Normal norms of carotid vessel wall volume in Taiwanese adults as measured using three-dimensional ultrasound

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Abstract

Purpose: The three-dimensional (3D) measurement of vessel wall volume (VWV) and plaque volume is sensitive for predicting cardiovascular risk. We established the normal norms of carotid VWV.

Methods: We retrospectively enrolled 352 patients with normal findings of the carotid ultrasound studies. Two-dimensional carotid intima-media thickness (IMT) was measured online. Grayscale 3D images of both sides of the carotid arteries were analyzed offline for measurement of IMT (QIMT) and VWV.

Results: The median age of the enrollees was 59 years. The median carotid IMT, QIMT, and VWV was 0.61 mm, 0.72 mm, and 90 mm^3, respectively. No differences in IMT and VWV were observed between men and women or between the right and left side. We stratified participants into four groups, namely young adults (≤50 years), middle-aged adults (51–65 years), older adults (66–75 years), and senior adults (≥75 years). All the values of measured variables increased with advancing age. The median VWV of each group was 84, 90, 100, and 112 mm^3, respectively. The increment percentage from young to senior adults was similar in terms of IMT and VWV. Nevertheless, the difference in the value of VWV (28 mm^3) was much larger than that in IMT (0.18 mm). All three measured variables exhibited a positive linear correlation with age.

Conclusion: Both IMT and VWV have positive linear correlations with age. The application of QIMT measurements was limited by its inconsistent accuracy. VWV not only has a strong correlation with IMT but also enables observation of dynamic vessel wall changes, which is valuable for clinical observational studies.

Keywords: carotid ultrasound, intima–media thickness, normal norms, three-dimensional ultrasound, vessel wall volume

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INTRODUCTION

The carotid arteries are one of the most easily screened arteries of the vascular system. Carotid atherosclerosis is associated with cardiovascular and cerebrovascular events(1,2), and the degree of carotid atherosclerosis has been used to estimate and classify individuals' cardiovascular risk(3). The prevalence of increased carotid

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intima–media thickness (IMT) and carotid plaque is increasing in the general population worldwide[4]. Carotid IMT is the combined thickness of the intimal (20%) and medial (80%) layers of the carotid artery[5]. Meta-analysis studies have demonstrated that carotid IMT only minimally improves predictive power beyond traditional risk factors[6]. Carotid plaque is a more powerful predictor of cardiovascular risk than carotid IMT alone. However, focal thickening of the IMT typically coexists with protuberant plaque, and the two conditions are indistinguishable from each other. Therefore, measuring the thickness of the vessel wall, which comprises the intima–media and protuberant plaque, is more reasonable than measuring the IMT or plaque alone[7].

Carotid ultrasound is a noninvasive and reproducible study and is generally regarded as the standard imaging technique for primary evaluation of carotid atherosclerosis and plaque burden[5,8,9]. With the continual advancements in ultrasound equipment and relevant software, the IMT, vessel wall, and plaque of the carotid artery can now be detected on a three-dimensional (3D) plane. Smaller values of measured IMT can be converted to higher vessel wall volume (VWV) values, which enhances the feasibility of monitoring the sequential changes of carotid plaque in a shorter duration and with fewer subjects during clinical research[3,10]. Furthermore, 3D assessment of plaque volume is progressively more sensitive in predicting cardiovascular risk than mere assessment of plaque presence[6]. We developed a standardized method of 3D ultrasound measurement of carotid VWV with a reasonable interobserver differences and high reliability[7]. In this study, we established the normal norms of carotid VWV in Taiwanese adults and their association with age and carotid IMT.

METHODS

A 3D transducer was available as part of the ultrasound equipment in our institute, and rapid 3D carotid ultrasound scanning of bilateral carotid arteries is included in the regular carotid ultrasonography program. Through a retrospective review, patients who were referred to the sonographic laboratory from the outpatient clinic for carotid duplex sonography and had normal findings of bilateral carotid arteries on a B-mode scan with available 3D images were enrolled in this study. Ethical approval

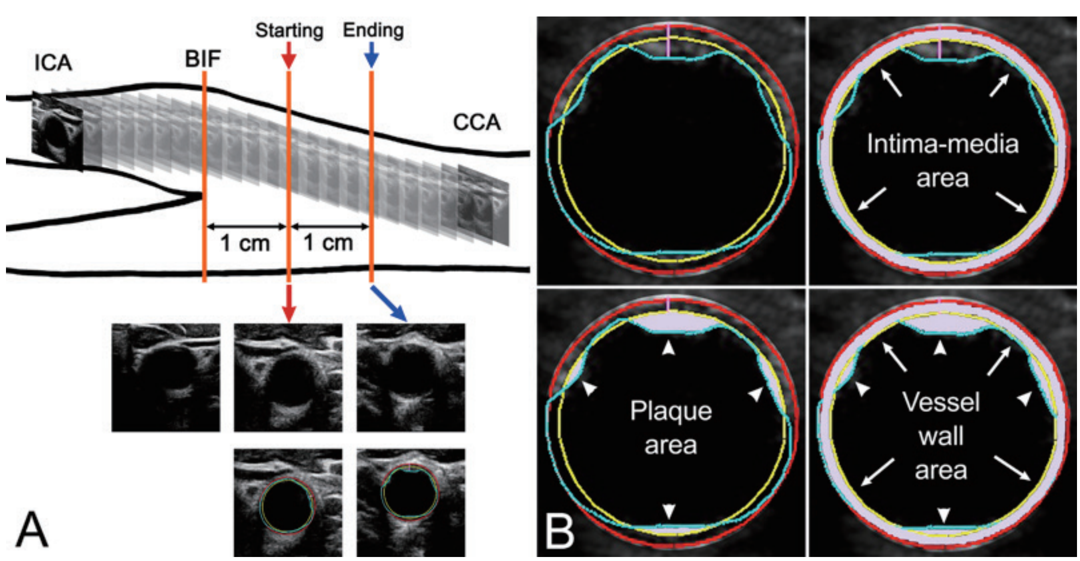

Figure 1. (A) Selection of the starting point (1 cm proximal to the bifurcation; red arrow) and end point (1 cm proximal to the starting point; blue arrow) from the extracted cross sections. (B) Measurement of the cross section of the selected frame. The outer wall was manually traced using an elliptical tracing tool (red coil line). The inner wall (edge of the 0.4-mm IMT; yellow coil line) and lumen boundary (green coil line) were automatically traced using relevant software.
BIF, bifurcation; CCA, common carotid artery; ICA, internal carotid artery; IMT, intima–media thickness

for this study was provided by the Institutional Review Board of Taipei Tzu Chi Hospital, New Taipei City, on August 7, 2020 (no. 09-X-063). Informed written consent was waived because the study constituted a retrospective data analysis. The detailed procedures of the two-dimensional (2D) and 3D carotid ultrasound were described in a previous report[7]. In brief, we used an Affiniti 70 ultrasound system (Philips Healthcare, Bothell, WA, USA) to measure the 2D carotid IMT at a mean distance of 1 cm from the far wall of the distal common carotid artery (CCA) bilaterally with the built-in autotrace function of the scanning equipment. Grayscale 3D images of the carotid artery from the distal CCA to the internal carotid artery on both sides were acquired using a single-sweep VL15-3 transducer. The 3D images were analyzed offline on a computer by using the vascular plaque quantification function of the Philips QLAB software. The standardized method of measuring the carotid VWV was employed, with measurements taken from a 1-cm segment of the distal CCA that was 1 cm proximal to the carotid bifurcation (Figure 1A) with a preset IMT of 0.4 mm. The intima–media area was defined as the area between the outer and inner vessel walls. Plaque area was defined as the area between the lumen boundary and inner vessel wall, and the wall area was defined as the sum of the intima–media area and plaque area (Figure 2B). Measured data from all frames were exported as an Excel file. From the exported Excel file, we manually computed the mean intima–media thickness (QIMT) and VWV of the measured 1-cm segment at the junction of the distal CCA and CCA bifurcation. The 3D image measurements were taken by a trained neurology resident.

Continuous variables were computed as the median (first to third quartile). The Mann–Whitney U and Kruskal–Wallis tests were used to evaluate differences in continuous variables. $P < 0.05$ was considered statistically significant. The correlation between the measured variables and age was analyzed through linear regression. All statistical analyses were performed using the MedCalc software package (version 18, Mariakerke, Belgium).

RESULTS

A total of 352 patients were enrolled in this study, including 147 men and 205 women. A total of 704 carotid arteries (including right and left sides) were measured. The median age was 59 (51–68) years, with no difference noted between men and women. The median 2D carotid IMT of the 704 carotid arteries in the 352 patients, which was automatically traced using the ultrasound equipment, was 0.61 (0.52–0.70) mm (Table 1). The median QIMT and VWV, which were manually measured using QLAB software, were 0.72 (0.63–0.85) mm and 90 (86–98) mm^3, respectively. No differences in IMT and VWV were observed between men and women or between the right and left side of the carotid arteries. A higher QIMT was observed in women and on the right side than in men and on the left side. The median value of the manually measured QIMT (0.74 mm [0.63–0.85 mm]) was higher than that of the automatically traced IMT (0.61 mm [0.52–0.70 mm]; $P < 0.0001$; Figure 2).

To identify the effect of age on the carotid vessel wall, we classified the enrollees into four age groups, namely young adults (≤50 years), middle-aged adults (51–65 years), older adults (66–75 years), and senior adults (age: ≥75 years). The number of participants in the senior adults group was only 23, which is possibly attributable to the lower proportion of senior adults with normal carotid

Table 1. Summary of the age and measured variables of the 352 enrollees

Variables	Total (n = 352)	Gender			Lateralization		
		Men (n = 147)	Women (n = 205)	P value	Right side	Left side	P value
Age (years)	59 (51-68)	58 (50-65)	59 (53-69)	0.1361	-	-	-
IMT (mm)	0.61 (0.52-0.70)	0.63 (0.52-0.71)	0.61 (0.52-0.69)	0.2439	0.61 (0.52-0.70)	0.62 (0.53-0.70)	0.6020
QIMT (mm)	0.74 (0.63-0.85)	0.72 (0.62-0.82)	0.76 (0.64-0.86)	0.0043	0.78 (0.64-0.86)	0.72 (0.62-0.81)	0.0003
VWV (mm^3)	90 (86-98)	90 (86-97)	91 (85-100)	0.2353	91 (85-99)	90 (86-98)	0.5756

IMT, intima-media thickness; QIMT, QLAB intima-media thickness; VWV, vessel wall volume

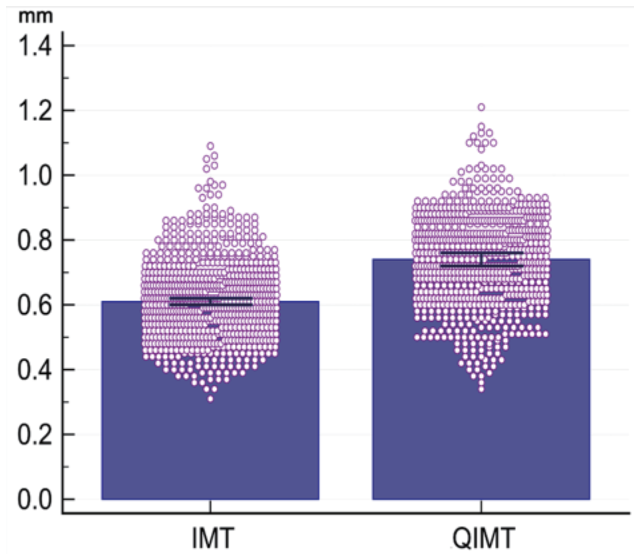

Figure 2. Median level of the offline manually measured IMT (QIMT) is higher than that of the online automatically traced IMT (0.74 vs. 0.61 mm, P < 0.0001).
IMT, intima–media thickness; QIMT, QLAB intima–media thickness

Table 2. Comparison of the measured variables of the 352 enrollees stratified by age and gender

	Age (years)	IMT (mm)	QIMT (mm)	VWV (mm^3)
Young adults (n = 84)	45 (40-49)	0.53 (0.46-0.62)	0.64 (0.55-0.72)	84 (81-87)
Men (n = 38)	46 (40-49)	0.55 (0.46-0.66)	0.67 (0.56-0.72)	85 (82-88)
Women (n = 46)	45 (37-48)	0.52 (0.46-0.68)	0.63 (0.54-0.72)	83 (80-86)
Middle-aged adults (n = 163)	58 (56-61)	0.61 (0.53-0.69)	0.74 (0.63-0.82)	90 (87-93)
Men (n = 74)	58 (56-61)	0.62 (0.54-0.70)	0.72 (0.62-0.80)	90 (87-92)
Women (n = 89)	58 (56-61)	0.61 (0.52-0.68)	0.76 (0.65-0.83)	91 (86-94)
Older adults (n = 82)	70 (68-71)	0.67 (0.59-0.75)	0.85 (0.72-0.90)	100 (93-107)
Men (n = 28)	70 (68-71)	0.69 (0.63-0.76)	0.82 (0.72-0.80)	101 (95-111)
Women (n = 54)	70 (68-71)	0.66 (0.59-0.73)	0.86 (0.73-0.90)	100 (93-107)
Senior adults (n = 23)	78 (76-82)	0.71 (0.63-0.85)	0.89 (0.85-1.02)	112 (114-118)
Men (n = 7)	80 (78-85)	0.74 (0.70-0.83)	0.89 (0.82-0.91)	111 (103-118)
Women (n = 16)	77 (76-81)	0.69 (0.62-0.86)	0.90 (0.86-1.03)	112 (106-118)
P value	<0.0001	<0.0001	<0.0001	<0.0001

IMT, intima-media thickness; QIMT, QLAB intima-media thickness; VWV, vessel wall volume
Young adults: ≤50 years; middle-aged adults: 51–65 years; older adults: 66–75 years; senior adults: ≥75 years

arterial walls. Table 2 presents the distributions of the measured variables across the four age groups. All the values of the measured variables (IMT, QIMT, and VWV) increased gradually with advancing age (P < 0.0001). The median VWV of the young, middle-aged, older, and senior adults was 84, 90, 100, and 112 mm^3, respectively. The percentages of increment from young to senior adults were similar in terms of IMT (34%, increased from 0.53 to 0.71 mm) and VWV (33%, increased from 84 to 112 mm^3). Nevertheless, the value of difference in VWV (28

Table 3. Linear regression analysis of the age and measured variables of the 352 enrollees stratified by gender

	Men			Women		
	Coefficient	R2	P value	Coefficient	R2	P value
Correlation with age						
IMT	0.005	0.199	<0.0001	0.005	0.191	<0.0001
QIMT	0.007	0.334	<0.0001	0.006	0.232	<0.0001
VWV	0.651	0.500	<0.0001	0.621	0.454	<0.0001
Correlation among measured variables						
QIMT vs IMT	0.587	0.240	<0.0001	0.450	0.205	<0.0001
VWV vs IMT	43.6	0.231	<0.0001	31.6	0.173	<0.0001
VWV vs QIMT	43.6	0.333	<0.0001	37.4	0.239	<0.0001

IMT, intima-media thickness; QIMT, QLAB intima-media thickness; VWV, vessel wall volume

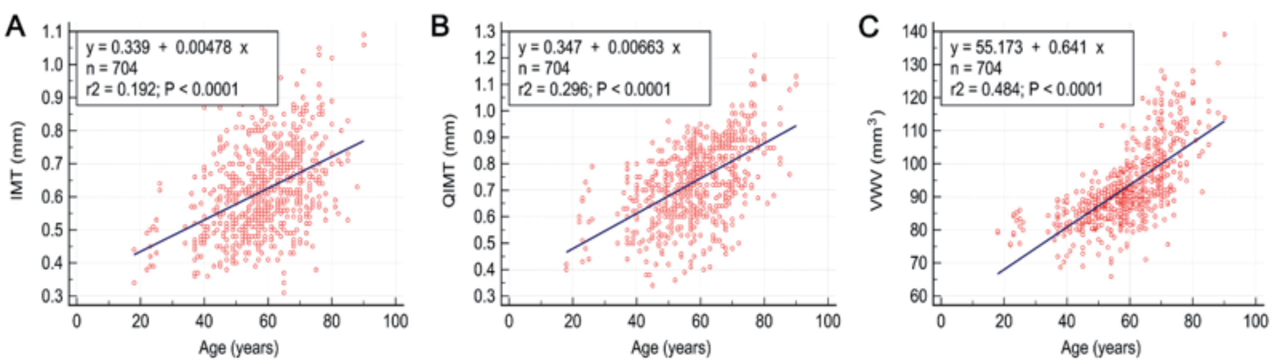

Figure 3. Linear regression plots for age with IMT (A), QIMT (B), and VWV (C). All the measured variables exhibited a positive linear correlation with age.

IMT, intima–media thickness; QIMT, QLAB intima–media thickness; VWV, vessel wall volume

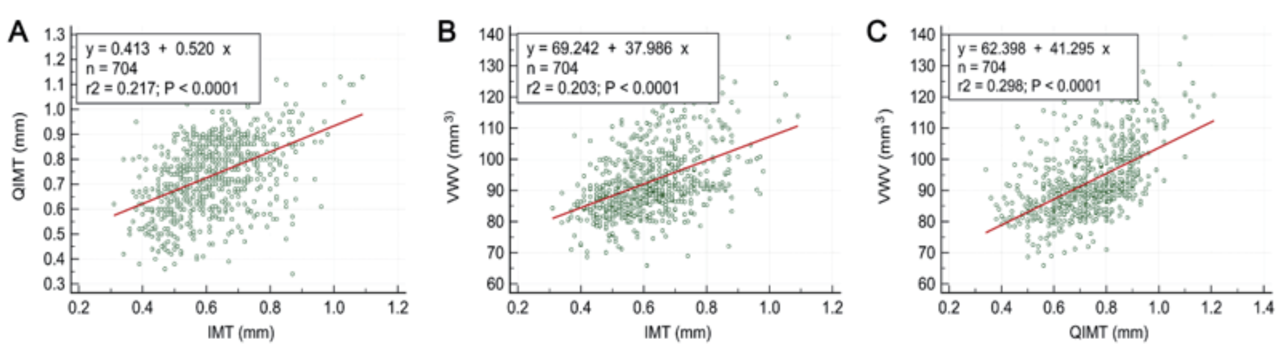

Figure 4. Linear regression plots among IMT, QIMT, and VWV. (A) Correlation of QIMT with IMT. (B) Correlation of VWV with IMT. (C) Correlation of VWV with QIMT.

IMT, intima–media thickness; QIMT, QLAB intima–media thickness; VWV, vessel wall volume mm^3) was much higher than that in IMT (0.18 mm). No difference in any variable was observed between men and women in each age group. However, we observed a trend of a higher median IMT in men (0.71 mm [0.64–0.72 mm]) than that in women (0.66 mm [0.59–0.75 mm]), with a P value of 0.0594 in participants aged over 65 years (older and senior adults); however, this result did not reach statistical significance (not shown in Table 2).

All the measured variables (IMT, QIMT, and VWV) exhibited a positive linear correlation with age, with fitted R-squared values of 0.192, 0.296, and 0.484, respectively ($P < 0.0001$; Figure 2A–C). We also identified the correlations among the automatically traced 2D IMT, manually measured QIMT, and VWV (Figure 3A–C). QIMT exhibited a positive linear correlation with IMT (R-squared = 0.217; $P < 0.0001$). VWV also exhibited a positive linear correlation with IMT (R-squared = 0.203; $P < 0.0001$). Furthermore, VWV exhibited a positive linear correlation with QIMT (R-squared = 0.298; $P < 0.0001$). These positive linear correlations were observed not only in all 704 arteries but were also present when the variables were distinguished in terms of men and women (Table 3).

DISCUSSION

On the basis of the established standardized method of combining single-sweep 3D carotid scanning and offline manual measurement using QLAB software, we could identify and quantify carotid VWV successfully. Similar to the well-recognized characteristics of the carotid IMT, the values of carotid VWV also exhibited an increment with advancing age.

The value of IMT was higher in the offline manually measured QIMT than in the online automatically traced 2D IMT. The American Society of Echocardiography determined through consensus that measuring the far wall of the distal CCA, with a starting point of approximately 1 cm from the distal CCA to an end point of 2 cm proximal to the carotid bifurcation, provides the most appropriate value to represent the carotid IMT[11]. However, vessel tortuosity and an inconstant insonation angle with indeterminate intimal boundary might be present at the transition of the CCA into the bifurcation. Sonographers tend to measure the 1 cm length of the IMT starting from 1.5 cm proximal to the bifurcation during regular carotid duplex study to obtain a more well-defined horizontal B-mode grayscale image on the screen without the need to rotate or tilt the transducer. In this study, we measured QIMT offline manually from 1 cm proximal to the bifurcation, where the IMT increases gradually from the distal CCA to the bifurcation. Therefore, the value of QIMT was higher than that of the 2D IMT. Nevertheless, QIMT still exhibited positive linear correlations with both the 2D IMT and age.

Although obtained from an average thickness of a 1-cm long longitudinal section, the 2D IMT simply represents a mean value for the far wall of the distal CCA. Unlike the 2D IMT, VWV is a summation of a 1-cm long vessel wall area in the transverse section derived from 42 to 43 2D frames. Hence, the diameter of the distal carotid artery plays a key role in constituting the vessel wall area. Compared with the near and lateral walls, the far wall normally presents a more well-defined grayscale pixel resolution. Adjusting the autotrace sensitivity of the IMT border allows us to modify the results of a circular vessel wall area. To avoid excessive intraluminal grayscale speckle noise and underestimation of the near wall boundary, an optimal setting of 80% tracing sensitivity with a preset of 0.4-mm IMT during QLAB software measurement can produce appropriate results in most cases.

Change in IMT is approximately 0.01–0.04 mm annually[12]. Spence et al. reported that the average annual change in total plaque area is 10 mm^2 [13]. As observed in this study, the 2D IMT and 3D VWV had similar increasing ratios of 33% to 34% from young to senior adults across 33 years. Only a median increment of 0.18 mm was observed in the 2D IMT, which is too small to assess changes from aging or the treatment effect. Regarding VWV across the same age groups, a median increment of 28 mm^3 is higher than the 0.18 mm increment in the 2D IMT and marks a more obvious difference. Furthermore, IMT is influenced by genetic determinants and is more affected by blood pressure than by atherosclerosis, whereas VWV with simultaneous plaque volume measurement is more associated with traditional vascular risk factors such as age, sex, hypertension, diabetes mellitus, and hyperlipidemia[14]. Increased carotid IMT is associated with an increased risk of myocardial infarction and stroke in older adults without a history of cardiovascular disease[15]. Measurement of IMT with plaque area is highly valuable for predicting cardiovascular disease and stroke[16]. Therefore, measurement of the 3D VWV through segmental cross-sectional scanning can avoid lesions being overlooked and provide considerable value for predicting vascular risk.

Age, sex, race, and ethnicity are crucial factors for IMT[11]. Older adults and men have been reported to have higher carotid IMT than younger adults and women[17]. Sun et al. reported that higher IMT was associated with male gender, and IMT was greater in the left CCA[18]. Chen et al. reported that no difference in lateralization of IMT was observed in a community study[17]. In the present study, no differences in IMT and VWV were observed between men and women or between right and left sides. Only a subgroup analysis revealed a trend of higher IMT in men among enrollees aged over 65 years (P = 0.0594). This could be attributable to the relatively small sample size and inadequate clinical information on comorbidities. In contrast, higher QIMT was observed in women and on the right side of CCA. The discrepant results between IMT and QIMT could be due to interference caused by the relative higher fat content in women's soft tissue, particular near the CCA bifurcation, which affects ultrasound resolution. Part of the interference was regarded as IMT by the automatic tracing function of the QLAB software. QIMT provided reference parameters for comparison with IMT and was not a main goal of this study. Compared with sex, age presents a stronger determinant influence on both IMT and VWV. IMT, QIMT, and VWV exhibited a positive linear correlation with age, and VWV also exhibited a positive linear correlation with IMT. This study indicated that the median VWV of a 1-cm segment of carotid artery at the junction between the distal CCA and CCA bifurcation for young, middle-aged, older, and senior adults was 84, 90, 100, and 112 mm^3, respectively. The percentage of the increment of the median IMT gradually decreased with advancing age from young to senior adults by 15%, 10%, and 6%, respectively; the percentage of the increment of the median VWV gradually increased with advancing age by 7%, 11%, and 12%, respectively. The meaning of these results requires further interpretation. According to the coefficients of the linear regression analysis, the increment in IMT with age was approximately 0.005 mm per year and that in VWV was approximately 0.641 mm^3 per year. Therefore, VWV provides a much greater dynamic range during follow-up than IMT does. The standardized 3D measurement methods and results of VWV in adults provide laboratory normal norms, which can be applied in future studies.

This study has some limitations. First, an insufficient number of enrollees was included in this study, particularly in the senior adult group. Second, no clinical information about the body weight, height, and comorbidities was collected. Although all the carotid ultrasound studies were interpreted as normal results without prominent carotid plaque by stroke neurologists, the influence of comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia on slight changes in the vascular wall cannot be ignored. Third, the grayscale pixel resolution of the images obtained using the single-sweep 3D transducer was not as high as that obtained using the 2D linear transducer, particularly at the near wall. A newly developed 3D matrix array probe that simultaneously provides real-time transverse and sagittal views is expected to improve pixel resolution[19]. Finally, although sufficient interobserver reliability was achieved in a previous study, bias from offline measurement remains. Furthermore, the time-consuming nature of offline analysis of VWV limits its clinical application. An upgraded version of QLAB software with an automatically generated value for VWV could greatly simplify the measurement process and shorten the measurement time.

CONCLUSION

This study provided normal laboratory norms for VWV measurement using 3D carotid ultrasound in Taiwanese adults. The accuracy of QIMT measurement may be interfered by fat tissue and QLAB software performance. Both IMT and VWV have positive linear correlations with age. VWV is not only strongly correlated with IMT but also enables observation of more dynamic vessel wall changes, which is valuable for clinical observational studies. More experience and future technical innovation can be expected to facilitate the clinical application of VWV.

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Competing interests: The authors declare that they have no competing interests.

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