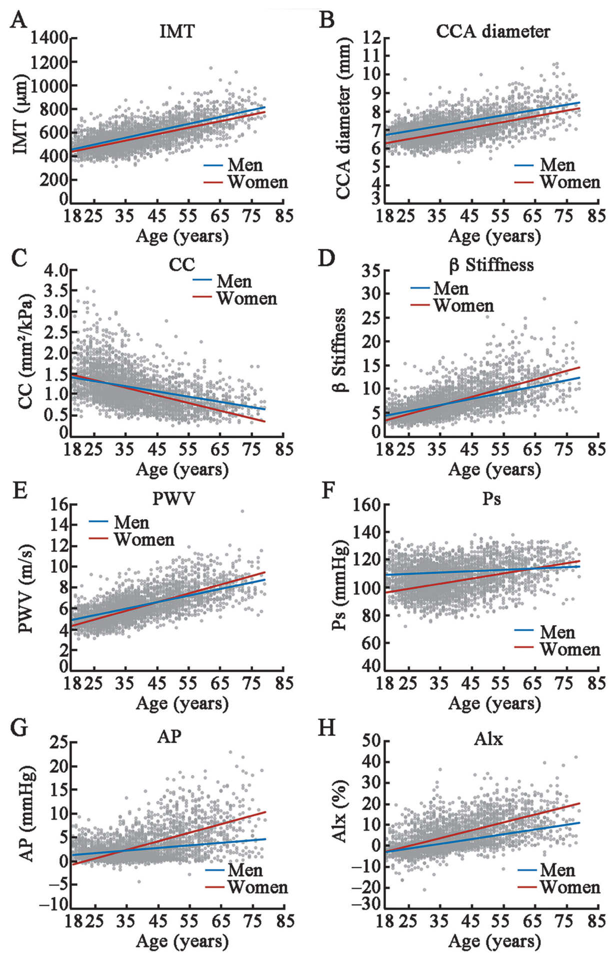

Figure 2: Simple linear regression for carotid property parameters and age. The solid lines were the corresponding regression lines for men and women. (A) IMT. (B) CCA diameter. (C) CC. (D) β stiffness. (E) PWV. (F) Local systolic blood pressure of CCA (Ps). (G) AP. (H) AIx. AIx: Augmentation index; AP: Augmented pressure; CC: Compliance coefficient; CCA: Common carotid artery; IMT: Intima-media thickness; PWV: Pulse wave velocity.

Table 4: The ANCOVA for BP, BMI, TC, TG categories, and carotid properties of the study population.

Clinical categories		IMT (μm)	CCA diameter (mm)	CC (mm²/kPa)	β stiffness	PWV (m/s)	Ps (mmHg)	AP (mmHg)	AIx (%)
BP	Optimal (n = 1635)	555 (551, 558)	7.02 (6.99, 7.04)	1.186 (1.167, 1.204)	7.10 (6.98, 7.22)	5.90 (5.85, 5.95)	100 (100, 100)	2.32 (2.19, 2.46)	3.080 (2.799, 3.361)
	Normal (n = 837)	567 (562, 573)*	7.12 (7.09, 7.16)*	1.053 (1.028, 1.078)*	7.41 (7.24, 7.57)*	6.35 (6.28, 6.41)*	112 (111, 112)*	3.22 (3.04, 3.40)*	4.484 (4.095, 4.872)*
	High normal (n = 581)	579 (572, 585)*,†	7.23 (7.18, 7.27)*,†	1.037 (1.006, 1.068)*	7.27 (7.06, 7.47)	6.55 (6.47, 6.63)*,†	120 (119, 121)*,†	4.07 (3.85, 4.30)*,†	5.666 (5.185, 6.146)*,†
BMI	Underweight (n = 241)	547 (537, 557)	6.96 (6.89, 7.02)	1.284 (1.236, 1.332)	6.37 (6.06, 6.68)	5.70 (5.57, 5.83)	104 (102, 105)	2.59 (2.24, 2.94)	3.582 (2.849, 4.315)
	Normal (n = 2027)	559 (555, 562)	7.05 (7.02, 7.07)*	1.128 (1.112, 1.145)*	7.13 (7.02, 7.24)*	6.08 (6.04, 6.13)*	106 (106, 107)*	2.83 (2.71, 2.95)	3.811 (3.558, 4.064)
	Overweight (n = 785)	578 (572, 583)*	7.23 (7.19, 7.27)*,†	1.053 (1.026, 1.080)*,†	7.69 (7.51, 7.86)*,†	6.44 (6.36, 6.51)*,†	110 (109, 111)*,†	3.16 (2.96, 3.36)*,†	4.436 (4.021, 4.850)†
TC	Appropriate level (n = 2711)	562 (559, 565)	7.09 (7.07, 7.11)	1.125 (1.111, 1.140)	7.19 (7.09, 7.28)	6.13 (6.09, 6.17)	107 (106, 107)	2.89 (2.77, 2.98)	3.943 (3.725, 4.161)
	Marginal increase (n = 342)	565 (557, 574)	7.06 (7.01, 7.12)	1.087 (1.046, 1.127)	7.43 (7.17, 7.69)	6.24 (6.13, 6.35)	107 (106, 108)	3.05 (2.76, 3.35)	4.033 (3.416, 4.649)
TG	Appropriate level (n = 2785)	564 (561, 567)	7.09 (7.07, 7.11)	1.123 (1.108, 1.137)	7.21 (7.12, 7.31)	6.15 (6.11, 6.19)	107 (106, 107)	2.85 (2.74, 2.95)	4.067 (3.845, 4.290)
	Marginal increase (n = 268)	577 (567, 586)*	7.18 (7.12, 7.24)*	1.075 (1.029, 1.120)*	7.65 (7.36, 7.94)*	6.36 (6.24, 6.48)*	107 (106, 108)	3.08 (2.75, 3.40)	4.394 (3.693, 5.095)

Data were reported as estimated marginal means and (95% confidence intervals). *P <0.05, *vs.* optimal category for BP; *vs.* underweight for BMI; *vs.* appropriate level for TG. †P <0.05, *vs.* normal category for BP and BMI. AIx: Augmentation index; ANCOVA: Analyses of covariance; AP: Augmented pressure; BMI: Body mass index; BP: Blood pressure; CC: Compliance coefficient; CCA: Common carotid artery; IMT: Intima-media thickness; Ps: Local systolic blood pressure; PWV: Pulse wave velocity; TC: Total cholesterol; TG: Triglyceride.

selected subsequently in the ANCOVA of carotid properties with age and sex as covariates using the established clinical criteria mentioned above. The estimated marginal means with 95% confidence intervals of carotid properties in corresponding groups are shown in Table 4. Higher BP and BMI categories were associated with thicker IMT, larger CCA diameter, decreased CC, increased β stiffness and PWV, higher Ps, larger AP, and AIx. TC category did not significantly affect carotid properties after adjustment of age and sex. The marginal increase level of TG was related with increased IMT, diameter, β stiffness and PWV, and decreased CC.

Discussion

In the present study, with the establishment of age- and sex-specific reference values of carotid properties in healthy Chinese adults, the major findings were as follows: (1) aging is associated with increased IMT, deterioration of the arterial stiffness, and augmented wave reflections [Figure 3]; (2) significant different age-related trajectories of carotid properties were observed between men and women; (3) BP, BMI, and TG were identified as the major clinical determinants of carotid property parameters.

Although the major aspects of arterial properties, such as IMT, PWV, and AIx, have been proven to be independent and important clinical biomarkers and risk predictors for cardiovascular diseases by numerous of studies,[6,8,21] the comprehensive assessment of arterial properties has yet be incorporated into routine clinical practice. The plethora of methods and devices make the carotid evaluation complex and inconvenient. Actually, except the direct transit time method of PWV measurements, the local non-invasive assessment of arterial stiffness and wave reflection were all based on the local diameter change and/or pressure estimations, which are most usually measured at CCA.[11,30] The RF ultrasound could track the CCA walls in real time using the raw ultrasound signal, which is of high spatial and temporal resolution.[12] The local carotid BP could also be estimated by converting the distension curves to

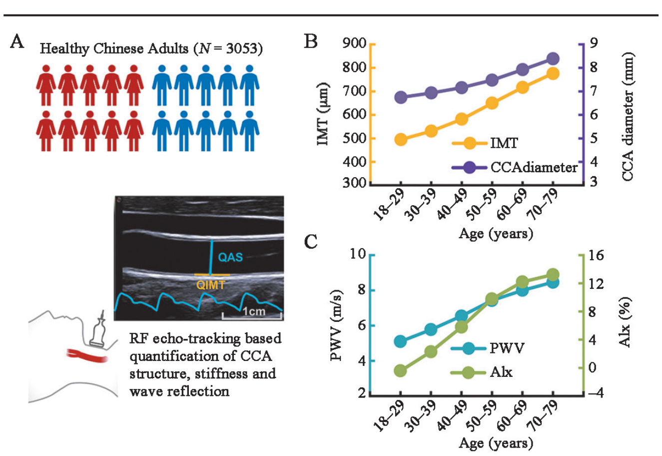

Figure 3: Illustration of the study design and main findings. The reference values of carotid properties, including the structure, stiffness, and wave reflections, were established based on a large Han Chinese population of 3053 healthy participants based on ultrasound RF signal. AIx: Augmentation index; CCA: Common carotid artery; IMT: Intima-media thickness; PWV: Pulse wave velocity; RF: Radio frequency.

pressure curves using a linear conversion factor. In combination with the well-established RF IMT measurement, the comprehensive assessment of carotid properties can be accomplished by a single RF ultrasound examination. The RF ultrasound system also provides immediate feedback of the quality control of the automatic measurement, which is more reliable and operator-independent,[26,31] and thus suitable for popularization in both hospitals and communities. Therefore, the advanced RF ultrasound was selected for the integrative assessment of carotid properties and establishment of corresponding normal reference values in the present study.

Age is the most important determinant of arterial properties.[32,33] With advanced aging, the arterial wall thickness increases, lumen enlarges, stiffness increases, and wave reflection enhances as measured by different methods.[9,34] The general age-related trend of our data by RF ultrasound for carotid properties was in accordance with previous reports of large-scale studies.[18–20,35] The yearly increase rate of IMT (5.5 μm/year in women and 5.8 μm/year in men) across the adult life span was similar with those previously reported in healthy subjects using ultrasound tracking technique.[18] The reference values of CCA diameter were larger than the reported B-mode-based values in similar age groups, which was largely attributed to the method difference, where RF ultrasound measures inter-adventitial diameter (distance between near-wall and far-wall media-adventitia interface), but B-mode measures intraluminal diameter.[35,36] The ethnic and corresponding body type difference may also contribute to the diameter differences.[35] The decrease of arterial compliance during aging is parallel with the increase of stiffness as shown by the age-related variation of CC, β stiffness, and PWV in this study. The age- and sex-specific reference values of corresponding parameters were comparable to previously reported values using similar RF ultrasound in the European population[37] or ultrafast ultrasound in the Chinese population.[22] In comparison with the carotid-femoral PWV,[19] the local carotid PWV obtained in the present study was relatively lower, which consisted with previous comparison studies of carotid-femoral PWV and carotid PWV in the same samples.[38,39] As the abdominal aorta and femoral artery had obvious higher PWV than proximal artery, the involvement of those segments in carotid-femoral PWV determination could account for the above differences.[40] The worse carotid stiffness in women as demonstrated by CC, β stiffness, and PWV compared with men since forties, should attribute to the loss of cardiovascular protective effect by endogenous estrogens, whose level begin to decline during the menopause transition.[41] The estimated Ps by RF ultrasound was quite close to that by tonometry (within ~5 mmHg) in corresponding age and sex groups.[20] The RF ultrasound-derived AP and AIx showed much smaller range of values but similar age-related trend compared with those of tonometry.[20,42] The obvious higher AP and AIx in women than men were in agreement with previous studies, which should be due to the lower height and higher HR of women.[20,43,44] Because lower height is related with shorter arterial system, leading to earlier backward wave, thus more AP; and higher HR is also associated with higher amount of wave reflection.[20,43,44] The large SD and thus high coefficient of variation (close to or >1) was in accordance with previous reports, suggesting the large biological variations of AP and AIx,[21,42] which may limit the clinical use of reference values.

The influence of BP on arterial properties has been well recognized both in normal subjects and hypertension patients.[18–20,32] In this study, BPs were identified as the major clinical determinants for all the parameters of carotid properties based on RF ultrasound. Higher BP categories even within the current normal BP range were associated with worse carotid properties after adjustment of age and sex, which was consistent with previous studies.[18–20,22] BMI was also reported to be related with multiple arterial properties, including IMT, stiffness, and central hemodynamics.[18,22,45] In line with those reports, the healthy overweight adults in the present study defined according to Chinese criteria (≥24.0 kg/m^2 and <28.0 kg/m^2) also showed significant increased IMT, diameter, and stiffness, and enhanced wave reflections. Although lipid levels within the blood are closely associated with vascular health,[46,47] only TG levels still significantly impact the CCA IMT, diameter, and stiffness after stepwise regression and ANCOVA. Similar advantages of the TG level over other lipid parameters as to the association with arterial stiffness have also been reported in previous cross-sectional and longitudinal studies.[21,48] Collectively, it was suggested that levels of BP, BMI, and TG should be considered in the clinical use of current normal reference values of carotid properties.

There are several limitations in the present study that should be acknowledged. First, it should be noted that the differences of reference values between age groups may not equal to the longitudinal changes in carotid properties within individuals due to the cross-sectional nature of the present study. Second, only Han Chinese adults were enrolled for this study, thus the results may not be applicable to non-Han Chinese or other racial population. Reference values of CCA properties for Chinese minorities merit further study. Third, a large number of healthy old subjects were not enrolled due to the strict exclusion criteria, leading to the much smaller sample size of participants older than 70 years than the other groups, which may account for the non-significant comparison results between men and women in the age group of 70–79 years. Fourth, considering the potential impacts of different lifestyle and other social-economic factors between urban and country population on cardiovascular system, the election of present research subjects based on urban populations may cause selectivity bias. However, as we used strict inclusion and exclusion criteria to recruit healthy subjects, the bias should only have quite limited influences on the general results.

In conclusion, in the present study, the age- and sex-specific reference values for the comprehensive evaluation of carotid properties were established based on a large Han Chinese population of 3053 healthy participants by RF ultrasound. The major clinical determinants of carotid properties, BP, BMI, and TG, should be taken into account when applying corresponding reference values. The normal reference values could promote the comprehensive evaluation of carotid properties (structure, stiffness, and wave reflections) by a single technique of RF ultrasound in clinical practice.

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Conflicts of interest

None.

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