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ORIGINAL RESEARCH

Evaluation of vascular wall elasticity of human digital arteries using alternating current-signal photoplethysmography

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Purpose: A simple method of estimating arterial elasticity in the human finger using a volume-oscillometric technique with photoplethysmography was principally studied under the various effects of age, sex, and cold-stress stimulation for testing the capability of using this technique in arterial elasticity analysis.

Methods: Amplitude variations in the alternating current signal of the photoplethysmograph during a continuous change in transmural pressure were analyzed to obtain the blood pressure and the transmural pressure–relative volume difference relationship of the arteries. We first tested the effect of the occluding cuff size on the arterial elasticity analysis in eight subjects (ages 20–45 years) to obtain a suitable cuff size, resulting in the selection of a middle cuff with a 22 mm diameter. Blood pressure and arterial elasticity were measured in six groups of subjects separated into three age-groups of women and men (ages 20–25, 32–45, and over 50 years) for testing the effect of age and sex. Twelve subjects (ages 20–25 years) also had their blood pressure and arterial elasticity measured in three conditions under the influence of the cold-stress stimulation.

Results: Age, sex, and cold-stress stimulation had an impact on mean blood pressure ($P < 0.0005, 0.025$), whereas pulse pressure and heart rate were statistically unchanged by those factors. Furthermore, an advanced age (over 50 years) was found to induce an increase in relative volume difference values ($P < 0.025$) and upward shifting of the transmural pressure–relative volume difference relationships, whereas sex, level of mean blood pressure, and cold-stress stimulation had no influence on these forms of the index.

Conclusion: This study showed the usefulness of the relative volume difference as being a mean blood pressure-independent indicator for changes in arterial elasticity.

Keywords: arterial elasticity, volume oscillometry, noninvasive technique, aging process, cold-stress stimulation

Introduction

Arteriosclerosis is a vascular disease caused by aging that can be seen throughout society.[1] When arterial blood vessels are subjected to the continuous stress of blood flow for long time periods, the elastin fibers in the media layer of the arterial wall become injured and fragmented, resulting in the recruitment of collagen fibers. This structural change in the arterial wall causes a slackening that progresses to a reduction in wall elasticity.[2] The stiffening of the arterial wall reduces the absorption and restoration capability of the vessels during systole and diastole, raising systolic blood pressure and pulse pressure.[3] A reduction in arterial elasticity is also associated with the existence and development of other cardiovascular diseases.[4,5]

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Several methods for measuring arterial stiffness have been developed over the last century. Pulse pressure has been widely used to define the influence of large artery stiffness. Pulse pressure explicitly increases with age, especially over the age of 60 years,[6] and is associated with a dominant rise in arterial stiffening. However, pulse-pressure amplification at the peripheral site may lead to misinterpretations of hypertension, particularly in young subjects.[7] Thus, pulse pressure may not be an excellent marker for assessing arterial stiffness. Pulse-wave velocity (PWV) and augmentation index (AIx) are widely used as standard arterial stiffness predictors. Increases in PWV and AIx in the elderly reflect arterial stiffening due to the aging process.[8–11] In addition, high PWV and AIx also relate to the morbidity and mortality of patients with associated cardiovascular diseases; for example, in patients with coronary heart disease,[12] hypercholesterolemia,[13] stroke,[4] diabetes, glucose intolerance,[14,15] end-stage renal failure,[16] and spinal cord injury.[17] Nonetheless, PWV depends on the mean blood pressure of subjects.[10,18,19] Vasodilation and vasoconstriction due to sympathetic nervous stimulation, such as heat- and cold-stress stimulations, also obviously influence the AIx.[20,21] Thus, using PWV and AIx for the arterial stiffness measurement under various conditions of mean blood pressure and vascular stimulations cannot definitely indicate the arterial stiffness, due to the structural peculiarities of the arterial wall. Furthermore, with advances in imaging technology, ultrasound and magnetic resonance imaging have been exploited to track the position of the arterial wall noninvasively. Various arterial stiffness indices can be calculated from these imaging techniques. However, these techniques are expensive to perform for daily health monitoring. In contrast, photoplethysmography (PPG) is another noninvasively optical technique that is simple, small, compact, and reasonable. PPG is broadly used in clinical monitoring, such as for cutaneous blood flow,[22] blood oxygen saturation, heart rate, blood pressure,[23,24] and vascular assessments, including arterial stiffness.[25]

The basic PPG system consists of essentially two components: an infrared light source and a photo sensor. The infrared light source generates infrared light that penetrates deeply to the target site, and is partly absorbed by the skin, tissue, bone, and blood, whereas the remaining light transmits and reflects outwards. A photo sensor is used to detect and change the remaining light to electric current before transforming it into the two components of the output signal through a filter process and signal amplification. These two signal components of PPG are a steady direct current signal (DC signal) and an alternating current signal (AC signal). The DC signal, which is associated with the light-absorption ability of the venous blood, nonpulsatile arterial blood, and the surrounding tissues, represents the total blood volume, while the AC signal reflects the light absorption caused by pulsatile arterial blood variation during the cardiac cycle.[22] Many researchers have utilized the components of the PPG signal for clinical monitoring, including arterial stiffness assessments. In 1986, Kawarada et al used the PPG to evaluate arterial elasticity in human fingers and rabbit forelegs. Their transmission-mode PPG system had an occluding cuff to induce vascular volume changes in arterial elasticity measurements using a volume-oscillometric method. The vascular elasticity markers – relative volume change and volume elastic modulus – were obtained from transmitted light intensity using the Lambert–Beer law. The relationship between transmural pressure and the vascular elasticity markers demonstrated the predictive value of PPG in arterial elasticity assessments performed under the influence of atheroma and a vasodilator.[26] The relationship between relative volume change and transmural pressure was also associated with the effects of aging, hypertension, and coronary disease in a study by Ando et al. In their study, the relative volume change declined with age, hypertension, and coronary disease.[27] Furthermore, the characteristics of the PPG pulse wave, including its derivative, were considered in the analysis of arterial stiffness using several parameters; for example, the arterial stiffness index,[10,15] AIx,[28–30] and the b/a, c/a, d/a, and e/a ratios from the systolic and diastolic waves of the second derivative of the PPG pulse wave.[30,31] Moreover, pulse-wave decomposition is another useful technique for obtaining indices of arterial stiffness.[32] All the aforementioned parameters were demonstrated to be affected by age and were valid for analyses of arterial stiffness.

Although amplitude variations in the PPG pulse wave can express arterial elasticity in the form of the finger arterial elasticity index, and the normalized finger arterial stiffness index,[33] PPG amplitude variations still have not prevailed for general measurements of arterial elasticity. Meanwhile, a few studies have focused on factors that affect arterial elasticity analysis using PPG amplitude variations. Therefore, in the present study, the significance of PPG amplitude variations was considered, and a simple alternative methodology for the quantification of arterial elasticity by analyzing amplitude variations in the PPG pulse wave in the human finger is proposed. We also applied this method for testing the capability of using PPG amplitude variations in arterial elasticity analysis under the influences of cuff size, age, sex, and cold-stress stimulation, which are basic factors in arterial elasticity measurements, excluding pathophysiological conditions.

Methods

Measurements and instruments

Blood pressure and heart rate measurement

Systolic blood pressure (P_{sys}), diastolic blood pressure (P_{dia}), and heart rate were measured using an automatic blood pressure monitor (HEM-7070; Omron, Dalian, People's Republic of China) positioned on the left brachium of subjects. The mean blood pressure (P_m) of the brachial artery was calculated by summing P_{dia} and one-third of the pulse pressure (ΔP), which is the subtraction of the P_{sys} from the P_{dia}.

Skin-temperature measurement

The skin temperature of subjects was measured using a noncontact thermometer (Thermo pipper; Sato Shouji, Kanagawa, Japan) placed 1 cm above the dorsal surface of the proximal phalanx of the index finger.

Finger-diameter measurement

The horizontal and vertical diameters of the right index finger were measured using a vernier caliper (series 503; Mitutoyo, Kawasaki, Japan) at the middle of the proximal phalanx of the right index finger.

Arterial elasticity measurement

In this study, the PPG signals of the human finger were measured using a developed optical plethysmograph device based on a commercial model (BP-98AL; Softron, Tokyo, Japan), as shown in Figure 1. A reflection-mode PPG has a light-emitting diode with a wavelength of 850 nm placed side-by-side with a photo sensor (wavelength 320–1100 nm) inside an occluding cuff. The device was positioned on the dorsal side of the proximal phalanx of the right index finger during the measurement. The PPG signal detected by the photo sensor was transformed and decomposed into AC and DC components of the electric current. The AC component was filtered using cutoff filters with a low frequency of 0.75 Hz (a second-order infinite impulse-response high-pass filter) and a high frequency of 10 Hz (100th-order finite impulse-response low-pass filter). Moreover, three sizes of occluding cuffs with inner diameters of 20 mm, 22 mm, and 24 mm were used to generate extravascular pressure or cuff pressure (P_c) on the index finger. In this measurement, P_c was gradually decreased from 180 mmHg to 0 mmHg with an approximate deflation rate of 4 mmHg/s. The AC, DC, and P_c signals were sampled at a rate of 1000 Hz per channel and were converted to digital outputs using a 24-bit A/D converter (PowerLab 4/26, ML846; ADInstruments, Dunedin, New Zealand) before storing them on a personal computer (Optiplex 980; Dell, Round Rock, TX, USA).

With this PPG measurement, the other tissues around the vascular system of the target site were assumed to be incompressible. The measurement started when both the venous and arterial systems were collapsed by the cuff pressure at 180 mmHg. During the deflation of the occluding cuff, the venous system was continuously collapsed,[24] whereas the arterial blood system started to

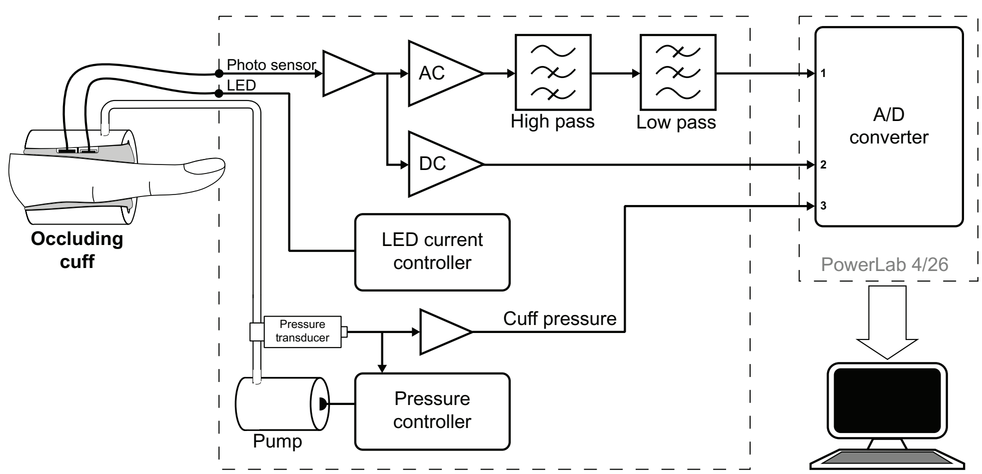

Figure 1 Schematic block diagram of a photoplethysmograph system for the human finger.
Notes: The light-emitting diode (LED) system generates an infrared light directed toward the finger. The pressure generator induces a vascular volume change through the occluding cuff. The photo sensor detects the reflected light from the finger. The electric current from the photo sensor is decomposed into an alternating current (AC) and a direct current (DC). The AC current is then filtered through a high-pass and a low-pass filter. The A/D converter converts the AC, DC, and cuff-pressure input signals to the digital outputs before storing them on the personal computer.

flow when the P_c was equal to the P_{sys}. At this stage, the fluctuation in the AC signal began to be recognizable, as shown in Figure 2. The fluctuation in the AC signal illustrated the existence of blood flow in the arterial system. The arterial volume change was controlled by the continuous change in the P_c and transmural pressure (P_{tr}), which corresponds to the difference between the P_m and P_c, during the deflation. At the maximum amplitude of the AC signal, this point expressed the equality between the P_c and P_m. At this point, the P_{tr} was equal to zero. Therefore, the P_{sys} and P_m were determined based on the correspondence between the AC and P_c signals. Furthermore, when the P_c was equal to or less than the P_m, the P_{tr} was greater than zero, and the amplitude of the AC signal represented the arterial volume difference between systole and diastole (ΔV). Therefore, when the P_{tr} increased from zero, the variation in the AC amplitude indicated a change in the arterial elastic property. The relative volume difference was proposed as an index of arterial elasticity. The relative volume difference was defined as the volume difference at any P_{tr} (ΔV) normalized with that for zero P_{tr} (ΔV_0) or $\Delta V/\Delta V_0$. This index was also derived from the light intensity of the AC signal as follows:

$$\Delta V/\Delta V_0 = I/I_0 \quad (1)$$

where I is the AC amplitude at any P_{tr}, in volts, and I_0 is the AC amplitude at zero P_{tr}, in volts.

The stored output data from PPG was analyzed offline using MatLab (MathWorks, Natick, MA, USA) to extract the peaks and the amplitudes from the AC signal to determine the P_m, P_{tr}, ΔV, ΔV_0, and $\Delta V/\Delta V_0$. In the output signal analysis, we could extract the amplitudes of the AC signal from the maximum amplitude until the end of the constant amplitudes. Because we found that the amplitudes of the AC signal were influenced by the withdrawal of the P_c from the finger during the last period of the occlusion, we did not therefore regard the signal during that period. The average minimum P_c that we took into account for the arterial elasticity analysis was approximated to be 28.5 ± 7.7 mmHg, which was different among the groups of data. Furthermore, a signal-matching algorithm was also utilized to obtain the starting point of the AC signal when determining the P_{sys}. Then, we calculated the P_{dia} and the ΔP from the P_{sys} and P_m as follows:

$$P_{dia} = (3P_m - P_{sys})/2 \quad (2)$$

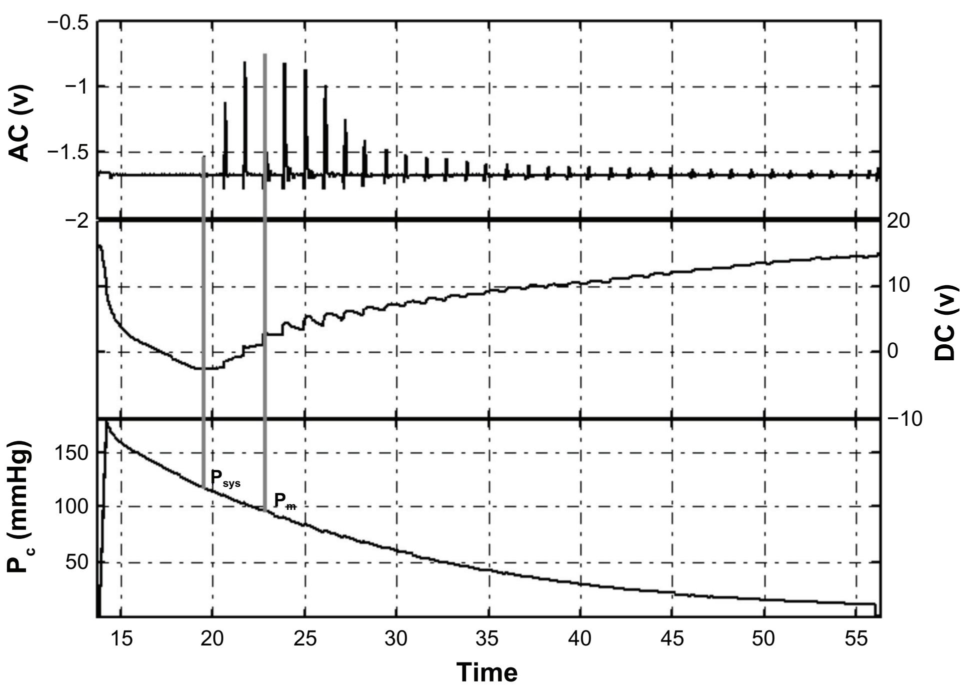

Figure 2 Example of the recorded output signals from the photoplethysmograph: the alternating current (AC), direct current (DC), and cuff-pressure (P_c) signals are shown.

Notes: The P_c started to compress and collapse the arterial system at 180 mmHg. The P_c gradually decreased because of the deflation of the occluding cuff. When the P_c was equal to the systolic blood pressure (P_{sys}), the fluctuation in the AC signal started to be recognized. When the P_c was equal to the mean blood pressure (P_m), the transmural pressure (P_{tr}) was zero and the amplitude of the AC signal reached its highest value. When the P_c was equal to or less than P_m, the amplitude of the AC signal implied the arterial volume difference between systole and diastole (ΔV). The relative volume difference ($\Delta V/\Delta V_0$) was derived from the light intensity of the AC signal using the ratio of the AC amplitude at any P_{tr} to the AC amplitude at zero P_{tr}.

$$\Delta P = P_{sys} - P_{dia} \quad (3)$$

Based on the PPG signal analysis performed using MatLab, the arterial elasticity of subjects was expressed as the relationship between P_{tr} and $\Delta V/\Delta V_0$. The $\Delta V/\Delta V_0$ values at a P_{tr} of 30 mmHg obtained from the linear interpolation of the two nearest data points were used for comparing the $\Delta V/\Delta V_0$ index at the specific P_{tr} among the groups of subjects.

Subjects and experiment

Subjects

In this study, 58 healthy subjects – 28 women 20–63 years old and 30 men 20–69 years old – participated in the experiments. The experimental protocol was approved by the ethics committee of the Shibaura Institute of Technology. The subjects were individually informed of the purposes and procedures of the experiments, and they also agreed in the informed consent before starting the measurements.

Effect of occluding cuff size on arterial elasticity analysis

The effect of the occluding cuff size on the arterial elasticity analysis was conducted using three cuff sizes (inner diameters of 20 mm, 22 mm, and 24 mm) in eight subjects (three women and five men, 20–45 years old) to determine the most suitable cuff size for the subsequent analyses. We performed the measurements in a quiet room at a temperature of 24°C ± 1°C. After the subjects had rested in a sitting position for 10 minutes, their P_{sys}, P_{dia}, and heart rate were measured at the left brachium. Next, the skin temperature and finger diameter of the right index finger were measured before applying the PPG cuff on the finger. Afterward, PPG measurement was performed by recording the PPG signals from the right index finger positioned at the same level as the heart.

Effects of age and sex on arterial elasticity analysis

After an acceptable cuff size was acquired, the arterial elasticity analysis of the amplitude variation in the AC signal of the PPG was performed in six groups of subjects – eight women and eight men, 20–25 years old; five women and five men, 32–45 years old; and six women and six men, over 50 years old – at a room temperature of 24°C ± 1°C. The subjects started the experiment by resting in a sitting position for 10 minutes. After that, blood pressure, heart rate, and skin temperature were measured at the left brachium and the right index finger. Finally, PPG measurement was conducted by recording the PPG signals from the right index finger positioned at the same level as the heart.

Effect of cold-stress stimulation on arterial elasticity analysis

The effect of cold-stress stimulation on the arterial elasticity analysis was investigated in six women and six men, 20–25 years old. We also conducted this experiment in a quiet room at a temperature of 24°C ± 1°C. In pre-cold-stress stimulation, the subjects had rested in a sitting position for 10 minutes, then their blood pressure and heart rate were measured at the left brachium. The skin-temperature measurement was performed at the right index finger. The PPG signals were subsequently recorded from the right index finger. Afterward, the subjects proceeded to the cold-stress stimulation by immersing their left hands into 5°C ± 1°C water positioned at the same level as the heart for 4 minutes. The blood pressure and the PPG measurements were continued at the left brachium and the right index finger, respectively, after starting cold-stress stimulation for 1 minute. After finishing the cold-stress stimulation, the subjects proceeded to post-cold-stress stimulation by repeating the procedures conducted before the cold-stress stimulation.

Statistical analysis

The P_m, ΔP, heart rate, and $\Delta V/\Delta V_0$ values were expressed as mean values and standard deviation. The relationships between the P_{tr} and the $\Delta V/\Delta V_0$ of each group were illustrated as average curves. We used Student's *t*-test to identify differences in P_m and ΔP between two locations: the brachium and the index finger. A two-way analysis of variance (ANOVA) was used to test differences in P_m, ΔP, heart rate, and $\Delta V/\Delta V_0$ among the six groups of subjects according to the effects of age and sex. In the study of the effects of age and sex on arterial elasticity, we tested two hypotheses with critical *P*-values of 0.05 and 0.001. To control the family-wise error rate of testing each hypothesis, we utilized the Bonferroni correction,[34] and the critical *P*-values of 0.05 and 0.001 were consequently adjusted to be 0.025 and 0.0005, respectively. One-way ANOVA was also used to estimate differences in P_m, ΔP, heart rate, and $\Delta V/\Delta V_0$ among the three conditions according to the influence of the cold-stress stimulation. We also determined mean differences in the average finger diameter, P_m, and $\Delta V/\Delta V_0$ between two groups of data using Student's *t*-test. The correlations of P_m against age, and the $\Delta V/\Delta V_0$ value at a P_{tr} of 30 mmHg against age were modeled using a linear regression.

Results

Effect of occluding cuff size on arterial elasticity analysis

To examine the effect of occluding cuff size on arterial elasticity measurements, subjects were separated into two groups according to average finger diameter. In the first group, five subjects had a moderate index finger size, with an average diameter of 16.9 ± 0.5 mm. Meanwhile, in the other group, three subjects had an average index finger diameter of 18.8 ± 0.3 mm, which was significantly larger than that of the first group ($P < 0.001$). When the PPG measurements were performed using three cuff sizes (20 mm, 22 mm, and 24 mm in inner diameter), the relationships between P_{tr} and $\Delta V/\Delta V_0$ were clearly dissimilar between the two groups. Figure 3 shows the P_{tr}–$\Delta V/\Delta V_0$ relationships for the three cuff sizes in the moderate-finger subjects. The mean $\Delta V/\Delta V_0$ produced by the different cuff sizes decreased at much the same rate over the range of P_{tr}. On the other hand, the cuff size apparently affected the P_{tr}–$\Delta V/\Delta V_0$ relationships in the large-finger subjects, as shown in Figure 4. Although mean $\Delta V/\Delta V_0$ decreased with P_{tr} and no significant difference in mean $\Delta V/\Delta V_0$ was observed at any P_{tr} for all three cuffs, the P_{tr}–$\Delta V/\Delta V_0$ curve for the 20 mm diameter cuff was shifted distinctly upwards, compared with the curves for both the 22 mm and 24 mm diameter cuffs. Furthermore, using the same occluding cuff size, the P_{tr}–$\Delta V/\Delta V_0$ relationship for the moderate-finger subjects significantly differed from that of the large-finger subjects ($P < 0.05$) when the 20 mm diameter cuff size was used, whereas the finger size of subjects did not significantly affect the P_{tr}–$\Delta V/\Delta V_0$ relationship obtained using the 22 mm and 24 mm diameter cuffs. Therefore, to avoid possible errors arising from the effect of the PPG cuff size, the medium cuff with a 22 mm diameter was used in subsequent arterial elasticity analyses.

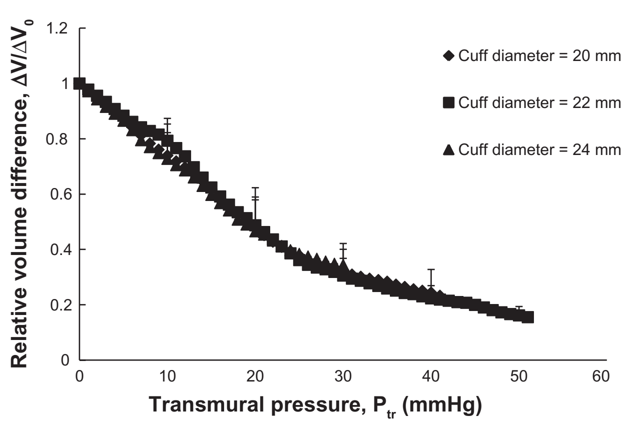

Figure 3 Relationships between the transmural pressure (P_{tr}) and the relative volume difference ($\Delta V/\Delta V_0$) in subjects with moderately sized fingers according to the occluding cuff size: 20 mm (♦), 22 mm (■), and 24 mm (▲) diameter cuffs.
Notes: $\Delta V/\Delta V_0$ is shown as the mean ± standard deviation (n = 5). The $\Delta V/\Delta V_0$ decreased with P_{tr}. There was no significant differences among the P_{tr}–$\Delta V/\Delta V_0$ curves obtained from the three cuff sizes.

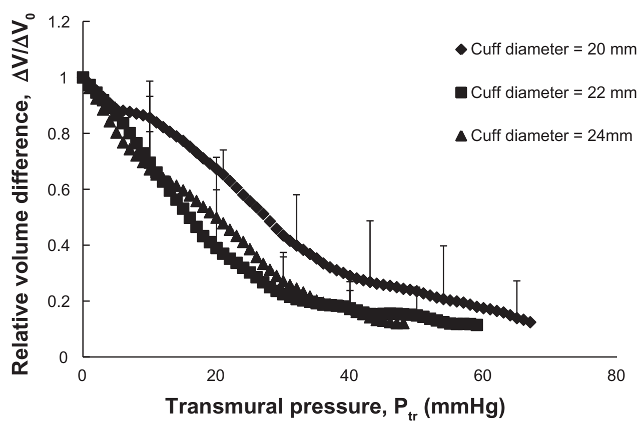

Figure 4 Relationships between the transmural pressure (P_{tr}) and the relative volume difference ($\Delta V/\Delta V_0$) in subjects with large fingers according to the occluding cuff size: 20 mm (♦), 22 mm (■) and 24 mm (▲) diameter cuffs.
Notes: $\Delta V/\Delta V_0$ is shown as the mean ± standard deviation (n = 3). The $\Delta V/\Delta V_0$ decreased with the transmural pressure. The curves for the 20 mm diameter cuff differed from the curves for the 22 and 24 mm diameter cuffs. The small cuff with the 20 mm diameter seemed to affect the P_{tr}–$\Delta V/\Delta V_0$ relationship in subjects with large fingers.

Effects of age and sex on arterial elasticity analysis

Blood pressure of subjects

The average P_m of the six groups of subjects (eight women and eight men, 20–25 years old; five women and five men, 32–45 years old; and six women and six men, over 50 years old) obtained from the left brachium and the right index finger are presented in Figure 5A. The P_m of the brachial artery was significantly greater than that of the digital artery in almost every group of subjects ($P < 0.0005$, 0.025) except for the 32- to 45-year-old men. However, the variations in the P_m among the different groups of subjects were similar at the brachium and the index finger. Using two-way ANOVA, the age and sex of the subjects were shown to have a significant impact on the differences in the P_m of brachial artery (age factor, $P < 0.025$; sex factor, $P < 0.0005$; and interaction, $P < 0.0005$), as in Figure 5C, and digital artery (age factor, $P < 0.025$; sex factor, $P < 0.025$; and interaction, $P > 0.025$), as in Figure 5D. In the digital artery, a comparison of the P_m values among the groups of women showed that women over 50 years of age had a significantly higher P_m than younger women ($P < 0.0005$). At the same time, 32- to 45-year-old women also had a significantly higher P_m than 20- to 25-year-old women ($P < 0.025$). In contrast, no significant differences in P_m were observed among the three age-groups of men. Within the same range of age, the P_m of the 20- to 25-year-old men was significantly larger than that of the 20- to

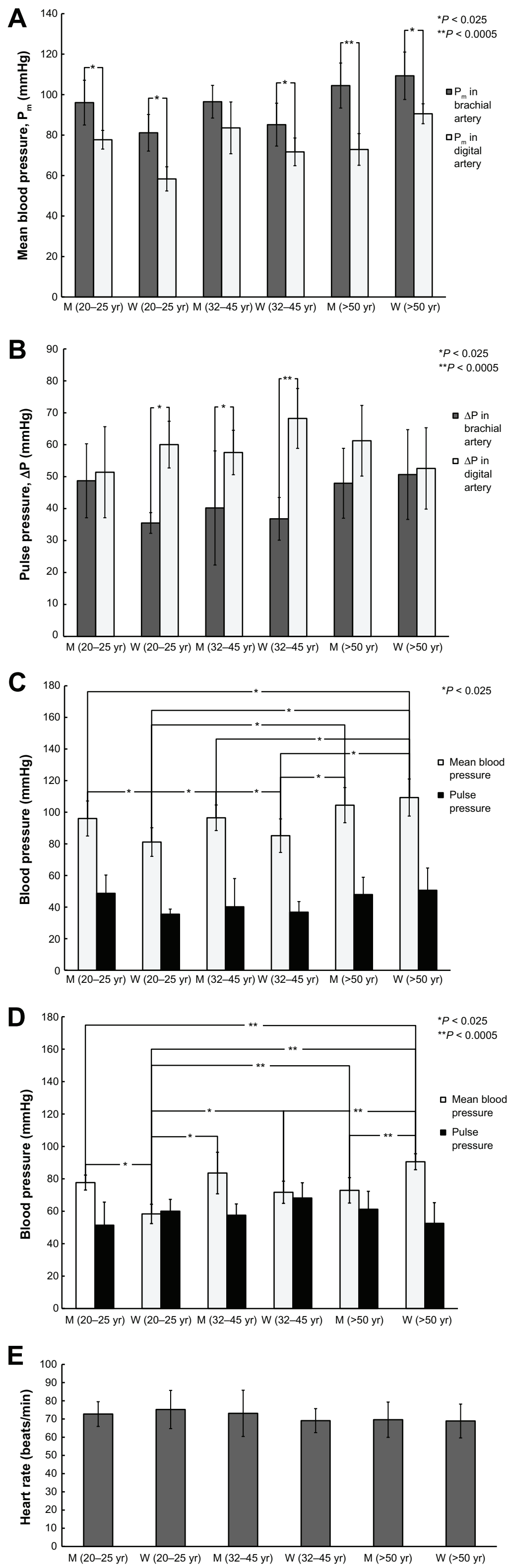

Figure 5 Average mean blood pressure (P_m), pulse pressure (ΔP), and heart rate in six groups of subjects (eight women and eight men, 20–25 years old; five women and five men, 32–45 years old; and six women and six men, over 50 years old) presented in five subfigures: (**A**) average P_m in the brachial (filled bars), and digital (open bars) arteries; (**B**) average ΔP in the brachial (filled bars), and digital (open bars) arteries; (**C**) average P_m (open bars), and ΔP (filled bars) in the brachial artery; (**D**) average P_m (open bars), and ΔP (filled bars) in the digital artery; and (**E**) average heart rate (filled bars).
Notes: *$P < 0.025$; **$P < 0.0005$.
Abbreviations: M, men; W, women.

25-year-old women ($P < 0.025$), while the men over 50 years old had a significantly lower P_m than the women over 50 years old ($P < 0.0005$). However, no difference in P_m between sexes was seen in the 32- to 45-year-old subjects. Furthermore, the overall relation between P_m and age in Figure 6 expressed a positive correlation ($R^2 = 0.1179$, $P < 0.025$), which inferred a rise in P_m with advancing age.

Figure 5B shows the average ΔP of the brachial and digital arteries. The ΔP of the brachial artery was significantly lower than that of the digital artery in the 20- to 25-year-old women and the 32- to 45-year-old men and women ($P < 0.0005$, 0.025). Nonetheless, the age and sex of the subjects had no significant influence on differences in ΔP among the groups for either the brachium (age factor, $P > 0.025$; sex factor, $P > 0.025$; and interaction, $P > 0.025$), as in Figure 5C, or the index finger (age factor, $P > 0.025$; sex factor, $P > 0.025$; and interaction, $P > 0.025$), as in Figure 5D. Moreover, Figure 5E shows no significant differences in heart rate among the six groups of subjects (age factor, $P > 0.025$; sex factor, $P > 0.025$; interaction, $P > 0.025$).

Effects of age and sex on the relationship between transmural pressure and relative volume difference

Based on the amplitude variation in the AC signal for the PPG measurement of the human index finger, the arterial elasticity of the six groups of subjects was analyzed and expressed as the average P_{tr}–$\Delta V/\Delta V_0$ relationship in Figure 7. Although mean $\Delta V/\Delta V_0$ decreased with P_{tr} nonlinearly in all the groups of subjects, mean $\Delta V/\Delta V_0$ of the 20- to 25-year-old and the 32- to 45-year-old subjects decreased relative to the P_{tr} at a higher rate, compared with that in subjects over 50 years old. Therefore, the P_{tr}–$\Delta V/\Delta V_0$ curves for subjects over 50 years old were shifted upwards from the curves of the 20- to 25-year-old and the 32- to 45-year-old subjects.

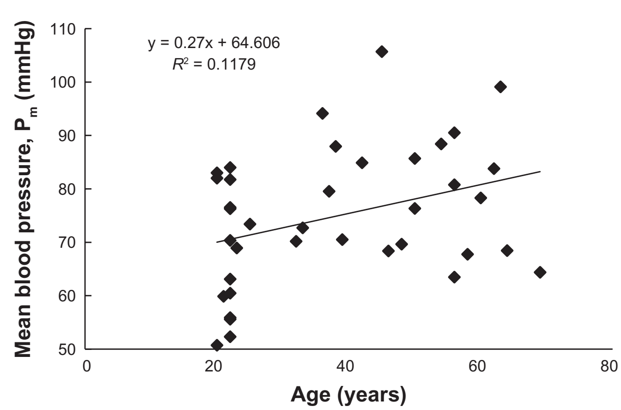

Figure 6 Positive correlation between mean blood pressure (P_m) and age.
Notes: P_m tended to increase with advancing age. The correlation coefficient of the regression model was 0.27 ($R^2 = 0.1179$, $P < 0.025$, n = 38).

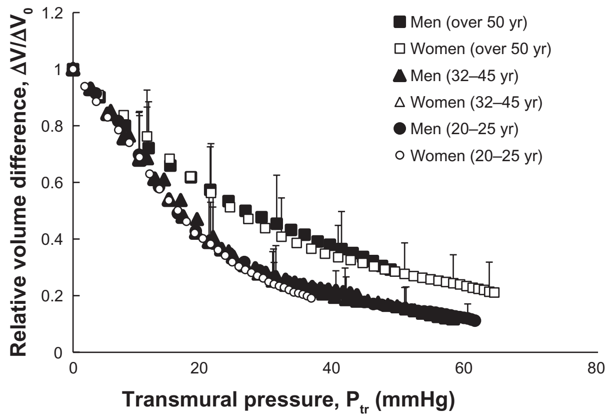

Figure 7 Relationships between transmural pressure (P_{tr}) and relative volume difference ($\Delta V/\Delta V_0$) in arterial elasticity analyses performed in six groups of subjects: eight women (○) and eight men (●), 20–25 years old; five women (Δ) and five men (▲), 32–45 years old; and six women (□) and six men (■), over 50 years old.
Notes: The mean ± standard deviation of $\Delta V/\Delta V_0$ in each group was plotted against the individual mean of P_{tr}. The P_{tr}–$\Delta V/\Delta V_0$ curves for the over 50-year-old subjects obviously differed from the curves of the younger subjects. Sex had no impact on the difference among the P_{tr}–$\Delta V/\Delta V_0$ curves.

However, no difference in $\Delta V/\Delta V_0$ variation at any P_{tr} was seen between 20- to 25-year-old and 32- to 45-year-old subjects. Within the same range of age, difference in sex had no impact on $\Delta V/\Delta V_0$ variation over the range of P_{tr}. Figure 8 shows mean $\Delta V/\Delta V_0$ values at a P_{tr} of 30 mmHg in all the groups, corresponding to the P_{tr}–$\Delta V/\Delta V_0$ relationships. At a P_{tr} of 30 mmHg, mean $\Delta V/\Delta V_0$ values of the subjects over 50 years old were significantly larger than those of 20- to 25-year-old and 32- to 45-year-old subjects ($P < 0.025$). Meanwhile, the mean $\Delta V/\Delta V_0$ values of 20- to 25-year-old subjects did not significantly differ from those of 32- to 45-year-old subjects. Two-way ANOVA showed a significant influence of age on differences in the mean $\Delta V/\Delta V_0$ values, while difference in sex had no impact on mean $\Delta V/\Delta V_0$ values (age factor, $P < 0.0005$; sex factor, $P > 0.025$; and interaction, $P > 0.025$). In addition, results of the linear regression between $\Delta V/\Delta V_0$ value at a P_{tr} of 30 mmHg and age ($R^2 = 0.2891$, $P < 0.0005$) obtained in the 38 subjects indicated an increase in the $\Delta V/\Delta V_0$ value with age, as shown in Figure 9.

Effect of cold-stress stimulation on arterial elasticity analysis

Effect of cold-stress stimulation on blood pressure

Average P_m, ΔP, and heart rate of the brachial and digital arteries of twelve subjects obtained from three conditions – pre-cold-stress, cold-stress, and post-cold-stress stimulations – are shown in Figure 10. One-way ANOVA showed significant differences in P_m among the three conditions ($P < 0.05$). While the P_m of the brachial artery was significantly greater than that of the digital artery for the pre-cold-stress ($P < 0.05$) and post-cold-stress stimulations ($P < 0.05$), there was no significant difference in P_m between the brachial and digital arteries for the cold-stress stimulation, as in Figure 10A. In the meantime, the P_m of both the brachial (Figure 10B) and digital arteries (Figure 10C) for the cold-stress stimulation were significantly higher than those for the pre-cold-stress and post-cold-stress

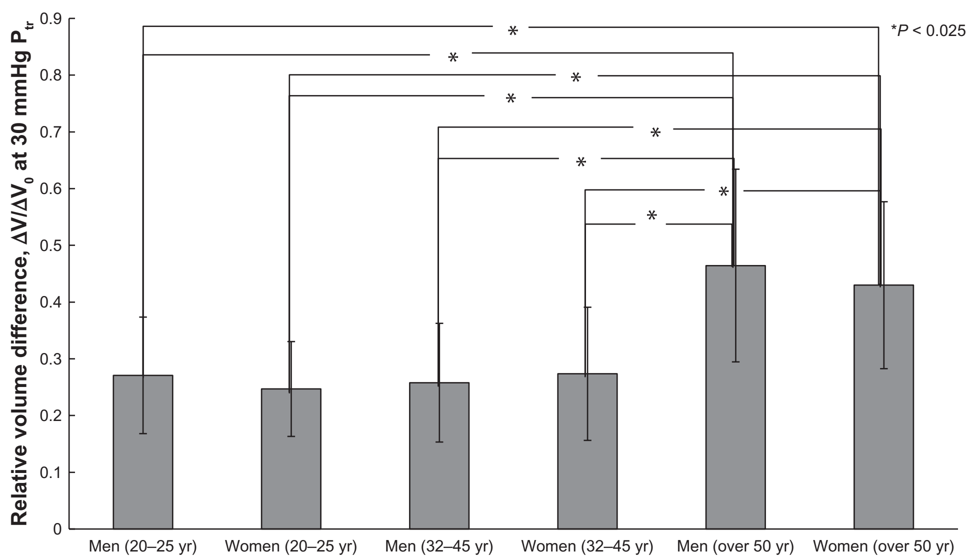

Figure 8 Relative volume differences ($\Delta V/\Delta V_0$) at a transmural pressure (P_{tr}) of 30 mmHg in six groups of subjects: eight women and eight men, 20–25 years old; five women and five men, 32–45 years old; and six women and six men, over 50 years old.
Notes: $\Delta V/\Delta V_0$ is shown as the mean ± standard deviation. $\Delta V/\Delta V_0$ values of those over 50 years old were significantly greater than those of the younger subjects ($P < 0.025$), while sex had no impact on the difference in the mean $\Delta V/\Delta V_0$ values at a P_{tr} of 30 mmHg.

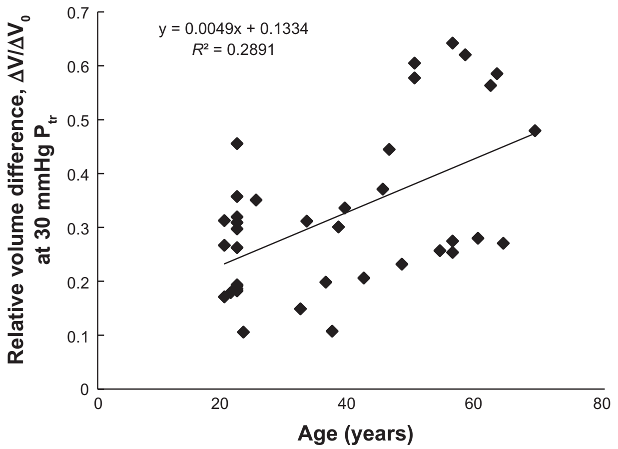

Figure 9 Positive correlation between the mean relative volume difference ($\Delta V/\Delta V_0$) value at a transmural pressure (P_{tr}) of 30 mmHg and age.

Notes: Mean $\Delta V/\Delta V_0$ value at a P_{tr} of 30 mmHg tended to increase with advancing age. The correlation coefficient of the regression model was 0.0049 ($R^2 = 0.2891$, $P < 0.0005$, n = 38).

stimulations ($P < 0.05$). The P_m of both the brachial and digital arteries for the pre-cold-stress stimulation did not differ from those for the post-cold-stress stimulation. Figure 10B shows the ΔP obtained from the brachial and digital arteries in the three conditions, and the ΔP of the brachial artery was significantly lower than that of the digital artery for all the three conditions ($P < 0.001$). Nonetheless, using one-way ANOVA, no significant differences in ΔP were observed for any of the three conditions in both the brachial ($P > 0.05$) and digital ($P > 0.05$) arteries. These results are illustrated in Figure 10C and D. Furthermore, there were no changes in heart rate for the three conditions ($P > 0.05$), as shown in Figure 10E.

Effect of cold-stress stimulation on relationship between transmural pressure and relative volume difference

Average P_{tr}–$\Delta V/\Delta V_0$ relationships obtained from PPG measurement in twelve subjects for three conditions – pre-cold-stress, cold-stress, and post-cold-stress stimulations – are illustrated in Figure 11. There were no significant differences in P_{tr}–$\Delta V/\Delta V_0$ relationships among the three conditions, and mean $\Delta V/\Delta V_0$ decreased at much the same rate over the range of P_{tr} for all three conditions. Moreover, there were no significant differences in mean $\Delta V/\Delta V_0$ values at a P_{tr} of 30 mmHg among the three conditions: pre-cold-stress stimulation, 0.31 ± 0.11; cold-stress stimulation, 0.29 ± 0.16; and post-cold-stress stimulation, 0.31 ± 0.10; using one-way ANOVA ($P > 0.05$).

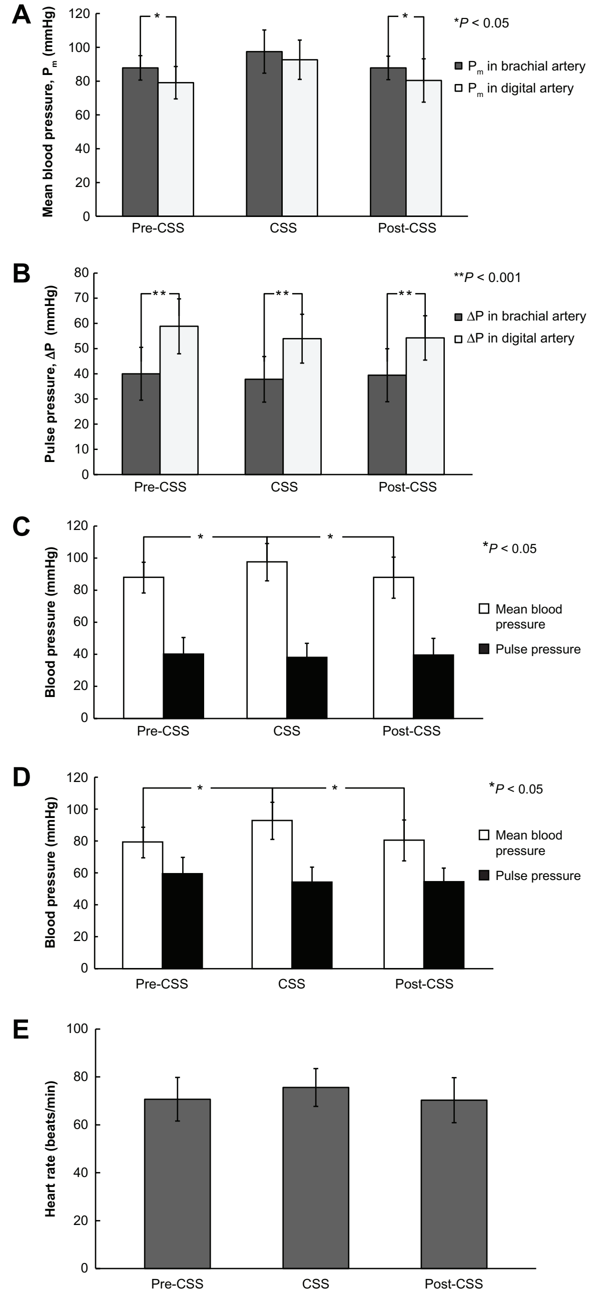

Figure 10 Average mean blood pressure (P_m), pulse pressure (ΔP), and heart rate in twelve subjects according to the three conditions: pre-cold-stress stimulation (Pre-CSS), cold stress stimulation (CSS), and post-cold-stress stimulation (Post-CSS) presented in five subfigures: (**A**) average P_m in the brachial (filled bars), and digital (open bars) arteries; (**B**) average ΔP in the brachial (filled bars), and digital (open bars) arteries; (**C**) average P_m (open bars), and ΔP (filled bars) in the brachial artery; (**D**) average P_m (open bars), and ΔP (filled bars) in the digital artery; and (**E**) average heart rate (filled bars).

Notes: *$P < 0.05$; **$P < 0.001$.

Discussion

In the arterial elasticity analysis using variation in AC signal derived from PPG, no effect of the occluding cuff size was found in subjects with moderately sized fingers. However, the cuff size apparently impacted PPG measurements in

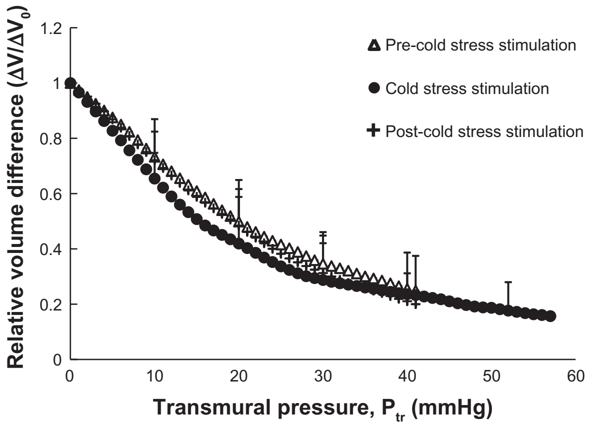

Figure 11 Relationships between transmural pressure (P_{tr}) and the relative volume difference ($\Delta V/\Delta V_0$) according to the effect of cold-stress stimulation separated into three conditions: pre-cold-stress stimulation (Δ), cold-stress stimulation (●), and post-cold-stress stimulation (+).

Notes: The mean ± standard deviation (n = 12) of the $\Delta V/\Delta V_0$ in each condition was plotted against the individual mean of the P_{tr}. There were no significant differences among the P_{tr}–$\Delta V/\Delta V_0$ curves obtained from all the three conditions.

subjects with large fingers by the upward shifting of the P_{tr}–$\Delta V/\Delta V_0$ curve obtained using the 20 mm diameter cuff (which differed from the curves produced by the 22 mm and 24 mm diameter cuffs). Consequently, the vascular expansion of the digital artery was limited when the small cuff size was used. As a result, the $\Delta V/\Delta V_0$ value obtained using the small cuff was greater than that obtained using the larger cuffs at the same level of P_{tr}. Thus, the excessively small cuff was not appropriate for arterial elasticity analyses using the AC signal of PPG. Meanwhile, Jones et al claimed that the oversize cuff was less accurate for assessments of PPG.[35] Moreover, if the oversize cuff was loosely applied to a finger, the P_c could have been ineffectively transmitted to the finger, resulting in an overestimation of the mean blood pressure. Therefore, we decided to apply the medium cuff, with a 22 mm diameter, for the subsequent arterial elasticity analyses, even though the 22 mm and the 24 mm diameter cuffs statistically provided the same P_{tr}–$\Delta V/\Delta V_0$ relationships for all finger sizes.

After the optimal cuff size was determined, this cuff size was used to measure blood pressure and arterial elasticity in six groups of subjects with a variety of ages and sexes. When mean blood pressures in the brachial and digital arteries of the subjects were examined, the P_m in the digital artery was significantly lower than that in the brachial artery. The difference in the P_m between these two locations was caused by an increase in vascular resistance of the small artery, leading to a pressure drop along the arterial tree.[36] Nevertheless, the variations in the P_m for both the brachial and the digital arteries were quite similar among the groups of subjects. These results affirmed the reliability and efficiency of using this PPG technique for measuring blood pressure, in agreement with the results for PPG measurements in normotensive and hypertensive subjects performed by Yamakoshi et al,[24] in which indirect systolic and mean blood pressure of the digital artery were positively correlated with direct brachial arterial pressure. PPG blood measurements are feasible not only for fingers but also for arms, and systolic blood pressure in the brachial artery obtained using PPG corresponds to that obtained through invasive blood measurements in the same region.[37] According to the results for P_m in the six groups of subjects, the P_m tended to increase with age,[38–40] especially in women. Additionally, sex also influenced the different P_m values in the 20- to 25-year-olds and the subjects over 50 years old. In the meantime, the higher ΔP of digital artery compared with that of brachial artery was due to a wave reflection at the peripheral site.[36] This pulse-pressure amplification resulted in equality of the ΔP in the digital artery among the groups of subjects.

When the arterial elasticity of these six groups of subjects was analyzed and expressed as $\Delta V/\Delta V_0$ index, we found that age impacted the P_{tr}–$\Delta V/\Delta V_0$ relationships and $\Delta V/\Delta V_0$ values at a P_{tr} of 30 mmHg in the subjects who were older than 50 years. The $\Delta V/\Delta V_0$ values in subjects over 50 years old were distinctly higher than those in younger subjects when the P_{tr} was higher than 20 mmHg. The larger $\Delta V/\Delta V_0$ values at a certain P_{tr} level indicated that the arterial blood vessels of subjects over 50 years old had lower expansibility than those of younger subjects because of the loss of arterial elasticity in subjects over 50 years old. Moreover, the correlation between the $\Delta V/\Delta V_0$ value at a P_{tr} of 30 mmHg and age also confirmed a reduction in arterial elasticity with age. The $\Delta V/\Delta V_0$ index was therefore capable of detecting changes in arterial elasticity with advancing age, similar to other arterial stiffness markers.[9–11,29,31,32]

However, when we considered arterial elasticity of subjects within the same age range, the P_{tr}–$\Delta V/\Delta V_0$ relationships and the $\Delta V/\Delta V_0$ values at a P_{tr} of 30 mmHg were not different between the sexes, while the men had different P_m from the women within some age ranges, such as the 20- to 25-year-olds and subjects over 50 years old. These findings implied that the differences in the P_m did not affect the P_{tr}–$\Delta V/\Delta V_0$ relationship or the $\Delta V/\Delta V_0$ value at certain P_{tr} values. In contrast, we found differences in the P_{tr}–$\Delta V/\Delta V_0$ relationships and $\Delta V/\Delta V_0$ values among subjects who had the same P_m. For instance, although no difference in the P_m was observed among each group of men, those who were over 50 years of age had larger $\Delta V/\Delta V_0$ values than the other two groups of men.

Similar results were also seen when the 32- to 45-year-old men and the women over 50 years old with the same P_m were compared, with the $\Delta V/\Delta V_0$ values of the women who were over 50 years of age being higher than those of the other group. According to these results, we therefore deduced that using the P_{tr}–$\Delta V/\Delta V_0$ relationship and the $\Delta V/\Delta V_0$ value at a certain P_{tr} could be used to indicate the change or the difference in arterial elasticity without the influences of sex and different P_m levels. On the other hand, many arterial stiffness parameters vary with the P_m of the subjects. Both the carotid-femoral PWV and the brachial-ankle PWV increase with the P_m of subjects, similar to the d/a and e/a ratios of the second derivative of the digital pulse volume and the index of arterial stiffness, whereas the arterial compliance and ankle-brachial index are negatively correlated with the P_m.[10,19,41] Thus, the P_m of an individual person is needed when the arterial stiffness of that person is evaluated using these parameters. In contrast, the P_m is not necessary when the $\Delta V/\Delta V_0$ at a certain P_{tr} from the AC signal of PPG is used.

Although the effect of the P_m is not found in an evaluation based on the DC signal of the PPG,[26,27] the effect of the tissues around the arterial system on the intensity of the DC component may reduce the accuracy of this technique. The existence of this effect was obviously seen when the P_c was greater than the P_{sys}, as there must be no flow in the arterial system because of the complete collapse of the artery as a result of the P_c. This situation should result in a constant intensity of the DC component during the primary stage of occlusion, rather than a slow reduction in the recorded DC signal (Figure 2). Meanwhile, using the AC component of the PPG enables the influence of other tissues to be eliminated, and therefore truly reflects the changes in the arterial system, similar to the basic method of pulse oxymetry.[42] Although ΔP amplification might also affect evaluations using the $\Delta V/\Delta V_0$ of subjects with different arterial elasticities, we assigned the ΔP to be a constant factor because of the equality of the ΔP in the digital artery among the groups of subjects. The ΔP consequently had no influence on the current investigations.

According to the results of the effect of the cold-stress stimulation on blood pressure, the cold-stress stimulation predominantly affected the P_m by increasing it. The cold exposure induces a rise in skin sympathetic nerve activity,[43] reduction of endothelial nitric oxide synthase activity, and higher affinity for noradrenaline on the plasma membrane.[36] These neurogenic and vascular responses lead to a vasoconstriction observed by a decrease in vascular conductance,[44] an increase in the P_m,[20,21,45] and reduction of cutaneous perfusion.[46] Furthermore, the higher P_m may be affected by the increase in myocardial oxygen demand, raising the oxygen uptake during body cooling.[47] In the meantime, no significant influence of the cold-stress stimulation on the ΔP was observed. In this experiment, the cold-stress stimulation mainly induced vasoconstriction, raising vascular resistance without changes in heart rate.[21,47] When cardiac output remains constant during cold exposure,[48] the unchanged heart rate maintains the constant level of the stroke volume. Consequently, both the P_{sys} and P_{dia} increased with the unaltered ΔP. Additionally, the large changes in the ΔP due to the cold exposure were found for central blood pressure rather than peripheral blood pressure.[45,47]

Regarding the effect of cold-stress stimulation on the P_{tr}–$\Delta V/\Delta V_0$ relationship, there were no significant differences in P_{tr}–$\Delta V/\Delta V_0$ relationships among the three conditions, while cold-stress stimulation manifestly affected the P_m. These results also confirmed that the P_{tr}–$\Delta V/\Delta V_0$ relationship was independent of the P_m. Although the cold exposure induced the reduction of amplitudes of the PPG AC signal,[46] this stimulation did not influence the arterial elasticity analysis using the $\Delta V/\Delta V_0$ index. On the contrary, some arterial stiffness parameters are influenced by vasoconstriction and vasodilation, such as the volume elastic modulus and the AIx.[20,21,26,47,49]

Limitations of the study

We did not evaluate the orientation and oxygenation levels of red blood cells that associate with changes in transmitted or reflected light intensity. These factors have caused the unreliable PPG measurement.[22]

The influences of some basic factors, ie, the occluding cuff size of PPG, age, sex, and cold-stress stimulation, on the arterial elasticity analysis using amplitude variations in the PPG pulse wave were evaluated in the small number of healthy subjects. The small number of subjects may be insufficient for confirmation of the aforementioned technique in the current clinical applications. This study is only the primary investigation of the development of the arterial elasticity analysis using PPG amplitude variation. Therefore, investigations of this technique under the influence of other factors, including pathophysiological conditions, in greater numbers of subjects are intended for future work. However, the present study can provide useful basic information for future analyses.

As for the results of the cold-stress stimulation, the P_{tr}–$\Delta V/\Delta V_0$ relationship tended to depend on the ΔP (which was constant for all the three conditions). Cold exposure is found to stimulate rising PWV and rising ΔP in old adults.[20]

Because we investigated the effect of cold-stress stimulation on the P_{tr}–$\Delta V/\Delta V_0$ relationship in young adults, we could not certainly deduce that cold-stress stimulation did not influence the ΔP or the P_{tr}–$\Delta V/\Delta V_0$ relationship for all ages. The effect of the ΔP is therefore necessary for future studies to prove progressively the capability of using this method for arterial elasticity analysis. Although the effect of the ΔP on the P_{tr}–$\Delta V/\Delta V_0$ relationship was beyond the scope of this study, the aforementioned results indicated the independence of the P_{tr}–$\Delta V/\Delta V_0$ relationship from the vascular stimulation, which predominantly influenced the P_m.

Conclusion

We proposed a simple methodology for analyzing arterial elasticity in the human finger by examining variations in the AC component of the PPG signal. We defined the $\Delta V/\Delta V_0$ as the vascular elasticity index and expressed it in the form of the P_{tr}–$\Delta V/\Delta V_0$ relationship and the $\Delta V/\Delta V_0$ value at a certain P_{tr}. This method was primarily applied to evaluate arterial elasticity under the effect of occluding cuff size for obtaining the suitable cuff size. We also evaluated the effects of basic factors (age, sex, and cold-stress stimulation) on arterial elasticity using this method. As the results of this study showed, an excessively small cuff seemed to be unsuitable for estimating the arterial elasticity using the $\Delta V/\Delta V_0$ from the AC signal of PPG, especially in large fingers. Meanwhile, the P_{tr}–$\Delta V/\Delta V_0$ relationship and the $\Delta V/\Delta V_0$ values changed with advancing age, whereas sex and differences in the P_m had no impact on them. Although the impact of cold-stress stimulation on the P_{tr}–$\Delta V/\Delta V_0$ relationship was not certainly deduced for all ages, this impact demonstrated the independence of the P_{tr}–$\Delta V/\Delta V_0$ relationship from the vascular stimulation, which directly affected the P_m. According to the results of this study, $\Delta V/\Delta V_0$ assessments using amplitude variations of the AC component of PPG could possibly be used as an alternative technique for analyzing arterial elasticity, which can be applied together with other techniques to increase the efficiency of medical diagnoses.

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Disclosure

The authors report no conflicts of interest in this work.

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