Age-Related Changes in Blood Volume Pulse Wave at Fingers and Ears

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Age-Related Changes in Blood Volume Pulse Wave at Fingers and Ears

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***Abstract*— *Objective:* The decline in vascular elasticity with aging can be manifested in the shape of pulse waves. The study investigated the pulse wave features that are sensitive to age and the patterns of these features change with increasing age were examined. *Methods:* Five features were proposed and extracted from the photoplethysmography (PPG)-based pulse wave or its first derivative wave. The correlation between these PPG features and ages was studied in 100 healthy subjects with a wide range of ages (20-71 years). Piecewise regression coefficients were calculated to examine the rates of change of the PPG features with age at different age stages. *Results:* The proposed PPG features obtained from the finger showed a strong and significant correlation with age (with r = 0.76 – 0.77, p < 0.01), indicating higher sensitivity to age changes compared to the PPG features reported in previous studies (with r = 0.66 – 0.75). The correlation remained significant even after correcting for other clinical variables. The rate of change of the PPG feature values was found to be significantly faster in subjects aged ⩾40 years compared to those aged < 40 years in the healthy population. This rate of change was similar to the age-related progression of arterial stiffness evaluated by pulse wave velocity (PWV), which is considered a gold standard for evaluating vascular stiffness. *Conclusions:* The proposed PPG features showed a high correlation with chronological age in healthy subjects and exhibited a similar age-related change trend as PWV. Significance: With the convenience of PPG measures, the proposed age-related features have the potential to be used as biomarkers for vascular aging and estimating the risk of cardiovascular disease.**

***Key Wards*— Age-related features, cardiovascular disease risk, photoplethysmography (PPG), vascular aging**

I. Introduction

CARDIOVASCULAR diseases (CVD) are a leading causes of death worldwide, and aging is a major, irreversible risk factor for CVD. Arterial stiffness, which increases with age, plays an important role in promoting structural and functional changes in the cardiovascular system. Pulse wave velocity (PWV), the gold standard for evaluating arterial stiffness, has been reported to be correlated with age in healthy subjects and has better predictive value for CVD than traditional risk markers [1]. The ability to identify age-related markers on cardiovascular system may be of importance in using these features as biomarkers for estimating vascular aging and for predicting and assessing CVD risk. It is of great value in the prevention of CVD.

Pulse wave monitoring is a simple, portable, cost-effective, and non-invasive technology that has broad applications in the field of wearable technology and telemedicine for real-time monitoring. Thus, it is highly suitable for use as a large-scale early screening tool. The pulse wave recorded in the peripheral artery measures changes in blood volume or blood pressure within the vascular tissue bed. The degradation of vascular elasticity with aging can be reflected in the shape of pulse wave [1], thus it is expected to find age-related features from pulse wave, which could be used as biomarkers for estimating vascular aging and for early screening and warning of CVD risk.

There have been some literatures investigating the effects of aging on the shape of pulse waveform. It has been reported that as age increases, the pulse peak shifted subtly to the right of the pulse cycle, and the dicrotic notch gradually weakens, resulting in a tendency for increased triangularization of the peripheral toe pulse wave shape [1]. It has also been reported that aging-related disturbance in arterial stiffness and wave reflection will lead to an increase in the augmentation pressure of central aortic blood pressure waves in the elderly [2]. Based on the changing characteristics of the pulse wave shape with age, previous studies have identified several key age-related markers from the pulse wave [3-12]. These markers include: 1) *pulse risetime (RT)*, which is computed as the time between the onset foot of a pulse and its peak [4]; 2) *augmentation index (AI)*, which is calculated as the ratio of augmentation pressure to the pulse pressure, expressed as a percentage [5,6]; 3) *aging index*, which can be calculated as the amplitude of *(b-c-d)/a* of the second derivative wave of photoplethysmography (SDPPG) [7-9],

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amplitude ratio of *c/a* and time span between a and *c* of the SDPPG [10]; 4) *large artery stiffness index (LASI)*, which is inversely related to the time interval between maximum peak and dicrotic peak [11,12]; 5) *stiffness index (SI)*, which is calculated as the ratio of subject height (cm) to the time interval between maximum peak and dicrotic peak (ms) [11,12], among others. Another study showed a high correlation between the estimated age using photoplethysmography (PPG)-based pulse wave and the real chronological age [13]. Additionally, several studies have explored the use of pulse wave analysis for the direct evaluation of arterial stiffness [14-16]. For example, it has been reported that the time delay between pulse waves captured at different sites correlated well with the reference carotid to femoral PWV (cfPWV) measured using the commonly known applanation tonometry method [15]. Another study reported a method to estimate the gold-standard cf-PWV using the subject's height and pulse transit time, which was calculated by processing the finger PPG signal [16].

Although several vascular stiffness and aging indices extracted from pulse wave have been reported, several issues remain to be clarified. Firstly, it is not yet clear which pulse wave features are the most informative, and whether there are more sensitive pulse wave features that vary with age? Additionally, it is uncertain whether confounding factors such as blood pressure and heart rate could affect the relationship between these pulse wave features and age? Furthermore, inconsistent normalization schemes of pulse wave in amplitude or width may affect the value of pulse wave markers and their sensitivity to age change. It is unclear how normalizing the amplitude and width of pulse waves could improve the sensitivity of pulse wave features to age changes. Thirdly, it is unclear whether the changing rate of the pulse wave feature values with age is linear at different stages of age and whether the progression pace of arterial stiffness at different at different stages of age? Fourthly, the effect measuring pulse wave at different vascular sites on the correlation between pulse wave features and age is unclear.

Accordingly, this study aims to explore pulse wave features that are highly sensitive to age, recorded at different vascular sites, and investigate the pattern variations of these pulse wave features with age in different age stages. Among which, the effect of different normalization schemes of PPG wave amplitude or width on the sensitivity of pulse wave features to age changes were studied.

The main contributions of this study included: (1) Five newly proposed pulse wave analysis-based features were found to be more sensitive to age changes than the previously reported PPG features. (2) The strong correlation between these features and age remained significant even after correcting for other clinical variables, including systolic blood pressure (SBP), diastolic blood pressure (DBP), height, heart rate (HR), arm length, and body max index (BMI). (3) The age-related changes in most of the proposed PPG features values were slower before 40 years old and faster after 40 years old. This pattern was similar to the age-related progression of arterial stiffness evaluated by pulse wave velocity, which is the gold standard for assessing vascular stiffness, indicating that the PPG features proposed in this study have the potential to be used as biomarkers for vascular aging assessment. (4) A systematic investigation of the influence of normalizing the PPG waveform and its derivatives was conducted. The amplitudes and pulse widths were either normalized or left unnormalized, and the best performance was achieved when only the amplitudes were normalized, while the widths of the PPG and its derivatives were not normalized. 5) All correlation values between the proposed PPG features and age were higher for fingers than for ears, indicating that the distal pulse wave is more suitable for arterial stiffness analysis than the proximal pulse wave. 6) All correlation values between the proposed PPG features and age were lower for females than for males. This difference may be due to the fact that arterial stiffness increases almost linearly with age in men from early adulthood onward, while women experience a curvilinear aging trend, with a flatter curve in younger age and a steep increase in arterial stiffness after menopause [16].

II. Methods

To identify age-related PPG features, the association between age and PPG features was investigated in a group of healthy subjects with a wide range of ages using Pearson's correlation analysis and univariate regression analysis. Among which, to investigate the effect of measuring PPG at different vascular sites on the correlation between age and PPG features, PPG was recorded at both the proximal ear and distal finger. And different normalization schemes of PPG wave in amplitude or width were adopted to investigate their effects on the correlation between age and PPG features. In addition, piecewise linear regression was used to analyze the different dependence of PPG features on age at different stages of age. Afterwards, multiple regression analysis including other clinical variables as covariates was conducted for correcting confounding factors (such as blood pressure, , heart rate, height, arm length, and BMI) that may influence the association between age and PPG features. A schematic diagram is shown

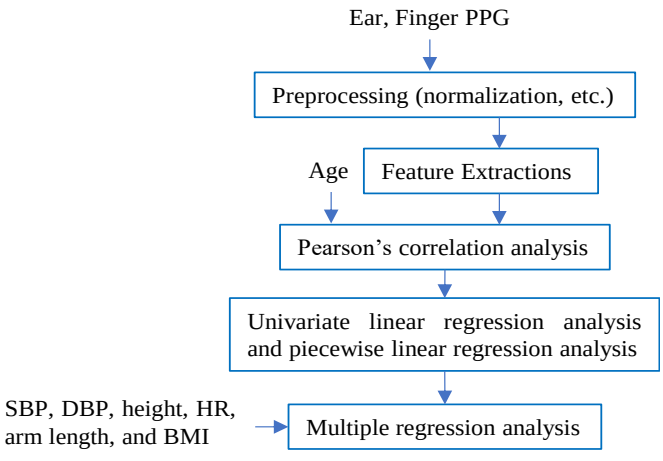

Fig.1. The flowchart for analyzing age-related PPG features.

in Fig.1. More details were described as follows:

A. Data Acquisition and Preprocessing

1) Subjects: To exclude the influence of vascular diseases on

arterial stiffness and pulse waveform characteristics, 100 healthy normotensive subjects without cardiovascular disease were recruited. To investigate the dependence on age of the PPG features at a wide range of ages, the subjects were between 21 to 70 years old (aged 44 ± 14 years), including young, middle-aged and old people, evenly distributed in five age groups: 20 ~ 29 years, 30 ~ 39 years, 40 ~ 49 years, 50 ~ 59 years and over 60 years, with 20 people in each age group. The subjects were recruited from staff, students and their relatives in Newcastle Hospitals and Newcastle University. The study received ethical permission from the Faculty Research Ethics Panel at Anglia Ruskin University (FMSFREP/17/18 205), and all subjects provided written informed consent.

2) Protocol: Before data collection, the subject lay down in supine position and rest for 5 minutes. Then, critical clinical measures including systolic blood pressure (SBP), diastolic blood pressure (DBP), height, arm length, and body max index (BMI) were measured. After that, the PPG sensor was lightly attached to the tip of the right index finger and earlobe to ensure a snug fit without constricting the blood vessels. This was done by an experienced operator to ensure consistency across all measurements. Ear PPG and finger PPG waves were recorded continuously and simultaneously for 2 minutes, with a sampling rate of 2500 Hz. Each PPG sensor was developed with an identical pair of surface-mount emitting diode (SME 2470-001, Honeywell) and photodiode (SMD 2420-001, Honeywell). The output of the emitting diode was near-infrared light with a wavelength of 880nm.The PPG sensors worked in reflective mode. The current of the LEDs was adjusted according to the amplitude of the detected PPG, but remained constant during one complete measurement. More details of the setup can be found one of our previous studies [18].

3) Filtering: Since the frequency response of the Butterworth filter is maximally flat (i.e. has no ripples) in the passband and rolls off towards zero in the stopband, the PPG signals were first pre-processed with a 4th-order Butterworth band-pass filter with a passband of [0.05, 10] Hz to remove the high-frequency noise, followed by a wavelet transformation to eliminate the low-frequency baseline drift. The time delay of the Butterworth filtering was compensated using "filtfilt" function in Matlab, which reverses the filtered sequence and runs it back through the filter after filtering the data in the forward direction, thus has the characteristics of zero phase distortion. The wavelet transformation was performed using Daubechies 8 wavelet (db8) with eleven-level decomposition, and the approximation coefficients at the eleventh level, which contain low frequency drift, were replaced by zero. Then, clean PPG signal was reconstructed from the new coefficients. Thereafter, the first derivative wave of PPG (FDPPG) was calculated. Since the first derivative of a signal is the rate of change of the y-axis (amplitud) with respect to the x-axis (time), or in other words, the slope of the signal at each point. Since the PPG signal is sampled at a constant rate, the first derivative can be approximated by calculating the difference between two adjacent samples, as the time interval between them is constant. The calculated FDPPG was then processed with a 4th-order Butterworth band-pass filter with a passband of [0.05, 10] Hz and time delay compensation. The second derivative wave of PPG (SDPPG) was obtained as the derivative of the FDPPG and was also processed with a 4th-order Butterworth band-pass filter with a passband of [0.05, 10] Hz and time delay compensation. All data used for analysis were anonymized.

4) Normalization: Despite the amplitude of PPG waves may contain information, it can be strongly affected by confounding factors (e.g., orientation of LEDs/detectors of the sensors, movement artifact), which may increase measure variability, thus the amplitude of PPG wave is usually normalized. However, there is no standardization as yet to the normalization of PPG wave in width, and to the normalization of the PPG derivative waves (i.e., FDPPG and SDPPG) in both amplitude and width. Therefore, in this study, amplitude of the PPG wave in each cycle was normalized, the other amplitude and width normalization schemes of the PPG and its derivatives (i.e., FDPPG and SDPPG) were set as follows to clarify the optimal normalized scheme that is helpful in finding age-sensitive PPG features. Four schemes were evaluated: S1, width of the PPG and its derivatives, and amplitude of the derivatives were normalized; S2, width of the PPG and its derivatives, and amplitude of the derivatives were not normalized; S3, width of the PPG and its derivatives was not normalized, while amplitude of the derivatives was normalized; and S4, width of the PPG and its derivatives was normalized, and amplitude of the derivatives was not normalized, as shown in Fig.2. In which, the amplitude was normalized between 0 and 1, and the width was normalized to 1 for each cardiac cycle. The purpose of this analysis was to identify the normalization scheme that best distinguishes age-related changes in the PPG signal.

B. Average PPG Contours in Each Group

To study the PPG profiles varying with age, the group average PPG waves were computed for the subjects in 20's, 30's, 40's, 50's, and >60 age groups, respectively. The group average PPG contours were obtained by ensemble averaging of the pulse waves of multiple cardiac cycles in each age group.

S1:

	Width normalized	Amplitude normalized
PPG	√	√
Derivatives (FDPPG, SDPPG)	√	√

S2:

	Width normalized	Amplitude normalized
PPG	X	√
Derivatives (FDPPG, SDPPG)	X	X

S3:

	Width normalized	Amplitude normalized
PPG	X	√
Derivatives (FDPPG, SDPPG)	X	√

S4:

	Width normalized	Amplitude normalized
PPG	√	√
Derivatives (FDPPG, SDPPG)	√	X

(1)

Fig.2. Different settings for normalizing the amplitude and width of PPG and its derivatives. FDPPG indicates the first derivative wave of PPG; SDPPG, the second derivative wave of PPG.

C. Fiducial Point Detections and Feature Extractions

1) Fiducial Points Detection: The fiducial points in the original PPG wave, the FDPPG, and the SDPPG were detected [9,19], as illustrated in Fig.3. They included: 1) Onset, peak of the forward wave of PPG (FP), maximum peak, dicrotic notch, dicrotic peak, and offset points of the original PPG wave; 2) Onset, *a* wave peak, *b* wave valley, offset points of the FDPPG; and 3) Onset, *a* wave peak, *b* wave valley, *c* wave peak, *d* wave valley, *e* wave peak, and offset points of the SDPPG. In more details, onset and offset the original PPG wave, FDPPG and SDPPG; Maximum peak of the original PPG wave; *a* wave peak of the FDPPG and SDPPG; and *e* wave peak of the SDPPG were firstly detected according to the points that have local maxima values or minimum values. Then, the dicrotic notch and dicrotic peak of the PPG wave were identified as the first inflection valley point before the *e* wave peak and the first inflection peak point after the *e* wave peak of the SDPPG, respectively, as shown in the example of subject 1 in Fig.3. However, if there were no inflection points (usually occur in the elderly), the *e* wave peak of the SDPPG was determined as dicrotic notch/dicrotic peak, as shown in the example of subject 2-3 in Fig.3. After that, *b* wave valley of the SDPPG was detected as the point that has a local minimum value after the *a* wave peak of the SDPPG. Afterwards, the *c* wave peak was identified as the first inflection peak point after the *b* wave valley of the SDPPG, while *d* wave valley was considered as the first inflection valley point before the *e* wave peak of the SDPPG. Then, *b* wave valley of the FDPPG was obtained as the first positive zero crossing (i.e., in the direction from negative to positive) of the SDPPG after *a* wave, as shown in the example of subject 1-2 in Fig.3. However, if a zero crossing was not present (usually occur in the elderly) before the *c* wave peak of the SDPPG, *b* wave valley of the FDPPG was then determined as the *c* wave peak of the SDPPG, as shown in the example of subject 3 in Fig.3. At last, the peak of the forward wave of the PPG wave was detected based on a Gaussian fitting method reported in one of our previous studies [6].

2) Features Definition: Five newly proposed and five previously reported features were extracted from the original PPG wave, FDPPG, and SDPPG. The details of the features definition are illustrated in Fig.4. These features included $TWRRF_{1/4}$ (n.u.): time width ratio of rising branch to falling branch at 1/4 pulse height of the PPG waveform; *TWRRF1/2* (n.u.): time width ratio of rising branch to falling branch at 1/2 pulse height of the PPG waveform; *FDPPG: b (n.u.)*: intensity of b wave valley of the FDPPG; *FDPPG:b-a* (n.u.): the intensity difference of *a* wave peak and *b* wave valley of the FDPPG; *FDPPG: b/a (%)*: the intensity ratio of *b* wave valley to *a* wave peak of the FDPPG as a percentage. For each feature, the feature value was computed for each cardiac cycle of each subject according to the feature definition. Then, the feature value for a subject was determined as the median of the feature values across all cardiac cycles of the subject. The reason for using the median value was to reduce the impact of noise. Additionally, heart rate (HR) was calculated as 60 seconds divided by the pulse width.

D. Statistical Analysis

The demographic characteristics of the subjects were analyzed. Values of the variables across the subjects were expressed as mean ± standard deviation.

1) Pearson's Correlation Analysis: After features extraction, Pearson's correlation coefficients were calculated between age and PPG features. To investigate the effect of different measured vascular sites on the correlation between age and PPG

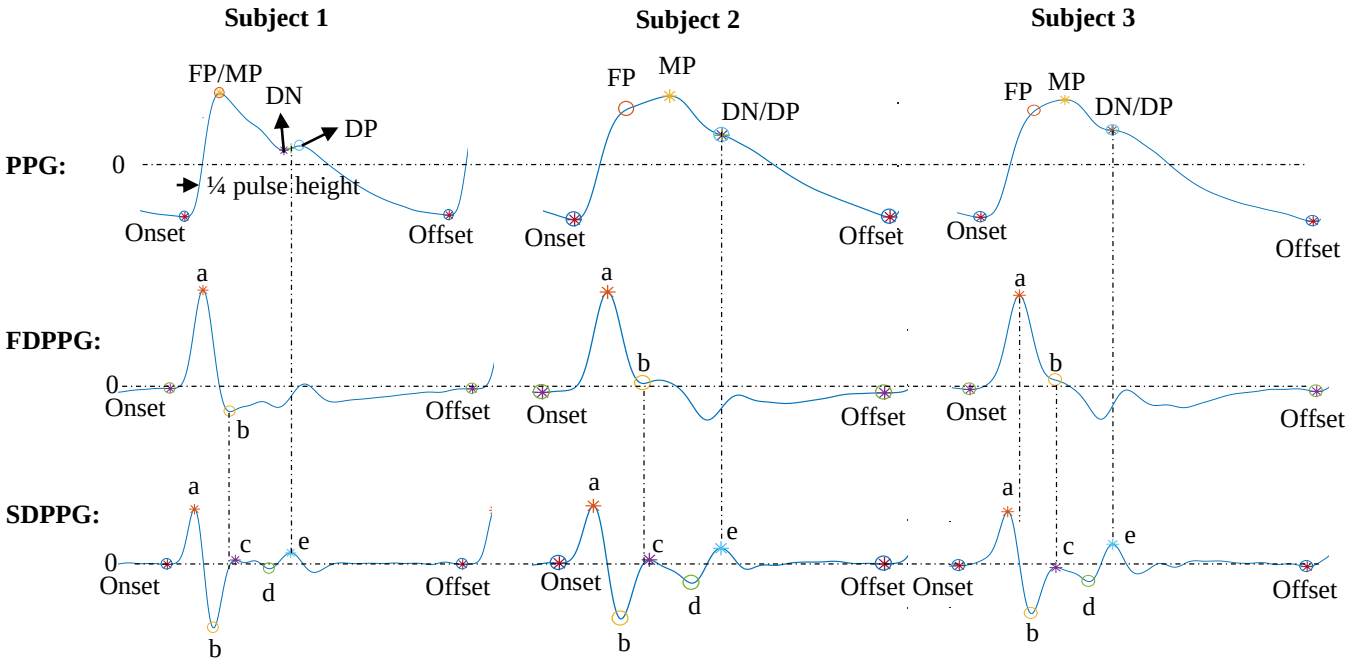

Fig.3. A schematic illustration of the fiducial points of PPG waveforms and their derivatives with various shapes in three representative subjects. PPG indicates photoplethysmography; FDPPG, the first derivative wave of PPG; SDPPG, the second derivative wave of PPG; FP, peak of the forward wave of PPG; MP, maximum peak; DN, dicrotic notch; DP, dicrotic peak.

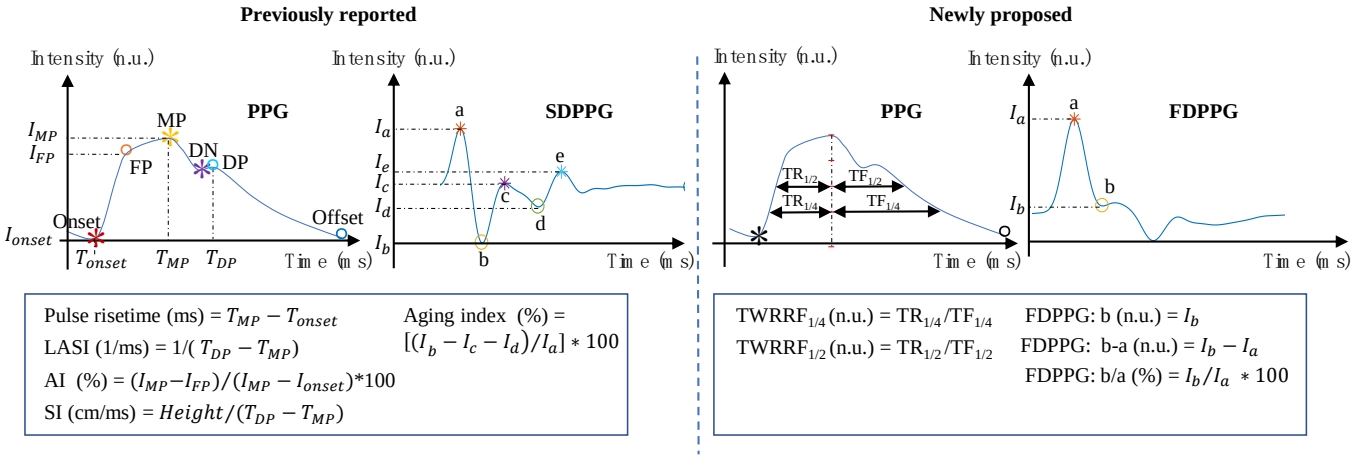

Fig.4. A schematic representation of the proposed and previously reported PPG features. LASI indicates large artery stiffness index; AI: augmentation index; SI: stiffness index; I: intensity; T: time; $TR_{1/4}$, $TR_{1/2}$: time width of the rising branch at 1/4 and 1/2 pulse height of the PPG waveform, respectively; $TF_{1/4}$, $TF_{1/2}$: time width of the falling branch at 1/4 and 1/2 pulse height of the PPG waveform, respectively.

features, the correlation analysis was conducted when the PPG was recorded at the finger and ear, respectively. In addition, to determine whether the correlation between age and PPG feature holds steady, the correlation analysis was conducted with the gender of subjects pooled initially and then separated, respectively. A p value of < 0.05 was considered statistically significant.

2) Univariate Linear Regression Analysis and Piecewise Linear Regression Analysis: Next, univariate linear regression analysis was performed on PPG features with age to investigate the changes of the PPG features with age. In addition, piecewise linear regression was performed to analyze the different dependence of PPG features on age at different stages of age.

3) Multiple Regression Analysis: Afterwards, as clinical measures such as SBP, DBP, height, HR, arm length, and BMI may also influence the values of PPG features, multiple regression analysis including these clinical variables as covariates (including SBP, DBP, height, HR, arm length, and BMI) was conducted for correcting confounding factors that influence the association between age and PPG features.

All the data was analyzed using MATLAB.

TABLE I
DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECTS

Characteristics	Values		
	Pooled-gender group	Male subgroup (n=44, 44%)	Female subgroup (n=56, 56%)
Age (years)	44 ± 14	48 ± 15	41 ± 13
Height (cm)	169 ± 9	175 ± 7	163 ± 7
BMI (kg/m2)	25 ± 4	25 ± 4	25 ± 4
SBP (mmHg)	120 ± 11	123 ± 10	118 ± 11
DBP (mmHg)	72 ± 8	73 ± 8	71 ± 8
HR (beats/s)	65 ± 10	61 ± 8	68 ± 11

Values were expressed as mean ± standard deviation.

III. RESULTS

The demographic characteristics of the subjects were shown in Table I.

A. Group Average PPG Contours Change with Age

Fig.5 shows the shape characteristics of the group average PPG/FDPPG/SDPPG waves changing with age. As shown, the shape of the group average PPG, FDPPG and SDPPG waves changed regularly with age regardless of the normalization schemes. Specifically, with increasing age, the PPG maximum peak shifted slightly to the right side of the cycle, and the dicrotic notch gradually weakened, consistent with previous studies [1]. The peak of the finger PPG waveform became blunt, while the peak of the ear PPG waveform became sharp. The *b* wave valley of the FDPPG moved up. The *b* wave of the SDPPG moved up, while *a*, *c*, *d*, and *e* wave of the SDPPG moved down. The fiducial points of dicrotic notch were more prominent when width was not normalized, as shown in Fig.5.B and 5.C.

B. Correlations between PPG features and Age

Fig.6 presented the correlation coefficients between PPG features at fingers and ears with age in the male subgroup, female subgroup, and the pooled-gender group, respectively. As shown, the correlations between age and the proposed PPG features were stable in different subject groups (male subgroup, female subgroup, and the pooled-gender group), proving that the correlations exist objectively and stably. In general, the correlation values for the proposed features were much higher and more stable than those for the previously reported features. Moreover, the correlations between age and the PPG features of fingers were generally greater than that of the ears. In addition, all correlation values are lower for females than for males.

Besides, the normalization scheme would not influence the correlation of age to the features of $TWRRF_{1/4}$, $TWRRF_{1/2}$, and *AI*. The correlation of age to the features of *FDPPG:b*,

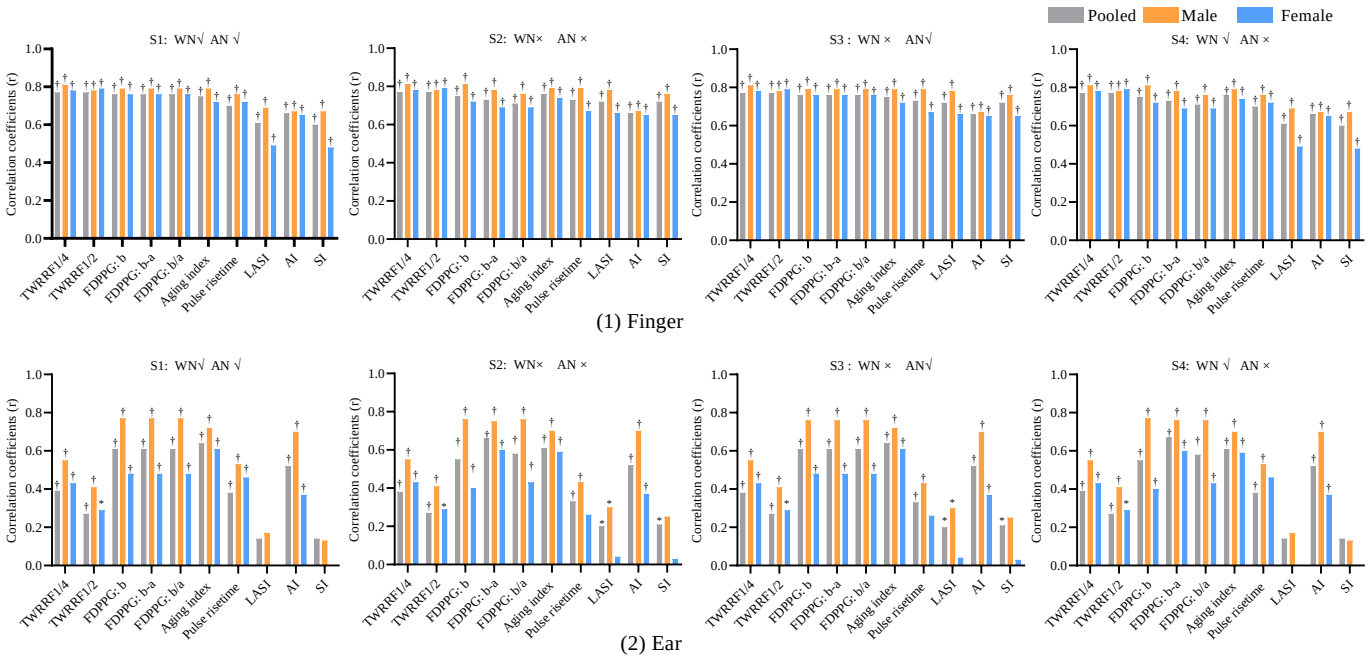

Fig.6. Correlation coefficients between PPG features and age, based on various normalization schemes and gender groups. WN indicates width normalized; AN, amplitude normalized; LASI, large artery stiffness index; AI, augmentation index, SI, stiffness index; PPG indicates photoplethysmography; FDPPG, the first derivative wave of PPG; SDPPG, the second derivative wave of PPG. *Statistically significant at the level < 0.05; † statistically significant at the level < 0.01.

FDPPG:b-a, and *FDPPG:b/a* were relatively higher in the case of amplitude normalized. In addition, the correlation of *LASI* and *SI* were relatively higher in the case of width unnormalized. The correlation of age to the features of *Pulse risetime* were relatively higher in the case of width unnormalized. In summary, the normalization scheme will influence some the correlation between age and PPG features, but not too much. The most PPG features showed high correlation with age under normalization scheme S3, which normalized the amplitude of PPG and its derivatives while leaving the width unnormalized.

Thus, the correlation values between age and PPG features were compared under normalization scheme S3 when PPG was captured at finger. The correlation values for the proposed finger PPG features in all subjects (i.e., the pooled-gender group) were $r = 0.76 – 0.77$, which were higher than those of the previously reported features ($r = 0.66 – 0.75$).

C. Univariate Linear Regression Analysis and Piecewise Linear Regression Analysis

Fig.7 shows the results of univariate regression analysis reflecting the changes in PPG features with age. Normalization scheme S3 which normalized the amplitude of PPG and its derivatives while leaving the width unnormalized was adopted. As shown, the values of PPG features in the peripheral finger changed slowly with age before 40 years old, but rapidly after 40 years old (40 ~ 71 years old). This suggested that the aging rate of blood vessels was slow before 40 years old and accelerated after 40 years old. Thus, piecewise linear regression analysis was further conducted for age of <40 and age of ≥40 years, respectively. The absolute β regression coefficients in the age ≥40 years ($\beta_{\geq 40}$) were much higher than those in the age <40 years ($\beta_{<40}$), indicating that the feature change per year was higher in the elderly group with age ≥40 years than in the younger group with age <40. This further supported the finding that the aging rate of blood vessels was slow before 40 years old and accelerated after 40 years old. This phenomenon was also observed in the features of *FDPPG:b*, *FDPPG:b-a*, *FDPPG:b/a*, and *Aging index* in the proximal ear, but not in other ear features.

D. Multiple Linear Regression Analysis

Table II presents the results of multiple regression analysis that examined the combined effects of clinical measures (i.e., SBP, DBP, height, HR, arm length, and BMI) with age on PPG features. The analysis revealed that critical clinical measures of SBP and DBP also had significant effects on most PPG features ($p < 0.05$), while height, HR, arm length, and BMI had significant effects on some PPG features {e.g., *Stiffness index*, $TWRRF_{1/4}$, $p < 0.05$}. However, the absolute β regression coefficient of age was much higher than that of other clinical measures, indicating that age still had a strong effect on PPG features even after the adjusting for the clinical measures of SBP, DBP, height, HR, arm length, and BMI.

IV. Discussion

This study aimed to explore age-sensitive features from pulse waves recorded at different vascular sites and investigate their pattern variations with age. The main findings included:

1) Five PPG features (i.e., $TWRRF_{1/4}$, $TWRRF_{1/2}$, *FDPPG b*, *FDPPG:b-a*, *FDPPG:b/a*) displayed progressive age-related variation and strong correlations with age in healthy individuals. These features were found to be more sensitive to age changes than previously reported PPG features. In addition, the correlation between age and PPG features was stable across different subject groups (male, female, and the pooled-gender groups), indicating the objective and stable existence of these

correlations. Besides, multiple linear regression analysis revealed that the strong correlation between age and PPG features remained significant even after adjusting for other clinical variables, such as SBP, DBP, height, HR, arm length, and BMI.

2) The shape characteristics of the group average PPG waves and its derivatives changed regularly with age in healthy individuals. Specifically, with increasing age, the PPG maximum peak slightly shifted to the right side of the cycle and the dicrotic notch gradually weakens. The peak of the finger PPG waveform became blunt, while the peak of the ear PPG waveform became sharp. The normalization scheme had some influence on the shape characteristics of the group average PPG waves and its derivatives, as well as on the correlation between age and some PPG features, but not to a significant extent. Under normalization scheme S3, which normalized the amplitude of PPG and its derivatives while leaving the width unnormalized, most PPG features showed the highest correlation with age.

3) The correlations between age and the PPG features of the fingers were generally greater than those of the ears.

4) The rate of change in most feature values was much faster

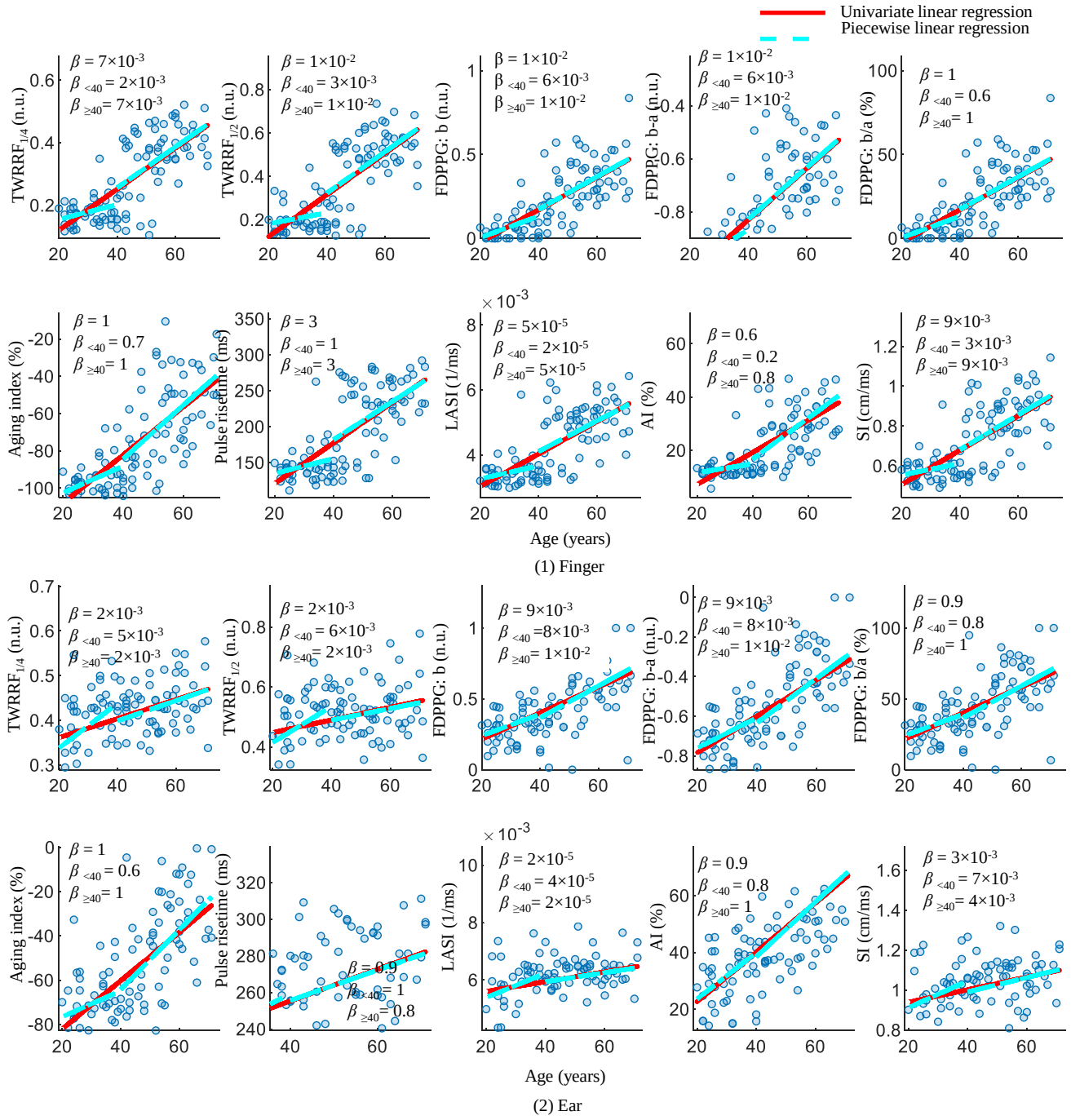

Fig.7. Scatterplots depicting the relationship between PPG features and age, as analyzed using univariate linear regression and piecewise linear regression. The features were extracted from PPG signals acquired at (1) the finger and (2) the ear.

in subjects aged ≥40 years than that in subjects aged < 40 years in the healthy population, particularly for the finger features, indicating the rate of blood vessel aging accelerates after the age of 40 in healthy individuals.

5) The correlation values between the PPG features and age were lower for females than for males.

A. Physiological Interpretation

An observed pulse wave is a combination of two waves: the forward wave, which travels from the heart towards small vessels and is generated by the cardiac output, and the reflected wave, which moves backward from the peripheral vessel towards the heart and is generated by the peripheral vascular resistance [2,20], as shown in Fig.8. The time of return of the reflected wave can vary due to changes in vascular elasticity caused by aging and recording position, which in turn results in variations in the PPG contours with age and measure site.

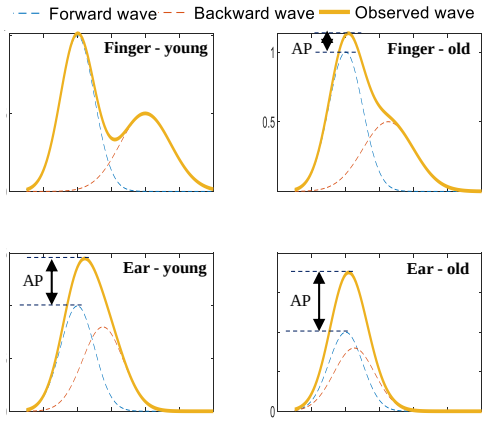

Fig.8. Simplified model demonstrating the effect of reflected wave return time on pulse wave shape. AP represents augmentation pressure, the amplitude difference between the observed and forward waves.

Fig.8 displays a simplified model showing the influence of the time of return of the reflected wave on the shape of the pulse wave. Specifically, in young people, the delayed return of reflected waves at the distal finger leads to less overlap between the forward and backward waves, resulting in a sharp pulse peak and dicrotic peak. In contrast, in elderly individuals, decreased vascular elasticity and a shorter return time of reflected waves cause more overlap between the forward and reflected waves, resulting in a blunt pulse peak, subtle shift to the right of the pulse cycle, gradual weakening of the dicrotic peak, and an increase in augmentation pressure, which is the amplitude difference between the observed wave and the forward wave.

Compared to the finger, the proximal ear is closer to the heart. In young people, the return time of the reflected wave is further shortened, and the overlap between the forward wave and the reflected wave is also greater, resulting in a blunt pulse peak under the influence of the reflected wave, and a further increase in the augmentation pressure. However, in the ear of the elderly, due to the further shortening of the return time of the reflected wave, the peak of the forward wave becomes very close to that of the reflected wave, which makes the pulse peak sharp again, and the augmentation pressure increases further.

This can explain the observations in this study that the peak of the finger PPG waveform became blunt with increasing age, while the peak of the ear PPG waveform became sharp. The augmentation index increased with age, and the values of the augmentation index in the ear were higher than those in the finger, with higher values in the elderly than in young people.

The pulse peak shifts to the right of the pulse cycle with aging, which means that the time width ratio of the rising branch to the falling branch at a particular height of the PPG waveform

TABLE II
DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECTS

Finger				Ear			
Dependent variable	Independent variable	*β regression coefficient*	*r*	Dependent variable	Independent variable	*β regression coefficient*	*r*
Age	f1: $TWR_{1/4}$	6.1×10^{-3}	0.77†	Age	f1: $TWR_{1/4}$	1.7×10^{-3}	0.38†
SBP		1.0×10^{-5}	0.44†	SBP		1.1×10^{-3}	0.27†
DBP		2.4×10^{-3}	0.41†	DBP		1.5×10^{-4}	0.21*
Age	f2: $TWR_{1/2}$	9.2×10^{-3}	0.77†	Height		-2.3×10^{-3}	-0.32†
SBP		3.0×10^{-4}	0.45†	HR		1.5×10^{-3}	0.32†
DBP		2.1×10^{-3}	0.38†	Armlength		-7.6×10^{-4}	-0.23*
HR		3.7×10^{-3}	0.2*	BMI		8.6×10^{-4}	0.2*
Age	f3: FDPPG: b	9.2×10^{-3}	0.76†	Age	f2: $TWR_{1/2}$	1.3×10^{-3}	0.27†
SBP		-9.0×10^{-4}	0.40†	SBP		1.9×10^{-3}	0.24*
DBP		4.2×10^{-3}	0.41†	Height		-3.4×10^{-3}	-0.32†
Age	f4: FDPPG: b-a	9.2×10^{-3}	0.76†	HR		1.8×10^{-3}	0.30†
SBP		-9.0×10^{-4}	0.40†	Armlength		-5.5×10^{-4}	-0.23*
DBP		4.2×10^{-3}	0.41†	BMI		3.2×10^{-3}	0.25*
Age	f5: FDPPG: b/a	9.2×10^{-1}	0.76†	Age	f3: FDPPG: b	9.3×10^{-3}	0.61†
SBP		-9.0×10^{-2}	0.40†	SBP		-3.2×10^{-3}	0.26†
DBP		4.2×10^{-1}	0.41†	DBP		5.8×10^{-3}	0.34†
Age	f6: Aging index	1.2	0.75†	Age	f4: FDPPG: b-a	9.3×10^{-3}	0.61†
SBP		-1.2×10^{-2}	0.40†	SBP		-3.2×10^{-3}	0.26†
DBP		0.3	0.35†	DBP		5.8×10^{-3}	0.34†
Age	f7: Pulse risetime	2.8	0.73†	Age	f5: FDPPG: b/a	9.3×10^{-1}	0.61†
SBP		-7.8×10^{-1}	0.32†	SBP		-3.2×10^{-1}	0.26†
DBP		1.4	0.37†	DBP		5.8×10^{-1}	0.34†
Age	f8: Large artery stiffness index	5.0×10^{-5}	0.72†	Age	f6: Aging index	1.1	0.64†
SBP		-2.0×10^{-5}	0.31†	SBP		-2.4×10^{-1}	0.29†
DBP		4.0×10^{-5}	0.43†	DBP		3.9×10^{-1}	0.30†
Age	f9: Augmentation index	5.5×10^{-1}	0.66†	Age	f7: Pulse risetime	8.3×10^{-1}	0.33†
SBP		1.7×10^{-2}	0.39†	HR		-2.3	-0.63†
DBP		2.2×10^{-1}	0.36†	Age	f8: Large artery stiffness index	2.0×10^{-5}	0.20*
Age	f10: Stiffness index	8.3×10^{-3}	0.72†	HR		-4.0×10^{-5}	-0.36†
SBP		-2.4×10^{-3}	0.36†	Age	f9: Augmentation index	8.6×10^{-1}	0.52†
DBP		6.4×10^{-3}	0.45†	DBP		5.0×10^{-2}	0.20*
				Age	f10: Stiffness index	2.8×10^{-3}	0.21*
				Height		2.1×10^{-3}	0.36†
				HR		-7.8×10^{-3}	-0.43†
				Armlength		1.1×10^{-2}	0.32†

The correlation coefficients (*r*) were computed between clinical variables (i.e., age, SBP, DBP, height, HR, arm length, and BMI) and PPG features. Only the clinical measures that showed significant correlations with the PPG feature ($p < 0.05$) were included in the multiple regression model and presented in the table. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body max index; HR, heart rate. *Statistically significant at the level <0.05; † statistically significant at the level < 0.01.

increases. Additionally, the augmentation pressure also increases with aging, leading to a further increase in the time width ratio of the rising branch to the falling branch at a particular height of the PPG waveform. This could explain the strong correlation between age and the time width ratio of the rising branch to the falling branch at 1/4 or 1/2 pulse height of the PPG waveform, indicated as $TWRRF_{1/4}$, $TWRRF_{1/2}$.

FDPPG:b represents the maximum slope of the descending branch of PPG wave. As the pulse peak shifts to the right of the pulse cycle with aging, the descending branch of the PPG wave falls faster, resulting in a larger maximum slope of the descending branch. This can explain why the b wave valley of the FDPPG moves up with the increase of age, leading to an increase in FDPPG:b, FDPPG:b-a, and FDPPG:b/a with age, (Fig.5, Fig.7). And can explain the significant strong correlation between age and *FDPPG:b*, *FDPPG:b/a*, and *FDPPG:b-a*.

The correlations between age and the PPG features of fingers were generally greater than that of the ears. The results were consistent with previous studies which showed that the PPG feature of *pulse risetime* at fingers and toes were more correlated with age than that at ears [4]. This phenomenon may be because the PPG waves recorded at distal blood vessels are more likely to be affected by the reflected waves caused by peripheral arterial stiffness, which increases with aging, than PPG waves recorded at proximal sites. Thus, PPG waves recorded at distal sites (e.g., fingers, toes) are more sensitive to vascular aging than that recorded at proximal sites (e.g., ears).

The correlation values between the PPG features in this study and age were lower for females than for males. This may be because that the arterial stiffness in men increases almost linearly with age from early adulthood onward, while the women experience a curvilinear aging trend, with a flatter curve in young and a steep increase in arterial stiffness after menopause [17, 21, 23, 24]. Previous studies have reported that the correlation between arterial stiffness (quantified as pulse wave velocity) and age during life from early adulthood onward were higher in men than in women [17, 21, 23, 24]. This was similar to the gender difference of the correlation values between the PPG features and age in this study, again indirectly demonstrating the potential of the proposed PPG features to be used as biomarkers for vascular aging and CVD risk assessment.

B. Age-related progression of arterial stiffness

Fig.7 demonstrates that most PPG features do not change uniformly and linearly with age. The piecewise linear regression analysis showed that PPG features, particularly those from the fingers, changed slowly with age before 40 years old, but then increased rapidly after 40 years old. This pattern is similar to the age-related progression of arterial stiffness, which is assessed by the pulse wave velocity (PWV), considered the gold standard for evaluating vascular stiffness [21, 22]. This suggests that the aging rate of blood vessels is slow before 40 years old and accelerates after 40 years old. In a study by Y. Lu et al, brachial-ankle pulse wave velocity (baPWV) was shown to increase with age in 80,415 healthy subjects. The slope of the increase in baPWV as a function of age is slower before the age of about 40 and faster after the age of about 40 [21]. In another study by M. AlGhatrif, aortic pulse wave velocity was reported to increase rapidly after 40 and slowly before 40 in 111 healthy subjects [22]. The trend of PPG features with age was consistent with the age-related progression of arterial stiffness assessed by the gold standard PWV, indicating that the PPG features proposed in this study have the potential to be used as biomarkers for vascular aging assessment and help predict and evaluate cardiovascular disease risk. However, it should be noted that the PPG signal waveform depends on the hardware setup and physiological conditions [25]. Therefore, a unified standard for the hardware, detection environment, and physiological state of the subject is necessary before promoting this technique.

C. Normalization

Currently, there is no standardization for the normalization of PPG waves and their derivatives, which can greatly affect the value of PPG features and their relationship with age. In this study, the group average PPG contours of different age groups and the correlation between age and PPG features were analyzed using different normalization schemes of PPG waves. The results indicated that the normalization scheme influences the shape characteristics of the group average PPG waves and their derivatives, as well as the correlation between age and some PPG features, although not significantly. The fiducial points of the dicrotic notch of the PPG wave were more prominent when the width was not normalized. Most PPG features showed a high correlation with age under normalization scheme S3, which normalized the amplitude of PPG and its derivatives while leaving the width unnormalized.

D. Limitations

One limitation of the study was that it did not include the subjects with very low age (< 20) and with very high age (> 70). Numbers of subjects with age >60 was too limited, which affect analyzing the vascular aging pace after 60.

In addition, although identifying PPG feature determinants may be a first step towards developing risk markers for cardiovascular disease, and the trend of PPG features with age was shown to be consistent with the age-related progression of arterial stiffness assessed by the gold standard pulse wave velocity, indicating that the proposed PPG features have the potential to be used as biomarkers for vascular aging assessment, further studies are needed to directly define disease markers. This could include demonstrating the association of these age-related PPG features with pulse wave velocity.

V. Conclusion

In summary, this study identified several PPG features that are highly sensitive to age in healthy individuals. Five PPG features (i.e., $TWRRF_{1/4}$, $TWRRF_{1/2}$, *FDPPG:b*, *FDPPG:b-a*, *FDPPG:b/a*) displayed progressive variation with age in the healthy population and showed a strong and significant correlation with age. These features were found to be more sensitive to age changes than previously reported PPG features, and the strong correlation remained significant even after

adjusting for other clinical variables such as SBP, DBP, height, HR, arm length, and BMI. In addition, the changing rates of these PPG features with age were slower before the age of about 40 and faster after the age of about 40, which was similar to the age-related progression of arterial stiffness evaluated by pulse wave velocity, the gold standard for evaluating vascular stiffness. This indicates that the proposed PPG features in this study have the potential to be used as biomarkers for vascular aging assessment. Furthermore, the correlation values between PPG features and age were higher for men than for women, which was similar to the gender difference of the correlation values between arterial stiffness and age, further supporting the potential of these PPG features for vascular aging assessment. Due to the convenience of measurement, pulse wave has been widely used in wearable devices and telemedicine, thus having the potential to be a large-scale and easy-to-use early screening tool. Therefore, the sensitive age-related pulse wave markers identified in this study have the potential to be used for vascular aging estimation, early prediction, and assessment of CVD risk.

REFERENCES

[1] J. Allen, and A. Murray, "Age-related changes in the characteristics of the photoplethysmographic pulse shape at various body sites," *Physiol. Meas.*, vol. 24, no. 2, pp. 297-307, May, 2003.

[2] M. E. Safar, J. Blacher, and P. Jankowski, "Arterial stiffness, pulse pressure, and cardiovascular disease-Is it possible to break the vicious circle?," *Atherosclerosis*, vol. 218, no. 2, pp. 263-271, Oct, 2011.

[3] P. H. Charlton, B. Paliakaitė, K. Pilt et al., "Assessing hemodynamics from the photoplethysmogram to gain insights into vascular age: A review from VascAgeNet," Am J Physiol Heart Circ Physiol, pp. 493-522, 2022.

[4] J. Allen, J. O'Sullivan, G. Stansby et al., "Age-related changes in pulse risetime measured by multi-site photoplethysmography," *Physiol. Meas.*, vol. 41, no. 7, Jul, 2020.

[5] L. A. Bortolotto, J. Blacher, T. Kondo et al., "Assessment of vascular aging and atherosclerosis in hypertensive subjects: second derivative of photoplethysmogram versus pulse wave velocity," *Am. J. Hypertens.*, vol. 13, no. 2, pp. 165-171, Feb, 2000.

[6] W.-H. Lin, D. Zheng, G. Li et al., "Investigation on pulse wave forward peak detection and its applications in cardiovascular health," *IEEE. Trans. Biomed. Eng.*, vol. 69, no. 2, pp. 700-709, 2021.

[7] H. J. Baek, J. S. Kim, Y. S. Kim et al., "Second derivative of photoplethysmography for estimating vascular aging," in 2007 6th International Special Topic Conference on Information Technology Applications in Biomedicine (ITAB 2007), Tokyo, Japan, 2007, pp. 70-72.

[8] K. Takazawa, N. Tanaka, M. Fujita et al., "Assessment of vasoactive agents and vascular aging by the second derivative of photoplethysmogram waveform," *Hypertension*, vol. 32, no. 2, pp. 365-70, Aug, 1998.

[9] M. Elgendi, "On the analysis of fingertip photoplethysmogram signals," *Curr. Cardiol. Rev.*, vol. 8, no. 1, pp. 14-25, Feb, 2012.

[10] J.W. Seo, J. Choi, K. Lee, "Age-related changes in the characteristics of the elderly females using the signal features of an earlobe photoplethysmogram," *Sensors*, vol. 21, no. 23, 2021:7782.

[11] D. N. Dutt, and S. Shruthi, "Digital processing of ECG and PPG signals for study of arterial parameters for cardiovascular risk assessment," in 2015 the International Conference on Communication Software and Information Processing (ICCSIP2015), Hongkong, China, 2015, pp. 1506-1510.

[12] S. C. Millasseau, R. P. Kelly, J. M. Ritter et al., "Determination of age-related increases in large artery stiffness by digital pulse contour analysis," *Clin. Sci. (Lond)*, vol. 103, no. 4, pp. 371-377, Oct, 2002.

[13] H. Shin, G. Noh, and B.M. Choi, "Photoplethysmogram based vascular aging assessment using the deep convolutional neural network," *Sci. Rep.*, vol. 12, 2022: 11377

[14] J. Park, H.S. Seok, S.S. Kim et al., "Photoplethysmogram analysis and applications: an integrative review," *Front Physiol*, vol. 12, 2022: 808451

[15] T. Sondej, I. Jannasz, K. Sieczkowski et al., "Validation of a new device for photoplethysmographic measurement of multi-site arterial pulse wave velocity," *Biocybern Biomed Eng.*, vol. 41, no. 4, pp. 1664-1684, Oct, 2021.

[16] A. Gentilin, C. Tarperi, A. Cevese et al., "Estimation of carotid-femoral pulse wave velocity from finger photoplethysmography signal," *Physiol. Meas.*, vol. 43, 2022:075011

[17] J.J. DuPont, R.M. Kenney, A.R. Patel AR et al., "Sex differences in mechanisms of arterial stiffness," *Br. J. Pharmacol.*, vol. 176, no. 21, pp. 4208-4225, Nov, 2019

[18] V. Hartmann, H. Liu, F. Chen F et al., "Toward accurate extraction of respiratory frequency from the photoplethysmogram: effect of measurement site," *Front. Physiol.*, vol. 10, 2019: 732

[19] E. Mejía-Mejía, J. Allen, K. Budidha et al., *Photoplethysmography signal processing and synthesis*, pp. 69-146: Elsevier, 2021.

[20] B. E. Westerhof, I. Guelen, N. Westerhof et al., "Quantification of wave reflection in the human aorta from pressure alone - A proof of principle," *Hypertension*, vol. 48, no. 4, pp. 595-601, 2006.

[21] Y. Lu, R. Pechlaner, J. J. Cai et al., "Trajectories of Age-Related Arterial Stiffness in Chinese Men and Women," *J. Am. Coll. Cardiol.*, vol. 75, no. 8, pp. 870-880, Mar 3, 2020.

[22] M. AlGhatrif, and E. G. Lakatta, "The conundrum of arterial stiffness, elevated blood pressure, and aging," *Curr. Hypertens. Rep.*, vol. 17, no. 2, Feb, 2015.

[23] R.M. Nethononda, A.J. Lewandowski, R. Stewart R, et al., "Gender specific patterns of age-related decline in aortic stiffness: a cardiovascular magnetic resonance study including normal ranges," *J. Cardiovasc. Magn. Reson.*, vol. 17, no. 1, 2015:20.

[24] P.G. Cunha, J. Cotter, P. Oliveira et al., "Pulse wave velocity distribution in a cohort study: from arterial stiffness to early vascular aging," *J. Hypertens.*, vol. 33, no. 7, pp. 1438-1445, Jul, 2015.

[25] A. Reisner, P. A. Shaltis, D. McCombie et al., "Utility of the photoplethysmogram in circulatory monitoring," *Anesthesiology*, vol.108, no.5, pp. 950-958, May, 2008.

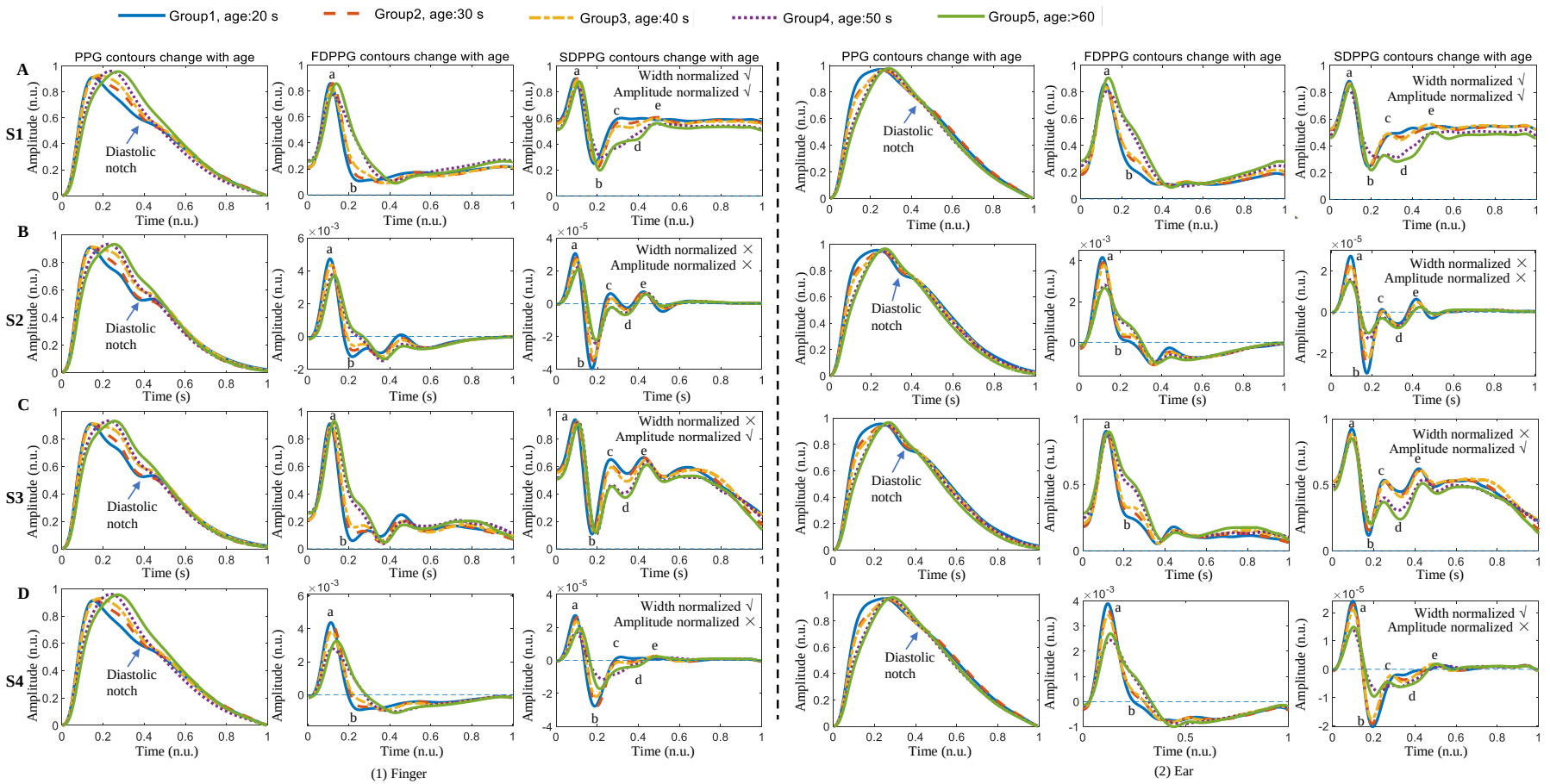

Fig.5. Group average PPG contours change with age under different settings of normalizing the PPG and its derivatives in amplitude and width. PPG were recorded at (1) finger and (2) ear. (A) S1: width of the PPG and its derivatives, and amplitude of the derivatives were normalized; (B) S2: width of the PPG and its derivatives, and amplitude of the derivatives were not normalized; (C) S3: width of the PPG and its derivatives was not normalized, and amplitude of the derivatives was normalized; and (D) S4: width of the PPG and its derivatives was normalized, and amplitude of the derivatives was not normalized. FDPPG indicates the first derivative wave of PPG; SDPPG, the second derivative wave of PPG.

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