European Journal of Integrative Medicine 28 (2019) 92–97

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Research paper

Multiple linear regression model for vascular aging assessment based on radial artery pulse wave

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ARTICLE INFO

Keywords:
Equal Pressure Pulse Transit Time
Multiple Linear Regression
Vascular aging
Radial artery pulse wave

ABSTRACT

Introduction: Vascular aging is an independent risk factor for cardiovascular diseases, which has always been a research hotspot. This study aims to establish a Multiple Linear Regression (MLR) model using radial artery pulse wave characteristic parameters to assess vascular aging.

Methods: Data from 111 males and 117 females were used to propose a new method for extracting pulse wave characteristic parameters called, Equal Pressure Pulse Transit Time (EP-PTT). Firstly, 10 EP-PTTs were extracted from pulse waves which were used to describe the shape characteristics of the pulse signal. Secondly, 10 EP-PTTs were fed into MLR model, which were used to optimize the model. Lastly, the predicted age of all subjects was calculated by the optimal model. We compared the correlation coefficients of predicted age with Pulse Transit Time (PTT) and Augmentation Index (AIx) with the correlation coefficients of chronological age with PTT and AIx.

Results: 9 EP-PTTs were relevant to predicting age in men and all EP-PTTs were age-related in women ($P < 0.05$). MLR analysis showed that EP-PTT$_3$ and EP-PTT$_7$ were potent predictors of vascular age in men but EP-PTT$_4$ and EP-PTT$_7$ were important predictors in women ($P < 0.001$). Comparing with the chronological age, the predicted age was closer to PTT ($P < 0.001$, $r=-0.53$ to $P < 0.001$, $r=-0.59$ in men; $P < 0.001$, $r=-0.57$ to $P < 0.001$, $r=-0.65$ in women) and AIx ($P < 0.001$, $r=0.64$ to $P < 0.001$, $r=0.81$ in men; $P < 0.001$, $r=0.51$ to $P < 0.001$, $r=0.56$ in women).

Conclusions: The predicted age can better reflect vascular aging than chronological age. This proved the validity of the proposed method for assessing vascular aging.

1. Introduction

Vascular aging is a normal physiological phenomenon. Due to the differences in individuals lifestyles, there are also individual differences in the degree of vascular aging [1,2]. In fact, researchers have suggested a number of indirect indicators to evaluate vascular aging. For instance, Intima-Media Thickness (IMT) [3], IMT is an important clinical diagnostic basis for atherosclerosis, which increases 2–3 times from 20 to 90 years old; Pulse Wave Velocity (PWV) [4], many studies have shown that PWV increased with age [5]; Ankle Brachial index (ABI) [6], is always used for the preliminary screening of vascular diseases and peripheral arterial diseases; Augmentation Index (AIx) [7], the researchers have demonstrated that the size of AIx is correlated with Framingham risk index score; Pulse Transit Time (PTT) [8], it is an important index of arterial stiffness.

It is a common method to assess vascular aging by analyzing the pulse wave. The degree of arterial stiffness varies with age and influences blood flow resistance, the shape of pulse wave affected by the blood flow resistance [9]. AIx and PTT are extracted from the pulse wave, they are also noninvasive and convenient evaluation indicators [10]. Both AIx and PTT have been proved to be closely related to age [11]. AIx is positively correlated with age, while PTT is negatively correlated. However, these two indicators both depend on the precise location of the first two pulse wave peaks which are not always clearly visible [12], so it is difficult to extract the two indicators directly in many cases. Many algorithms have been used to estimate the position of the special points of the pulse wave [13], fourth derivative and Savitsky-Golay filter were always used [14].

In addition, the method used to analyze the features of the pulse signal is another key point. At present, classification is the main objective in most instances. For example, Zhang [15] proposed K-Nearest Neighbor (KNN) classifier for distinguishing five typical pulse patterns.

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https://doi.org/10.1016/j.eujim.2019.05.006
Received 21 January 2019; Received in revised form 5 May 2019; Accepted 5 May 2019
1876-3820/

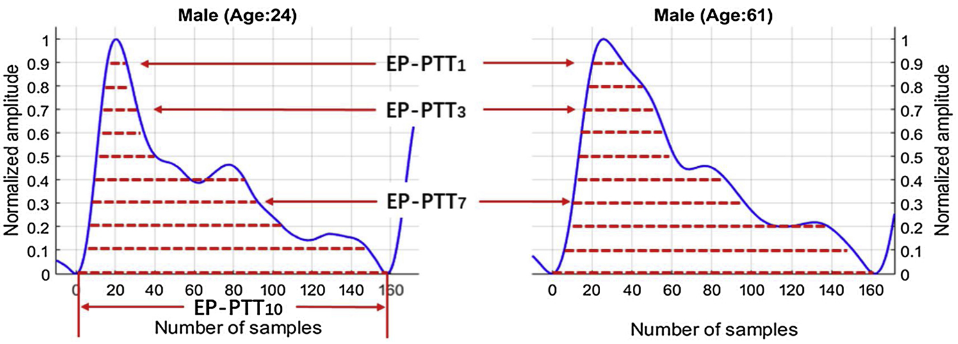

Fig. 1. Extracting 10 EP-PTTs from radial pulse wave. The ages of the two male subjects were 24 and 61.

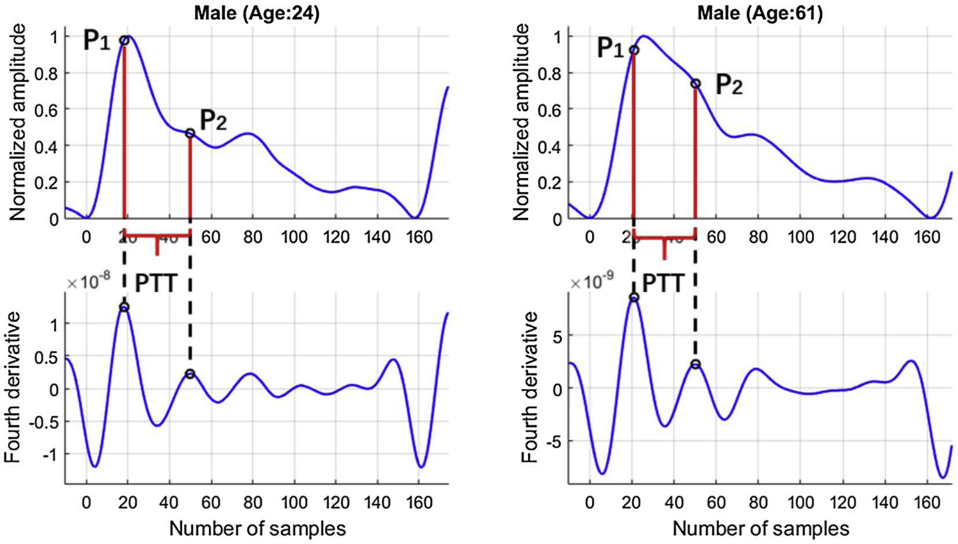

Fig. 2. PTT is represented by the time interval of the first two peaks, AIx is represented by the ratio of P_2 to P_1 ($AIx = P_2/P_1$).

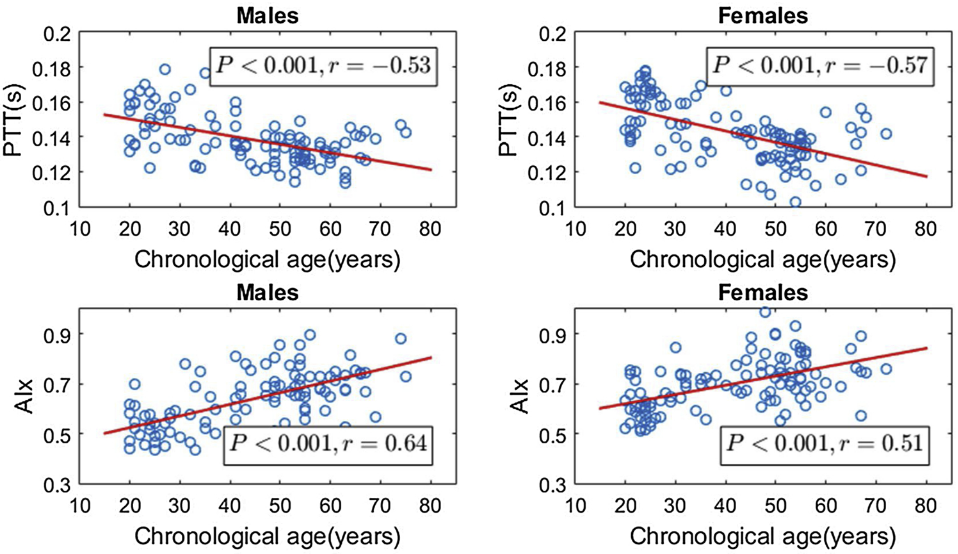

Fig. 3. The correlation of chronological age with PTT and AIx.

Fuzzy Neural Network (FNN) was used in pulse image recognition, which can identify 16 patterns at the accuracy of over 90% [16]. Song [17] used Cubic Support Vector Machine (CSVM) to distinguish healthy individuals and lung cancer patients. Fuzzy C-Means (FCM) was taken to classify the pulse signals of 100 healthy persons and 88 patients [18]. Classification and regression are the two most common methods of machine learning, which have many similar key links in model building.

Many indicators (such as AIx, PTT, etc) reflect vascular aging from different perspectives, but there are few studies to assess vascular aging directly. In this study, we proposed a novel method to predict vascular age of all subjects. Besides, to avoid the dependence of PTT on the

Table 1
The difference of each EP-PTT between men and women.

Variable	Male	Female	*P*-value
Age	43.58 ± 15.28	41.36 ± 14.66	$P > 0.05$
EP-PTT$_1$	0.065 ± 0.012	0.072 ± 0.016	$P < 0.001$
EP-PTT$_2$	0.099 ± 0.018	0.110 ± 0.022	$P < 0.001$
EP-PTT$_3$	0.130 ± 0.023	0.144 ± 0.024	$P < 0.001$
EP-PTT$_4$	0.162 ± 0.025	0.178 ± 0.022	$P < 0.001$
EP-PTT$_5$	0.214 ± 0.052	0.228 ± 0.043	$P < 0.05$
EP-PTT$_6$	0.313 ± 0.087	0.315 ± 0.087	$P > 0.05$
EP-PTT$_7$	0.418 ± 0.100	0.421 ± 0.103	$P > 0.05$
EP-PTT$_8$	0.517 ± 0.101	0.512 ± 0.107	$P > 0.05$
EP-PTT$_9$	0.632 ± 0.108	0.621 ± 0.113	$P > 0.05$
EP-PTT$_{10}$	0.759 ± 0.073	0.744 ± 0.082	$P > 0.05$

Table 2
The relevance between each EP-PTT and chronological age in men and women.

Variable	Male		Female	
	P-value	*r*	*P*-value	*r*
EP-PTT$_1$	$P < 0.001$	0.60	$P < 0.001$	0.50
EP-PTT$_2$	$P < 0.001$	0.64	$P < 0.001$	0.52
EP-PTT$_3$	$P < 0.001$	0.64	$P < 0.001$	0.45
EP-PTT$_4$	$P < 0.001$	0.54	$P < 0.05$	0.23
EP-PTT$_5$	$P > 0.05$	0.07	$P < 0.001$	−0.32
EP-PTT$_6$	$P < 0.001$	−0.39	$P < 0.001$	−0.55
EP-PTT$_7$	$P < 0.001$	−0.48	$P < 0.001$	−0.56
EP-PTT$_8$	$P < 0.001$	−0.42	$P < 0.001$	−0.49
EP-PTT$_9$	$P < 0.001$	−0.53	$P < 0.001$	−0.54
EP-PTT$_{10}$	$P < 0.001$	−0.49	$P < 0.001$	−0.45

position of the first two peaks, we put forward a new way to extract features from pulse wave, which called EP-PTT. 10 EP-PTTs were extracted to describe the general shape characteristic of the pulse signal.

2. Methods

2.1. Subjects

A total of 228 healthy adults (111 men and 117 women) aged 20–82 years (43.0 ± 15.3 years) were recruited from subjects who participated in routine health examination at Hangzhou Health Management Center and students of Hangzhou Normal University. Participants who had had a history of cardiovascular disease were excluded. During an initial physical examination all underwent the measurements of 10 EP-PTTs, PTT and AIx of the radial artery pulse wave.

All subjects agreed to participate and undertake the tests given by the doctor. A signed informed consent form was provided before testing. This study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of our institution.

2.2. Measurements

Before testing, all subjects were asked to have a rest in the sitting position for at least 5 min. The left radial artery pulse waves were collected by using pressure sensing equipment (HK-2010; Hefei Huake Electronic Technology Research Institute, Hefei, China). The sampling frequency of the device is 200 Hz. Data collection was performed by experienced doctors. Each time recorded approximately 10 s data, the cycles with a cycle length shorter or longer than 20% of the mean cycle were deselected. Finally, we extracted 10 EP-PTTs from the data of each cycle. PTT and AIx of each cycle were calculated by fourth derivative [12,13].

2.3. Evaluating predicted age

Firstly, 10 EP-PTTs were extracted as the shape features of pulse signal, Secondly, all EP-PTTs were taken as the independent variables, the chronological age as the dependent variable, then establish and optimize the MLR model. Finally, the predicted age of all subjects was calculated by the optimal MLR model, then we compared the correlation coefficients of predicted age with AIx and PTT with the correlation coefficients of chronological age with AIx and PTT.

2.3.1. Extracting EP-PTT

In this study, we propose a novel method to extract features called EP-PTT from pulse signal, which used to express the shape characteristic of the pulse wave. Firstly, the pressure difference of pulse wave is standardized to a range of 0–1, secondly, we divide normalized amplitude into 10 segments on average, lastly the time intervals of the all segments in each pulse wave are taken (Fig. 1). According to the studies about AIx and PTT, the first maximum systolic peaks of the radial pulse wave will widen with age increasing, and EP-PTTs will also change at this point.

2.3.2. Establishing MLR model

10 EP-PTTs were taken as the independent variables, the chronological age as dependent variable, then establish MLR model. Backward elimination method was used to optimize the MLR model [19], and the variance inflation factor (VIF) was used to correct the collinearity of the model [20]. Any EP-PTT must be significant in the optimal MLR model ($P < 0.05$) and the VIF of any EP-PTT must be less than 5.

2.3.3. Assessing vascular age

The vascular age of all subjects was predicted by the optimal MLR model. The correlation coefficients of PTT and AIx to chronological age and predicted age were calculated. We compared the correlation coefficients of predicted age with PTT and AIx with the correlation coefficients of chronological age with PTT and AIx.

2.4. Statistical analysis

All values were shown as mean ± s.d., if not specified. The differences of each EP-PTT between men and women were evaluated by analysis of variance. The relevance between each EP-PTT and chronological age in men and women was analyzed by unary linear regression. The correlation of chronological age and predicted age with PTT and AIx was analyzed by unary linear regression. MLR model was applied to predict vascular age for all subjects. Backward elimination method was used to optimal the model, and the VIF was used to correct the collinearity of the model. A probability value $P < 0.05$ was

Table 3
The optimized MLR model for age in men and women.

Variable	Male				Female			
	β	*t*	*P*-value	*VIF*	*β*	*t*	*P*-value	*VIF*
EP-PTT$_3$	402.44	9.68	$P < 0.001$	1.01	\	\	\	\
EP-PTT$_4$	\	\	\	\	172.93	3.52	$P < 0.001$	1.01
EP-PTT$_7$	−65.81	−6.85	$P < 0.001$	1.01	−81.30	−7.63	$P < 0.001$	1.01

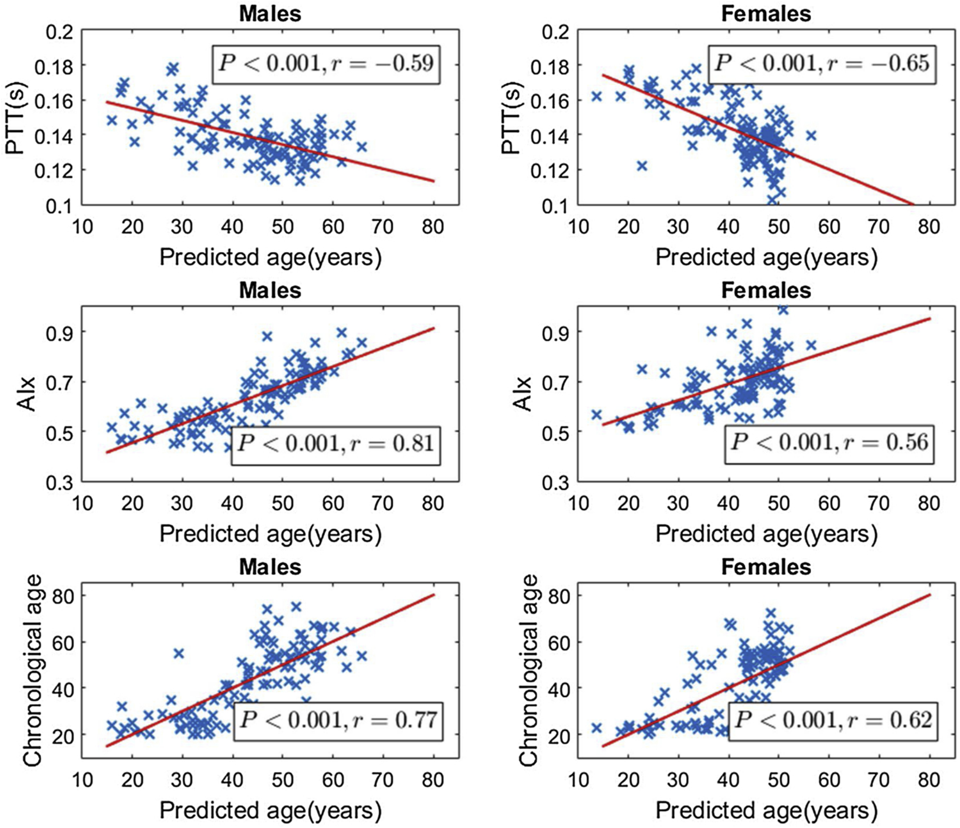

Fig. 4. The correlation of predicted age with PTT and AIx.

Table 4
The correlation coefficients of PTT and AIx to chronological age and predicted age.

Variable		Male		Female	
		P-value	*r*	*P*-value	*r*
PTT	Chronological age	$P < 0.001$	−0.53	$P < 0.001$	−0.57
	Predicted age	$P < 0.001$	−0.59	$P < 0.001$	−0.65
AIx	Chronological age	$P < 0.001$	0.64	$P < 0.001$	0.51
	Predicted age	$P < 0.001$	0.81	$P < 0.001$	0.56

considered to indicate statistical significance. All data were calculated with MATLAB 2015a.

3. Results

3.1. PTT and AIx

PTT and AIx are important indices for evaluating arterial stiffness, they are calculated by fourth derivative in this study (Fig. 2).

The relevance of the chronological age with PTT and AIx are shown in Fig. 3, PTT and AIx were closely related to the chronological age both in men and women ($P < 0.001$).

3.2. Chronological age and EP-PTT

From Table 1, the means of first 7 EP-PTTs were higher in women than men except EP-PTT$_8$, EP-PTT$_9$, and EP-PTT$_{10}$. There was significant difference for the first 5 EP-PTTs ($P < 0.05$) between men and women, while the differences for the last 5 EP-PTTs were not ($P > 0.05$). Hence, the MLR model should be established separately in the light of the genders.

Table 2 gives the results of unary linear regression between each EP-PTT and the chronological age. 9 EP-PTTs were age-related ($P < 0.001$) except EP-PTT$_5$ ($P > 0.05$) in men, the first 4 EP-PTTs were positively correlated with age, while the last 5 EP-PTTs were negatively. In women, all EP-PTTs were age-related ($P < 0.05$), the first 4 EP-PTTs were positively correlated with age while the last 6 EP-PTTs were negatively.

3.3. MLR model

MLR was taken to analyze the relation between all EP-PTTs and age in this study, backward elimination method was used to optimize the MLR model. Moreover, the variables with collinearity were removed by VIF. The final results were shown in Table 3. For men, EP-PTT$_3$ and EP-PTT$_7$ were independent variables in assessing vascular aging, while EP-PTT$_4$ and EP-PTT$_7$ were significant in women.

3.4. Predicted age

The predicted age of all subjects was assessed by the MLR model which built with the EP-PTTs. We analyzed the correlation of the predicted age with PTT and AIx (Fig. 4). PTT and AIx were closely related to the predicted age both in men and women ($P < 0.001$).

From Table 4, The summaries of Figs. 3 and 4 are given. The correlation coefficients of the predicted age with PTT and AIx were stronger than the chronological age both in men and women.

4. Discussion

Vascular aging is an important predictor of cardiovascular disease [21,22]. PTT and AIx are the most important indices in assessing arterial stiffness based on pulse wave [23]. But the first two peaks of the radial pulse wave must be found when calculating PTT and AIx [24]

(Fig. 2). In view of this, we propose EP-PTT in this study (Fig. 1), the method is simpler and does not require estimating the location of the second peak. 10 EP-PTTs of each cycle were extracted in our experiment. The difference of the first 5 EP-PTTs were statistically significant between men and women ($P < 0.05$), as shown in Table 1.

10 EP-PTTs were extracted to describe the general shape characteristic of the pulse signal in this study. From Table 2, 9 EP-PTTs were age-related in men and it is 10 in women ($P < 0.05$). Furthermore, the correlation between EP-PTT$_5$ and chronological age was not significant in men ($P > 0.05$), there was an age-related increase in the first 4 EP-PTTs but age-related decrease in the last 5 EP-PTTs. For women, the first 4 EP-PTTs were positively correlated with age but the last 6 EP-PTTs were negatively correlated. This indicates that EP-PTTs can effectively describe the shape characteristic of the pulse signal in different age groups.

10 EP-PTTs were selected and fed into the MLR model as the independent variables both in men and women. The independent variables in the optimal MLR model must satisfy two conditions at the same time: Firstly, any independent variable must be significant in the MLR model ($P < 0.05$). Secondly, the VIF of any independent variable must be less than 5. The results of optimal MLR revealed that EP-PTT$_3$ and EP-PTT$_7$ were entered into the model as important predictors of age in men, while EP-PTT$_4$ and EP-PTT$_7$ were potent predictors in women (Table 3). The predicted age of all subjects was evaluated by the MLR model in this study. From Fig. 4, the correlations of predicted age with PTT and AIx were significant ($P < 0.001$).

In addition, the relevance of the chronological age and predicted age to PTT and AIx was summarized in Table 4. We compared the correlation coefficients of predicted age with PTT and AIx with the correlation coefficients of chronological age with PTT and AIx. The results showed that the correlation coefficients of predicted age with PTT and AIx were stronger than chronological age, and the predicted age is closer to PTT and AIx than chronological age both in men and women. Furthermore, the predicted age is more accurate to directly evaluate the degree of vascular aging than chronological age.

However, there are also limitations in this study. Objectively, 226 samples are not enough to represent the characteristics of the whole group. It is necessary to use the existing information technology to establish a larger sample bank. Subjectively, each point of pulse wave is indispensable. 10 EP-PTTs are extracted, which cannot fully describe the characteristic of the whole pulse wave. Besides, the research for the physiological significance of EP-PTT is also an important work in the next step.

5. Conclusions

The EP-PTTs proposed in this study are very useful in the future research, because they are simple and easily to obtainable, which satisfy the needs of the public health. The predicted age was estimated by the MLR model established in this study. The correlation coefficients of predicted age with the PTT and AIx were stronger than chronological age, and the predicted age can better directly reflect vascular aging than chronological age.

Conflict of interest

The authors have no conflicts of interest to disclose.

Author contributions

Pan developed the idea and designed the research. Huang and Tang developed the search strategy, selected included and extracted studies and analyzed the data. Tang interpreted the analysis. All authors read and approved the final manuscript.

Financial sources

This research was supported by Zhejiang Province Key Laboratory of Health Intelligence Kitchen System Integration (No. 2017F04).

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