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ORIGINAL ARTICLE

Accurate quantitative measurements of brachial artery cross-sectional vascular area and vascular volume elastic modulus using automated oscillometric measurements: comparison with brachial artery ultrasound

Yuuki Tomiyama[1], Keiichiro Yoshinaga[2], Satoshi Fujii[3], Noriki Ochi[4], Mamiko Inoue[5], Mutumi Nishida[1], Kumi Aziki[2], Tatsunori Horie[5], Chietsugu Katoh[4] and Nagara Tamaki[1]

Increasing vascular diameter and attenuated vascular elasticity may be reliable markers for atherosclerotic risk assessment. However, previous measurements have been complex, operator-dependent or invasive. Recently, we developed a new automated oscillometric method to measure a brachial artery's estimated area (eA) and volume elastic modulus (V_E). The aim of this study was to investigate the reliability of new automated oscillometric measurement of eA and V_E. Rest eA and V_E were measured using the recently developed automated detector with the oscillometric method. eA was estimated using pressure/volume curves and V_E was defined as follows ($V_E = \Delta$ pressure/ ($100 \times \Delta$ area/area) mm Hg/%). Sixteen volunteers (age 35.2 ± 13.1 years) underwent the oscillometric measurements and brachial ultrasound at rest and under nitroglycerin (NTG) administration. Oscillometric measurement was performed twice on different days. The rest eA correlated with ultrasound-measured brachial artery area ($r = 0.77$, $P < 0.001$). Rest eA and V_E measurement showed good reproducibility (eA: intraclass correlation coefficient (ICC) = 0.88, V_E: ICC = 0.78). Under NTG stress, eA was significantly increased (12.3 ± 3.0 *vs.* 17.1 ± 4.6 mm^2, $P < 0.001$), and this was similar to the case with ultrasound evaluation (4.46 ± 0.72 *vs.* 4.73 ± 0.75 mm, $P < 0.001$). V_E was also decreased (0.81 ± 0.16 *vs.* 0.65 ± 0.11 mm Hg/%, $P < 0.001$) after NTG. Cross-sectional vascular area calculated using this automated oscillometric measurement correlated with ultrasound measurement and showed good reproducibility. Therefore, this is a reliable approach and this modality may have practical application to automatically assess muscular artery diameter and elasticity in clinical or epidemiological settings.
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INTRODUCTION

Arterial diameter enlargement is thought to be an early indicator in the progression of atherosclerosis.[1,2] Increasing brachial artery diameter is related to conventional cardiovascular risk factors.[3] Brachial artery ultrasound has been used to obtain this measurement and is considered to be the standard measurement. However, data acquisition and data analysis require experienced operators, and therefore an alternative simple automated measurement approach should be developed.

Functional deterioration appears before the development of anatomical vascular changes.[4–6] Arterial elastic mechanics are linked to arterial stiffness.[7–9] Determination of arterial diameter at very low or zero transmural pressure makes calculation of vessel strain and volume elastic modulus (V_E) possible.[10] Some studies have estimated the V_E in different approaches. Bank *et al.*[10] estimated this marker using a water-filled blood pressure (BP) cuff with an external ultrasound. Kinlay *et al.* estimated this marker using intravascular ultrasound and a catheter.[11] Both approaches measured vascular area changes during various pressure changes. Kinlay *et al.*[12] obtained intraarterial pressure from the side arm of the arterial sheath, and Bank *et al.*[10] obtained arterial pressure information using applanation tonometry. These earlier approaches were either complex or invasive, and hence a simple noninvasive V_E measurement that could be widely used in clinical settings was sought. Recently, we developed a new automated

[1]Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, Hokkaido, Japan; [2]Department of Molecular Imaging, Hokkaido University Graduate School of Medicine, Hokkaido, Japan; [3]Department of Laboratory Medicine, Asahikawa Medical University, Hokkaido, Japan; [4]Faculty of Health Sciences, Hokkaido University Graduate School of Medicine, Hokkaido, Japan and [5]Division of Clinical Laboratory and Transfusion Medicine, Hokkaido University Hospital, Hokkaido, Japan
Correspondence: Dr K Yoshinaga, Department of Molecular Imaging Research, National Institute of Radiological Science, 4-9-1 Anage, Inage-Ku, Chiba 263-8555, Japan.
E-mail: kyoshi@nirs.go.jp
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oscillometric method to measure a brachial artery's estimated area (eA) and V_E. The main control unit created various fixed precise volumes of air that are capable of changing the tube size, giving rise to the so-called tube law.[13] Changing tube size may be associated with vascular cross-sectional area. Differences between intramural BP and cuff pressure (CP) can be obtained using oscillometric measurements. This is the fundamental concept of this automated system. Using the pressure/volume curves, this oscillometric method quantitatively estimates eA and V_E. Preliminary data by Otsuka *et al.*[14] showed a close relationship between eA and cardiovascular risk factors during health checkups. However, this approach has not been validated using other standard measurements, and its reproducibility has not been evaluated.

The aim of this study was to investigate the reliability of the new automated and quantitative oscillometric measurement of eA and V_E. Therefore, we compared eA with ultrasound measurements as a standard and evaluated the reproducibility of these measurements.

METHODS

Study subjects

Sixteen volunteers participated in the study. Volunteers were recruited from our Hokkaido University Hospital staff members, Postgraduate School of Medicine staff members and Department of Health Sciences, Hokkaido University staff members. All participants were men and two participants were cigarette smokers. All participants had a normal resting electrocardiogram and did not have a history of cardiovascular disease. They were not taking any cardiac medications. Fourteen healthy control subjects had a low pretest likelihood of coronary artery disease (<5%) based on risk factors.[15]

Among 16 healthy individuals, 8 subjects ⩽35 years of age were classified as the younger group. The remaining 8 who were >35 years of age were categorized as the older group.[16]

The study was approved by the Hokkaido University Graduate School of Medicine Human Research Ethics Board. Written informed consent was obtained from all subjects.

Study protocol

We evaluated vascular function using brachial artery ultrasound and automated oscillometric methods at rest and after sublingual nitroglycerin (NTG) administration. In the ultrasound study, we obtained data at rest, after flow-mediated dilatation and after NTG administration. However, we used only rest and NTG stress data in this study because we did not perform reactive hyperemia for oscillometric measurements.

We also performed oscillometric measurements twice, on different days, to evaluate the reproducibility of this automated technique. These measurements were performed in randomized order. All examinations were performed within a 3-week period.

We obtained blood samples on the day of the first oscillometric measurements.

Blood sampling and biochemical measurements

We performed venous blood sampling after the oscillometric measurement under overnight fasting conditions.[17,18] Fasting blood sugar was measured using the glucose oxidase method. Serum cholesterol and triglycerides were measured using standard enzymatic methods. High-density lipoprotein cholesterol concentration was measured from the serum supernatant after precipitation of very-low-density lipoprotein and low-density lipoprotein subfraction. Low-density lipoprotein cholesterol was calculated by the Friedewald formula.[19]

Brachial artery ultrasound measurements with flow-mediated vasodilatation: subject preparation

Participants were instructed to abstain from caffeine-containing products (coffee, tea, chocolate and cola) for at least 24 h and vitamin C-containing beverages for at least 6 h.[5] They fasted for ⩾8 h (overnight fasting) before the ultrasound measurements.[11,20] Two smokers were instructed to abstain from smoking for at least 12 h in order to minimize acute smoking effects. The ultrasound study was conducted in the morning (0800 h) after overnight fasting (Figure 1a). Subjects rested in a supine position for 10 min before the study in a temperature-controlled room (21 to 23 °C). An automated sphygmomanometer cuff was positioned on the left arm for measurement of BP.[11]

Image acquisition

High-resolution Doppler ultrasonography equipment (Aplio XG, Toshiba, Tokyo, Japan) with an 18-MHz transducer was used to evaluate the right brachial artery. The onset of the R wave was used to identify end-diastolic vascular diameter, and the peak of the T wave was used to identify end-systolic diameter.[21]

The brachial artery was longitudinally scanned ~5 cm above the antecubital fossa. We also evaluated brachial artery diameter 8.5 cm above the antecubital fossa before the standard rest measurement, which was 5 cm above the antecubital fossa, in order to compare oscillometric measurements. After an appropriate probe position was determined, the skin was marked and the arm was retained in the same position throughout the study. The echo transducer was supported by a stereotactic probe-holding device.

After 10 min of rest in a supine position, brachial artery diameter was measured at rest as a baseline study.

Endothelium-independent vasodilatation with NTG

At 15 min after the flow-mediated dilatation study, a new baseline image was obtained. After the second baseline data acquisition, subjects received 0.3 mg of sublingual NTG (TOA EIYO, Fukushima, Japan). Just after sublingual NTG administration, brachial artery image acquisition was started and continued for 5 min.[11]

Image analysis

Brachial artery diameter was measured from the anterior to the posterior medial–adventitial interface at the end-diastole. We evaluated the vascular diameter for four cardiac cycles and calculated the mean value. The means of the two measurements by independent observers were calculated. The inter-operator reproducibility of ultrasound measurement in our facility had an intraclass correlation coefficient (ICC) of 0.92. The percentage increase of diameter by NTG (%NTG) was calculated as follows:[22]

$$\%NTG = \text{brachial artery diameter at NTG stress/average of baseline diameter} \times 100.$$

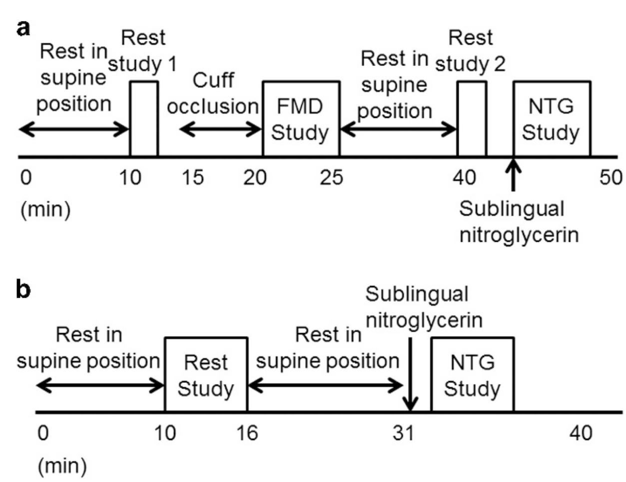

Figure 1 Study design. (**a**) Data acquisition protocol of ultrasound measurements. (**b**) Data acquisition protocol of oscillometric measurements. FMD, flow-mediated dilatation; NTG, nitroglycerin.

Automated vascular volume/pressure detector measurements: oscillometric measurement protocol

Subjects followed the same instructions they had received for ultrasound measurements before the studies. Participants underwent oscillometric measurements after overnight fasting. We performed rest brachial arterial cross-sectional area and functional measurements using a newly developed device, the Health Chronos TM-2771 prototype (A&D Company, Tokyo, Japan) (Figure 2a).[14] Data acquisition took 6 min (Figure 1) and included measurements of BP, eA and V_E (that is, vascular stiffness). After the rest data acquisitions, participants rested for 15 min. Then, subjects received sublingual NTG (0.3 mg). At 2 min after sublingual NTG administration, the second measurements were performed (Figure 1b).

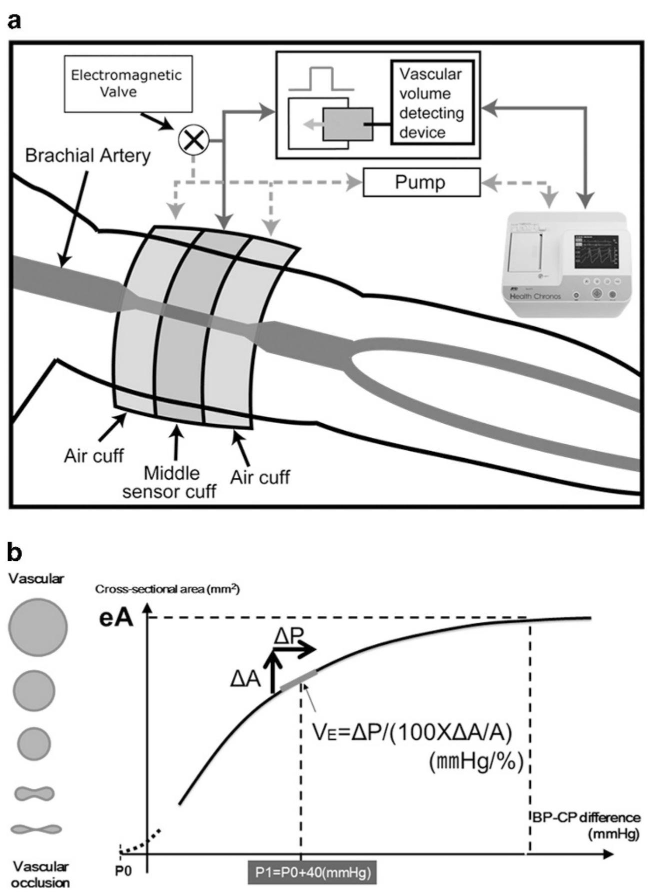

Figure 2 (**a**) Oscillometric measurement set-up. A triple lumen cuff was put on the upper arm. The triple lumen cuff included central pressure sensor cuff and two outside cuffs. The central part of the triple lumen cuff detected the exact vascular volume change. A main control unit generated a precise amount of air into all three cuffs. After sending the precise amount of air, two tubes to the outside cuffs were occluded. These amounts of air changed the vascular volume and added a stable pressure to the vessel. After sending the air, the main control unit changed a valve connection to the central cuff and the central cuff changed its role. The central cuff then sensed the vascular volume change and controlled the cuff pressure. The central pressure sensor cuff detected BP–CP differences during heartbeats. Using this information, the main control unit made pressure/volume curves. (**b**) Calculation of estimated cross-sectional area (eA) and volume elastic modulus (V_E) using pressure/volume curves. When cuff pressure became zero, the calculated cross-sectional vascular area represented baseline vascular area. BP, blood pressure; CP, cuff pressure. A full color version of this figure is available at the *Hypertension Research* journal online.

Data analysis

We measured brachial artery absolute volume and V_E using a newly developed device, the Health Chronos TM-2771 prototype. Details of this device are addressed elsewhere.[14] In brief, this device consists of a main control unit and two outside cuffs for oscillometric measurement and plethysmography at the right and left brachial arteries (Figure 2a). The exteriors of the three occlusive lumen cuffs are composed of a hard material to avoid expansion with increases in arterial volume. Therefore, the CP changes accurately reflected volumetric changes of the brachial artery. To measure a brachial artery's absolute volume, the device initially sought the lowest CP that indicated complete occlusion of the brachial artery (volume = 0) at end-diastole. During the measurement, the main control unit put air into the central cuff for a calibration. This calibration made it possible to determine the absolute volumetric changes of the brachial artery from the plethysmogram under the condition of outside cuff inflation. The CP was gradually decreased and the calibrated plethysmogram was recorded several times at regular CP intervals. Thus, pressure and area curves were obtained.

To estimate the cross-sectional area of the brachial artery, the brachial arterial volume was divided by the length of the central cuff, which was a pressure-sensor cuff.

The eA was defined as the estimated cross-sectional area at the point where the BP–CP difference was identical to the diastolic BP (Figure 2b). The highest CP, indicating complete collapse of the brachial artery, is usually a little higher than BP. Therefore, the corresponding point (P0) on the pressure axis of the curve was set at less than zero.

V_E was defined as the change in the BP–CP difference (DP1) per 1% increase in cross-sectional area at P1, where P1 = P0+40 mm Hg. The original calculation of V_E was as follows:[23] ($V_E = \Delta$ Pressure/ $(100 \times \Delta$volume/volume) mm Hg/%). This system estimated the absolute value of cross-sectional vascular area instead of vascular volume. Thus, the original V_E equation was modified as follows:[14] ($V_E = \Delta$pressure/ $(100 \times \Delta$area/area) mm Hg/%). The principal concept of V_E estimation was to evaluate the association between ΔA and ΔP while the blood vessel remained circular. The correct measurements should be performed with cuff pressure below a certain point so that the vessel remains circular and does not have buckling. Based on our basic preliminary experimental laboratory data analysis, in most cases vessels remained circular when pressure was 40 mm Hg higher than P0.

Although we obtained the values of eA and V_E for both right and left brachial arteries, the values for eA and V_E for the right brachial artery were used in the subsequent statistical analysis as the ultrasound measurements we performed were for the right brachial artery.

The percentage increase of eA and V_E with NTG (%NTG) was calculated as follows: %NTG = eA or V_E at NTG stress/rest eA or $V_E \times 100$.

The measurement was similar to that obtained using ultrasound.

Statistical analysis

Continuous variables were presented as means and s.d. Categorical data were expressed as a percentage of total. The paired Student's *t*-test and unpaired Student's *t*-test were used for continuous variables. Pearson's correlation coefficient was analyzed to determine the simple correlation between variables. In the analysis, all statistical tests were two sided. A *P*-value of <0.05 was considered indicative of a statistically significant difference. The reliability of oscillometric measurement was assessed using an ICC. The strength of the ICC was determined using the cutoffs of 0.5, 0.3 and 0.1 for high, moderate and low levels of agreement according to Cohen's effect size convention.[23] Statistical calculations were carried out using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Reliability of oscillometric measurements

Subject characteristics. The baseline characteristics of the 16 subjects are shown in Table 1a. Among 16 individuals, 2 subjects were cigarette smokers. Lipid profiles, including total cholesterol and low-density cholesterol, fasting blood sugar and hemoglobin A1c, were within

Table 1a Baseline characteristics

	Subjects (n = 16)
Normal/smoker	14/2
Age (years)	35.2 ± 13.1
Height (cm)	169.4 ± 4.4
Weight (kg)	68.0 ± 9.2
BMI (kg m^{-2})	23.7 ± 3.2
Systolic BP (mm Hg)	115.2 ± 15.1
Diastolic BP (mm Hg)	72.5 ± 11.7
HR (b.p.m.)	62.1 ± 9.8
T-CHO (mg dl^{-1})	199.3 ± 39.9
LDL-CHO (mg dl^{-1})	119.1 ± 62.9
FBS (mg dl^{-1})	88.3 ± 8.7
HbA1c (%)	4.9 ± 0.2

Abbreviations: BMI, body mass index; BP, blood pressure; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HR, heart rate; LDL-CHO, low-density lipoprotein cholesterol; T-CHO, total cholesterol.
Data are presented as mean ± s.d.

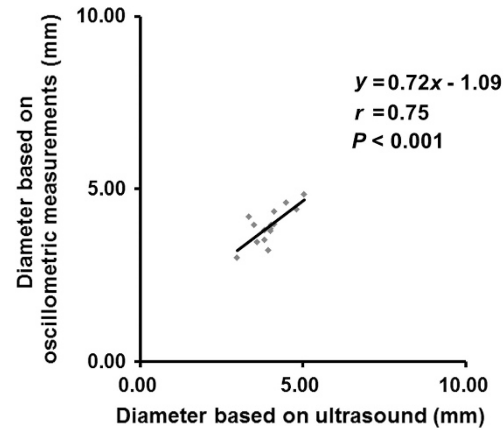

Figure 3 Correlation between ultrasound measurements and oscillometric measurements of rest brachial artery diameter. Rest estimated area (eA) was converted to vascular diameter.

Table 1b Baseline characteristics of younger and older groups

	Younger (n = 8)	*Older* (n = 6)	P-*value*
Age (years)	23.0 ± 1.2	44.3 ± 5.8	< 0.001
Height (cm)	169.4 ± 4.1	169.3 ± 5.8	0.99
Weight (kg)	66.6 ± 9.6	68.5 ± 10.3	0.72
BMI (kg m^{-2})	23.3 ± 3.5	23.9 ± 5.8	0.73
Systolic BP (mm Hg)	118.1 ± 17.0	107.8 ± 6.6	0.18
Diastolic BP (mm Hg)	72.3 ± 10.6	68.7 ± 9.1	0.52
HR (b.p.m.)	66.2 ± 10.6	56.7 ± 7.5	0.09
T-CHO (mg dl^{-1})	193.3 ± 32.6	204.5 ± 50.2	0.61
LDL-CHO (mg dl^{-1})	109.6 ± 16.2	129.5 ± 53.7	0.33
FBS (mg dl^{-1})	88.3 ± 9.3	87.5 ± 7.0	0.87
HbA1c (%)	4.9 ± 0.2	5.0 ± 0.2	0.23

Abbreviations: BMI, body mass index; BP, blood pressure; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; HR, heart rate; LDL-CHO, low-density lipoprotein cholesterol; T-CHO, total cholesterol.
Data are presented as mean ± s.d.

normal range. The interval between the ultrasound and oscillometric measurement was 4.9 ± 3.7 days.

Association between ultrasound measurements and oscillometric measurements

Ultrasound showed upper-arm brachial artery diameter 8.5 cm above the antecubital fossa as 3.93 ± 0.49 mm. Vascular cross-sectional area measured by oscillometric measurement was 12.3 ± 3.0 mm^2. This value was converted to diameter (3.97 ± 0.51 mm) for comparison with ultrasound measurements. There was no difference in brachial vascular diameter between ultrasound and oscillometric measurement ($P = 0.65$). Brachial vascular diameter derived from oscillometric measurements significantly correlated with ultrasound brachial artery diameter measurements ($r = 0.75$, $P < 0.001$, Figure 3).

Rest reproducibility of eA and V_E measurements

All 16 subjects had two oscillometric measurements. The mean interval between the two oscillometric measurements was 7.2 ± 5.2 days. There was no significant difference in subjects' baseline condition between the first and second studies including height ($P = 0.33$), weight ($P = 0.32$), systolic BP ($P = 0.64$), diastolic BP ($P = 0.35$) or heart rate ($P = 0.67$).

There was no significant difference in rest eA (11.9 ± 3.0 *vs.* 11.5 ± 2.9 mm^2, $P = 0.32$) or V_E (0.82 ± 0.16 *vs.* 0.77 ± 0.16 mm Hg/%, $P = 0.09$) between the first and second studies. Rest eA and rest V_E showed good reliability (eA: ICC = 0.88, V_E: ICC = 0.78).

NTG stress responses

NTG administered sublingually significantly decreased systolic BP (115.2 ± 15.1 to 108.2 ± 13.9 mm Hg, $P = 0.0004$) and increased heart rate (62.2 ± 9.8 to 67.8 ± 7.2 b.p.m., $P = 0.002$) in oscillometric measurements.

Ultrasound showed increasing arterial diameter after NTG administration (4.46 ± 0.72 to 4.73 ± 0.75 mm, $P < 0.001$). The percentage change of arterial diameter with NTG was 15.7 ± 5.0%. eA was significantly increased after NTG administration (12.3 ± 3.0 *vs.* 17.1 ± 4.6 mm^2, $P < 0.001$). V_E was significantly decreased after NTG administration (0.81 ± 0.16 *vs.* 0.65 ± 0.11 mm Hg/%, $P < 0.001$). Percentage change of eA (%eA) was 39.6 ± 18.2% and percentage change of V_E (%V_E) was − 19.5 ± 10.4%.

However, there was no significant correlation between the percentage change of brachial artery diameter by ultrasound and the percentage eA or percentage V_E (%eA: $r = 0.31$, $P = 0.25$, %V_E: $r = 0.19$, $P = 0.48$).

Age-related vascular function: baseline characteristics

In this additional analysis, we excluded two smokers because smoking attenuated vascular function. Thus, we analyzed a total of 14 subjects in this analysis.

There were 8 younger subjects (⩽35 years old)[16] (younger group) and 6 older subjects (older group). The baseline characteristics of the two groups are addressed in Table 1b. As expected, the older group was older than the younger group ($P < 0.001$). Otherwise, there were no significant differences between the two groups in terms of baseline characteristics.

Association between eA, V_E and aging

There was no significant difference in the rest ultrasound measurements of brachial artery diameter between the two groups (younger: 3.79 ± 0.38 *vs.* older: 4.05 ± 0.62, $P = 0.35$). Oscillometric measurement also did not show significant differences in rest eA between the two groups (younger: 10.9 ± 2.0 *vs.* older: 13.3 ± 3.8 mm^2, $P = 0.15$). In contrast, the older group showed significantly higher V_E compared

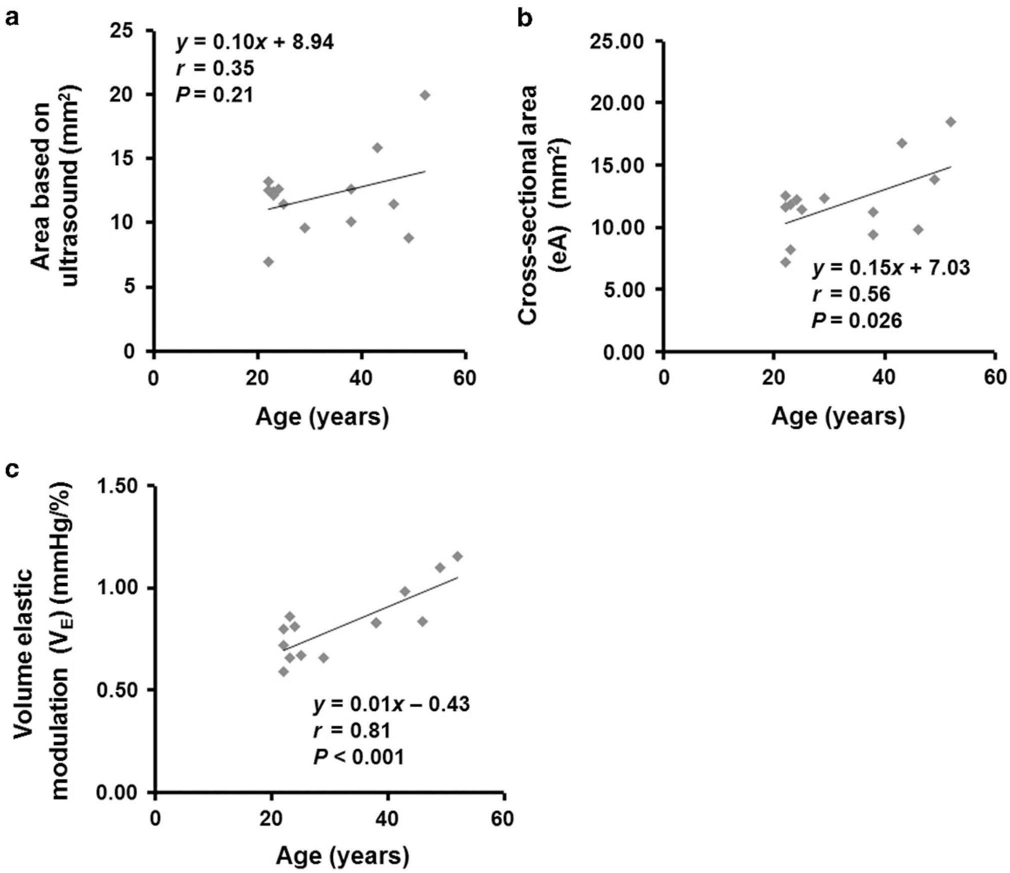

Figure 4 Correlation between age and other parameters. (**a**) Correlation between age and ultrasound measurements of brachial artery diameter. (**b**) Correlation between age and oscillometric measurement of estimated cross-sectional area (eA). (**c**) Correlation between age and oscillometric measurement of volume elastic modulus (V_E).

with the younger group (younger: 0.72 ± 0.09 *vs.* older: 0.95 ± 0.14, $P = 0.003$).

There was no significant correlation between ultrasound-measured brachial artery diameter and age ($r = 0.32$, $P = 0.26$, Figure 4a). In contrast, there was a significant correlation between eA and increasing age ($r = 0.56$, $P = 0.026$, Figure 4b). Rest V_E also showed significant correlation with increasing age ($r = 0.81$, $P < 0.001$, Figure 4c).

DISCUSSION

The absolute value of rest brachial artery estimated cross-sectional area using oscillometric measurement showed good correlation with brachial artery ultrasound measurements. The estimated cross-sectional area and V_E measurements using this new modality showed good reproducibility. Oscillometric measurement automatically detected the changes in eA and V_E after NTG administration. In addition, eA and V_E increased in association with increasing age.

Reliability of automated oscillometric measurement: comparison between oscillometric measurement and ultrasound measurements

In the current system, the oscillometric method quantitatively estimates cross-sectional vascular area. In this study, we converted cross-sectional area to brachial vascular diameter in order to compare it with ultrasound measurements. The converted estimated arterial diameter was similar to that determined using ultrasound measurements. The rest estimated vascular diameter also significantly correlated with the ultrasound-measured brachial artery diameter. Therefore, this oscillometric method should be a reliable approach and may provide similar useful anatomical information to that determined by ultrasound measurement.

Ultrasound measurement provides a visualization of the vascular lumen and therefore allows for an exact measurement of the vascular diameter, whereas oscillometric methods do not provide for such visualization and therefore provide an approximation of the vascular cross-sectional area. Given the characteristics of the oscillometric approach, soft tissues surrounding arteries may be included in cross-sectional area measurements, possibly leading to an overestimation of volume. Even when this concern was taken into account, the current data showed good correlation with ultrasound measurements that are part of the standard approach.[11] In fact, the current data showed the estimated brachial vascular diameter to be slightly larger than brachial artery diameter determined using ultrasound. However, there was no significant difference between the two measurements.

The cross-sectional area estimation showed high ICC. Previous data[23] reported that reproducibility of ultrasound brachial artery diameter measurement had an ICC of 0.84.[24] Oscillometric measurements agree with those of previous studies. Based on these data, oscillometric measurements would be reliable and can be used in clinical or epidemiological settings.

NTG response is an endothelium-independent vascular dilatation function.[25] In this study, eA significantly increased after NTG administration. The response to NTG was similar to that found using ultrasound. On the other hand, there was no correlation between the percentage change in diameter as measured by ultrasound and eA. The range of data for %NTG was narrow because of the normal study population. This may be a reason for the lack of correlation in NTG response between the two tests. Oscillometric measurements may have included brachial artery and surrounding vascular areas, and therefore the value of eA may have appeared to be higher than it was found to be with ultrasound, especially under NTG stress. This also may have been the reason that there was no significant correlation between percentage eA change with NTG stress determined by oscillometric measurement and that determined by ultrasound measurement. Although we did not show the correlation, the oscillometric approach was able to detect vascular cross-sectional area change during NTG stress.

Automated measurements of V_E

The rest V_E showed good reproducibility. This reproducibility is similar to that for other vascular functional evaluations.[12]

Arterial elastic mechanics including V_E are linked to arterial stiffness.[7,8] Bank *et al.*[10] reported that brachial artery elastic mechanics accurately evaluated vascular stiffness over a wide range of BP and vascular smooth muscle tone. Therefore, V_E should be examined in clinical practice. However, previous methods of doing so were either complex or invasive.[10,11] The current oscillometric approach may build on these previous studies and may allow for practical measurements of vascular elasticity in clinical settings or epidemiological study settings.

V_E was also reduced under NTG stress. NTG dilates brachial arteries by causing smooth muscle relaxation. The oscillometric system automatically detected changing vascular tone with NTG, and these data agree with those from the previous study by Bank *et al.*[10] The current data may imply that this approach could be used to detect anatomical and functional change during NTG stress.

Relation between eA, V_E and aging

In addition to showing the reliability of this new approach, we further looked at the association between those markers and age-related vascular anatomical and functional changes. Vascular function alters in association with aging.[19,22] A previous study showed brachial artery diameter increases in relation to aging.[1] In this study, the older group tended to have higher brachial vascular diameter and eA. However, the differences between the values for the younger group and those for the older group were not significant, perhaps because of the small sample size with a wider range of standard deviation. Thus, our results may partly agree with those of previous studies. Further studies are required to confirm these data in a larger study population. On the other hand, over the total study population, rest eA showed significant correlation with increasing age. These data agree with previous data acquired using the same method.[14]

Vascular stiffness and vascular function also alter in association with aging.[22] Rahmani-Cherati *et al.*[26] reported that vascular elastisty was associated with vascular stiffness. Thus, attenuated V_E in the current study may indicate that older subjects had increasing vascular stiffness. The current data may agree with those of the previous study.

A previous study by Otsuka *et al.*[14] showed very limited relationships between V_E and other cardiovascular risk factors including age, possibly due in part to the difference in the study design. In the previous study, subjects had BP measurements before oscillometric measurements and they did not have enough resting time before vascular function measurements.[14] These factors may have had a significant impact on vascular function such as V_E.[11] Further evaluation looking at the value of V_E measurements is required. In this study, we applied a standard approach to vascular function measurement.[11,27] With the appropriate preparation, we showed that there were significant differences between the V_E measurements of the two groups. Moreover, increasing V_E was significantly correlated with increasing age. Other imaging methods such as ultrasound, positron emission tomography and pulse wave velocity showed attenuated vascular function in the older population.[22,28,29] The current data agree with those from these previous studies. The current data add new insights regarding V_E to those from the previous study by Otsuka *et al.*[14] This new method may be able to automatically detect age-related vascular dysfunction.

The current data show an association between rest eA and V_E with increasing age. Measuring brachial artery diameter and vascular elasticity might be useful in clinical and epidemiological settings for evaluating atherosclerosis.

Applied measurements model

In the present study, we measured V_E and eA while the vessel remained circular. We applied models for thin-walled tubes.[13] The current study population comprised healthy individuals whose arterial walls should be thin. Therefore, the current approach using thin-walled tube law should be appropriate.

When the vessel is compressed and buckles, measuring vascular area and diameter may become challenging. Therefore, we applied the measurement point before changing the vascular shape. However, the vessel may be buckled during measurement and hence it would be important to develop a new algorithm to estimate the cross-sectional area of the buckled vessel. This should be the next step in the development of this oscillometric measurement.

Some of the targeted study population who require vascular function measurements may have thick arterial walls. Therefore, it would be useful to add corrections factors to the thin-shelled theories[30] or to apply one-dimensional general tube law as proposed by Kozlovsky *et al.*[31]

Limitations

Our study had a small population. The current protocol included two oscillometric measurements and one ultrasound study, each on a separate day (Figure 1). As each study had rest and NTG stress, it would be difficult to apply this comprehensive study protocol to a large number of subjects. Even with a small sample size, with careful preparation we showed good reproducibility of eA and V_E. Although a small sample size may have had a minimal impact on the current data, we definitely need further study using a larger study population and a simplified protocol.

All study subjects were male. Women have vascular functional changes during their menstrual cycle that may have impacts on vascular function. For this initial study, we wanted to avoid these effects. However, we need to apply this measurement to women. Such studies are currently under way.

In the present study, we evaluated only normal individuals and smokers. Applying the current comprehensive protocol to coronary artery disease patients would have been difficult. However, this measurement technique should be applied to subjects with atherosclerotic risk factors and coronary artery disease patients as a next step.

In the present study, we applied the same pulse pressure, 40 mm Hg, to estimate V_E. However, using individual pulse pressure would be ideal for setting P1. This possibility should be tested in the future and should be applied to this oscillometric measurement.

CONCLUSION

This new quantitative automated oscillometric measurement accurately assessed brachial artery cross-sectional area and vascular elasticity. This measurement technique can also detect morphological and functional change under NTG stress and is a reliable approach. Therefore, this modality may have practical application in quantitatively assessing muscular artery elasticity and diameter responses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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