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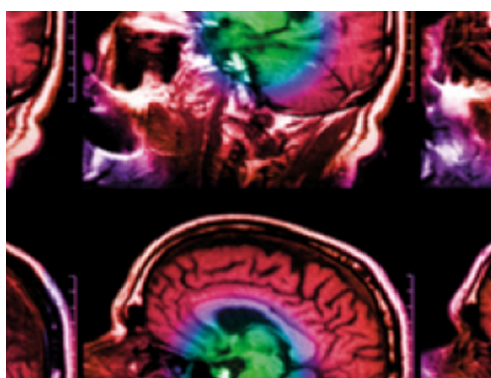
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PAPER

Age-related changes in pulse risetime measured by multi-site photoplethysmography

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Abstract

Objective: It is accepted that changes in the peripheral pulse waveform characteristics occur with ageing. Pulse risetime is one important feature which has clinical value. However, it is unclear how it varies across the full age spectrum from child to senior and for different peripheral measurement sites. The objectives of this study were to determine the association between age and pulse risetime characteristics over an 8-decade age range at the ears, fingers, and toes, and to consider effects arising from differences in systolic blood pressure (SBP), height and heart rate. *Approach*: Multi-site photoplethysmography (MPPG) pulse waveforms were recorded non-invasively from the right and left ears, fingers, and toes of 304 normal healthy human subjects (range 6–87 years; 156 male and 148 female). SBP, height, and heart rate were also measured. Multi-site PPG pulse risetimes, and their site differences, were determined. *Main results*: Univariate regression analysis showed positive correlations with risetime for age (ears, fingers and toes: + 0.8, + 1.9, and + 1.1 ms/year, respectively), SBP (+0.5, + 1.3, and + 0.9 ms/mmHg) and height (+0.5, + 1.2, and + 1.0 ms/cm), but with a clear inverse association with heart rate (−1.8, − 2.5, and − 1.6 ms min) (P < 0.0001). No significant differences between male and female subjects were found for pulse risetime. *Significance*: Normative multi-site PPG risetime characteristics have been defined in over 300 subjects and are shown to increase with age linearly up to the 8th decade. In contrast, we have shown that heart rate has a clear inverse relationship with risetime for all measurement sites.

1. Introduction

The peripheral pulse is often used in the assessment of health and disease. It can provide information about the cardiovascular system, such as heart rate or pulsatility, and hence indirectly the properties of blood vessels, including arterial elasticity, and narrowing due to stenosis with occlusive disease (Millasseau *et al* 2002, Allen *et al* 2008, Vlachopoulos *et al* 2011).

The peripheral pulse can be measured using the low-cost optical technology known as photoplethymography (PPG) (Allen 2007), which measures changes in microvascular blood volume with each heart beat. PPG can be configured to collect these optical pulses from head to foot to give PPG pulse waveforms that can characterized in several ways including using timing, amplitude, shape, and also their variability (Murray and Foster 1996). One component of the peripheral pulse is the risetime feature, i.e. the time between the foot of a pulse and its peak, but the significance of changes in it is not fully understood. Researchers have considered that risetime relates to arterial stiffness, i.e. compliance (Akl *et al* 2014, Lui *et al* 2015, Nirala *et al* 2018) and to peripheral resistance with vasodilatation and vasoconstriction changes (Allen and Murray 1999, Kyle *et al* 2017), and also to potential presence of arterial occlusive disease (Sherebrin and Sherebrin 1990, Allen *et al* 2005 and also, 2008, Allen and Hedley 2019, Peltokangas *et al* 2019). Pulse risetime and dynamics therein have also found other relevance with researchers studying sleep (Chua *et al* 2007), blood pressure estimation with machine learning methods (Khalid *et al* 2018), ageing by using a

second derivative or 'acceleration' PPG (Takada *et al* 1996, Elgendi 2012), wearable sensors applications (Castaneda *et al* 2018), and also the study of vasospastic disease (Cooke *et al* 1985, Mckay *et al* 2014). There is limited data to describe how aging itself as a factor affects the pulse risetime across a wide range of decades of years from the young to the old and over a range of different peripheral body sites (Zahedi *et al* 2007). The interpretation of such age data is further complicated by the influence of changes associated in key clinical variables, such as blood pressure, height, and heart rate. It is very important to know the effect of age on the waveforms and ultimately utilize appropriate normal ranges for comparing with patient groups (Allen and Murray 2002, Allen *et al* 2005).

In this study we build on the normal ranges of MPPG which we have determined and published for the pulse arrival time (PAT) characterization of optical pulse signals (Allen and Murray 2002, Allen *et al* 2008, Sharkey *et al* 2018). We have shown for ears, fingers and toes the similarity between right and left sides, and differences between the sites. The aims of this study are to quantify, for the first time, the MPPG pulse risetimes over body sites from head to foot over an 8-decade span, exploring the age-related changes and studying the inter-relationships with key clinical variables of blood pressure, height, and heart rate.

2. Methods

2.1. Measurement system
The multi-site pulse system is described in an earlier publication (Allen and Murray 2000). Briefly, the system comprised six PPG pulse amplifier channels, matched electronically in right and left pairs, and used to collect pulses from the right and left ear lobes, index fingers, and great toes. The pulse probes were all reflection mode devices (Artema, Denmark: ear type 75 331–9, finger and toe type 75 333–5). The bandwidth of the PPG amplifiers was 0.15 to 20 Hz. A single lead electrocardiogram (ECG, lead II) was also recorded to provide a cardiac timing reference for the subsequent pulse wave analysis. The six PPG waveforms and ECG waveform were all recorded to computer at a sampling rate of either 2000 or 2500 Hz.

2.2. Measurement protocol
All measurements were collected by trained operators. Subject age, gender and height were first recorded. Each subject was rested for at least 5 min and the brachial systolic blood pressure (SBP) measured at the right arm using a pressure cuff and ausculation method (for the adult participants the study design detected return of flow by a Doppler ultrasound probe and for the paediatric participants their study design employed a stethoscope to help detect the return of flow on cuff release). They lay relaxed and supine in a standard symmetrical and comfortable position in preparation for the multi-site pulse recording (Allen 2002): with right and left limb positions mirroring each other; hands placed palm upwards so that the fingers do not press against the body or the couch; feet in a 'V' position with heels closer together and right and left side toes apart. The great toe pads were cleaned with an alcohol wipe and the pulse probes applied to them using black Velcro cuffs. The subject was asked to confirm that the probes felt of similar tightness and location. If necessary, the probes were re-adjusted. The ear probes were applied to each ear lobe, and cabling adjusted to prevent tugging at the measurement site such as from chest wall movements with breathing. Finally, the ECG electrodes and connectors were applied to obtain a single lead II monitoring ECG. The subject was asked to lie still, and to breathe gently throughout the recording. These considerations helped produce good quality pulse recordings. The pulses from the six sites and the ECG were collected to a computer for at least 2.5 min.

2.3. Pulse wave analysis
The pulses were processed off-line using purpose-built algorithms developed in Matlab (The MathWorks Inc. USA). Two features were located for all pulses (the foot of the pulse and the first dominant peak of the pulse, Allen and Murray 2003) from which the Risetime measure was calculated for each body site from 60 consecutive heart beats. A semi-automatic process was then used to check each pulse manually for signal quality and pulse foot recognition. Individual pulses with visible movement artefact, noise, or poor landmark recognition, ectopic beats, were each marked and an interpolated value calculated from surrounding good quality beats. The right and left sides in each subject were averaged to obtain a better estimate for ears, fingers and toes. The subject heart rate (HR) was calculated from the median RR interval over the 60 beats. The recorded data were processed off-line by a single operator (JA).

2.4. Subjects
Multi-site pulse data from three of our earlier and separately published studies containing healthy control cohorts from paediatric and adult subjects were combined (from Allen *et al* 2005 and also 2008, Sharkey *et al* 2018). The combined three studies gave a total of 340 potential subjects for study, enabling risetime data from head to foot to be studied over a wide 8-decade range. In order to make all three groups consistent it

was necessary to remove those subjects who smoked cigarettes, and those who had ischaemic heart disease or diabetes. Consistently noisy PPG signals or those with clear uncertainty in pulse foot/peak landmark identification at any one of their body measurements sites were also excluded.

2.5. Statistics

Measurements were summarized using median and inter-quartile range [IQR, 25th percentile to 75th percentile]. Boxplots graphically expressed these along with upper and lower whisker lines to show the data range after any outliers were excluded. Differences between male and female subjects were assessed using the Mann–Whitney test. Univariate regression analysis explored the separate effects of age, SBP, Height, and HR on Risetime for ears, fingers and toes; multivariate regression analysis explored the combined effects of the four clinical measures on Risetime for the three sites, with correlation analysis used to determine if these effects were independent or not. As weight and diastolic blood pressure were not measured in all of the subjects from our three earlier studies these variables were not explored in the regression analysis. In addition, the relationships between Risetime and heart period, and also Risetime normalized to heart period and age, were briefly explored using univariate regression analysis. A P value of less than 0.05 was considered statistically significant.

3. Results

A total of 304 subjects (156 male/148 female subjects) could be included, with age range spanning 8 decades, i.e. 6 to 87 years (IQR [12–48]) years. Their median [IQR] SBP was 115 [104–128] mmHg, Height 1.63 [1.46–1.72] m, and HR 71 [62–79] min^{-1}. The measurements for pulse Risetime for ears, fingers and toes for all 304 subjects are presented in figure 1(a) (median [IQR] values of 257 [238–275] ms, 176 [149–245] ms, 203 [183–223] ms, respectively). The differences between body sites are shown in figure 1(b) between ears and fingers (+61 [24–97] ms), between ears and toes (+51 [34–69] ms), between fingers and toes (−21 [−46–18] ms), each comparison being significantly different (P < 0.0001) (figure 1(c)). No significant differences between male and female subjects were found for Risetime.

The relationship between age and Risetime for the ear, finger and toe site is shown in figures 2(a)–(c). The linear regression gradients were + 0.8, + 1.9, and + 1.1 ms/year respectively, and all were highly significant (all P < 0.0001). The changes in Risetime for the toes with increasing SBP, Height, and HR are shown in figures 3(a)–(c), respectively. The slopes for the Risetimes at the fingers and ears sites were similar to the toes, with SBP and height having positive slopes, and HR having negative slopes.

A summary of the univariate analysis of the contributions of age, SBP, Height and HR to changes in Risetime are presented in table 1. Heart rate was a strong contributor to changes in Risetime at all three sites (P < 0.0001), each site showing a clear inverse linear relationship. For subject age the greatest effect was at the fingers (+1.9 ms yr^{-1}, $r^2 = 0.54$, P < 0.0001). An influence of changes in Risetime with SBP was also found (between + 0.5 and + 1.3 ms mmHg^{-1} for the three sites, each P < 0.0001), but since SBP was not independent of age (+0.7 mmHg yr^{-1}, $r^2 = 0.55$, P < 0.0001) multivariate analysis highlighted SBP was not as clearly influential in the model. The multivariate linear regression analysis of Risetime with age, SBP, Height and HR gave values of r^2 (the fraction of Risetime variability explained by the relationship, where r is the correlation coefficient), with r^2 values between 50%–60% for the 3 body sites (table 2) (P < 0.0001 for all sites).

Exploratory univariate regression analysis showed clear linear relationships between Risetime and pulse period for the ears (+0.138, $r^2 = 0.37$, P < 0.0001), fingers (+0.199, $r^2 = 0.29$, P < 0.0001), and toes (+0.124, $r^2 = 0.29$, P < 0.0001). The relationship between subject age and the Risetime normalized to the pulse period was significant for the fingers (+1.3 ms yr^{-1}, $r^2 = 0.29$, P < 0.0001) and the toes (+0.4 ms yr^{-1}, $r^2 = 0.04$, P < 0.0001), but was not significant for the ear site (P = 0.07).

4. Discussion

In this study we have aimed to quantify the multi-site photoplethysmography pulse risetime characteristics and define expected ranges in relation to age in over 300 healthy subjects. We have shown that this measure increased with age at all of the measurement sites, and the increases taking place starting from an early age. The rate of increase in risetime was of the order of 1–2 ms per year, depending on site. It is known from the literature that arterial stiffness (loss of compliance) also increases with age and from an early age (Vlachopoulos *et al* 2011) and can be accelerated in certain patient groups including renal patients, diabetic patients and those with hypertension (Man and Wang 2017, Nirala *et al* 2018). Our research group has previously shown that with advancing age there is shortening of the pulse arrival time (PATf), i.e. a pulse transit time (PTT) type measure, at all peripheral sites head to foot (Allen and Murray 2002), and a tendency
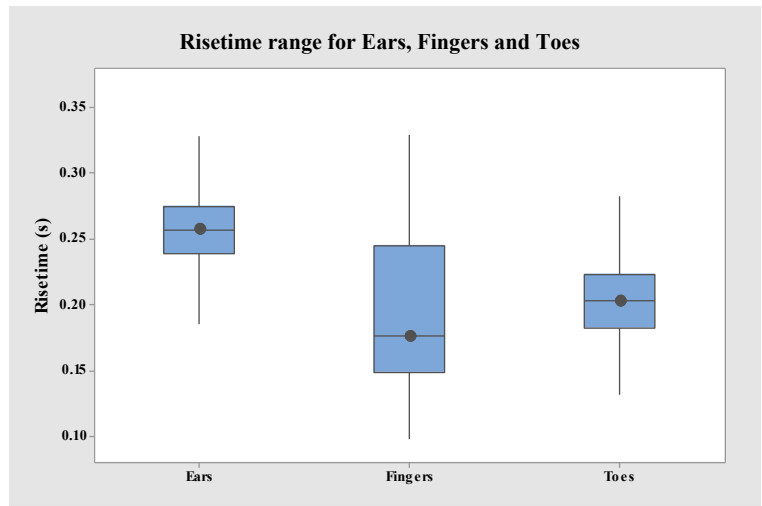
(a) By site
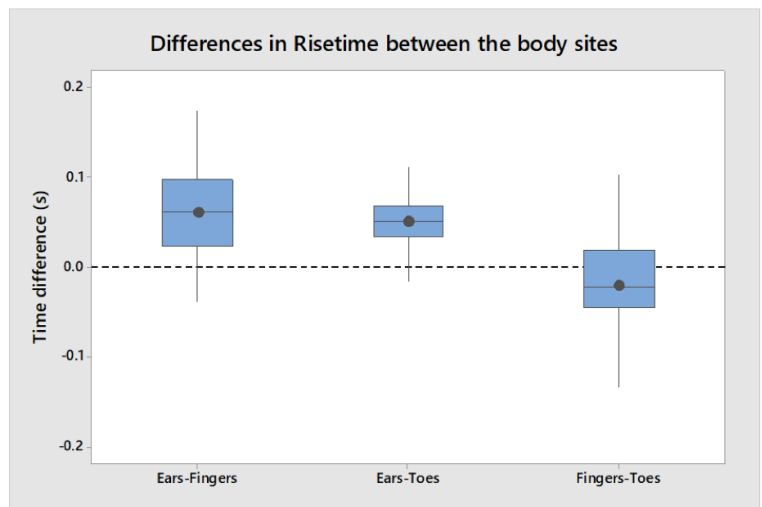
(b) Site differences
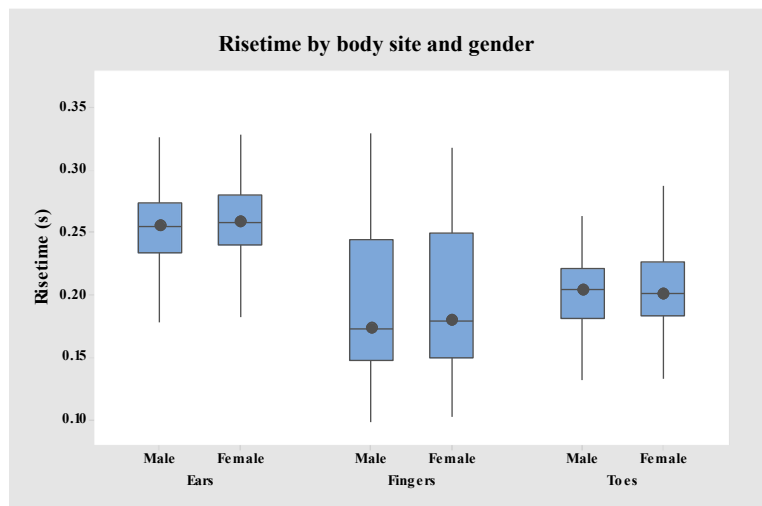
(c) By gender

Figure 1. Median IQR, i.e. Q1-Q3 and range for Risetime at (a) each of the three body sites; (b) differences in Risetime between the body sites for ears-fingers, ears-toes and fingers-toes comparisons; (c) a comparison of Risetime by subject gender, showing no clear differences.

to mild increases in overall triangulation of pulse shape (Allen and Murray 2003). It has also been shown in these studies and also with this risetime study that the different peripheral sites appear to be influenced by age at different rates. The apparent increases in risetime with age will have a contribution from the shortened pulse arrival time but not all of the increases are solely related to age. By normalizing the risetime to pulse period we have shown the ageing effects appear less at the finger and toe sites and are not significant for the

(a)   Ears
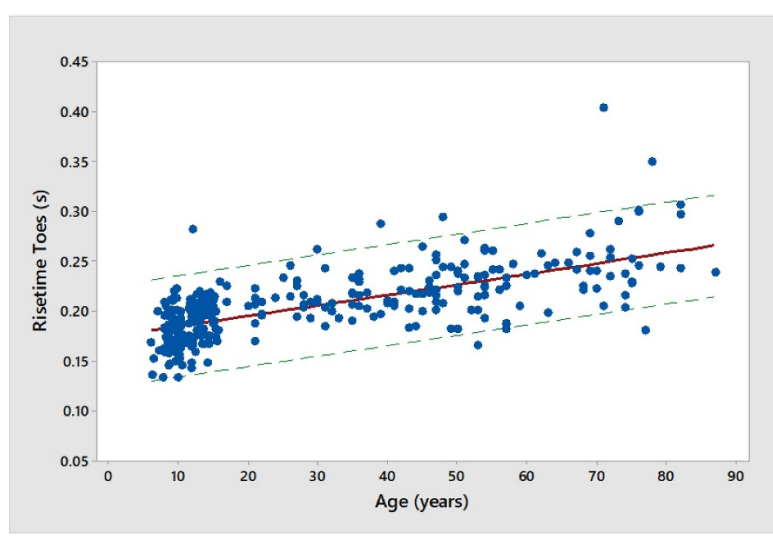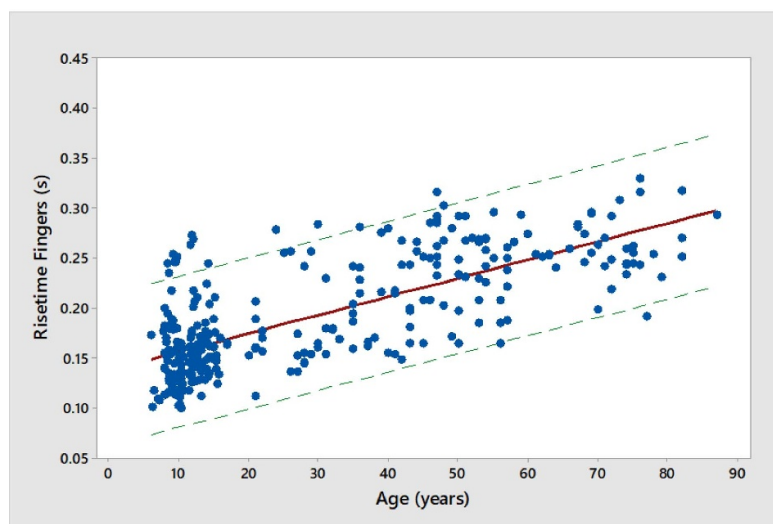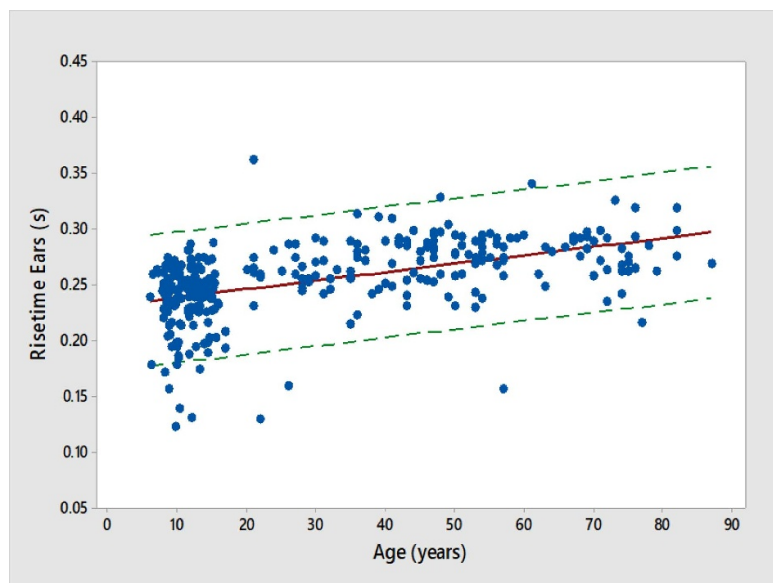
(b) Fingers

(c) Toes

Figure 2. Relationships between Risetime and age for (a) ears (slope $+ 0.8$ ms yr^{-1}), (b) fingers ($+1.9$ ms yr^{-1}), and (c) toes ($+1.1$ ms yr^{-1}). The linear regression lines are shown.
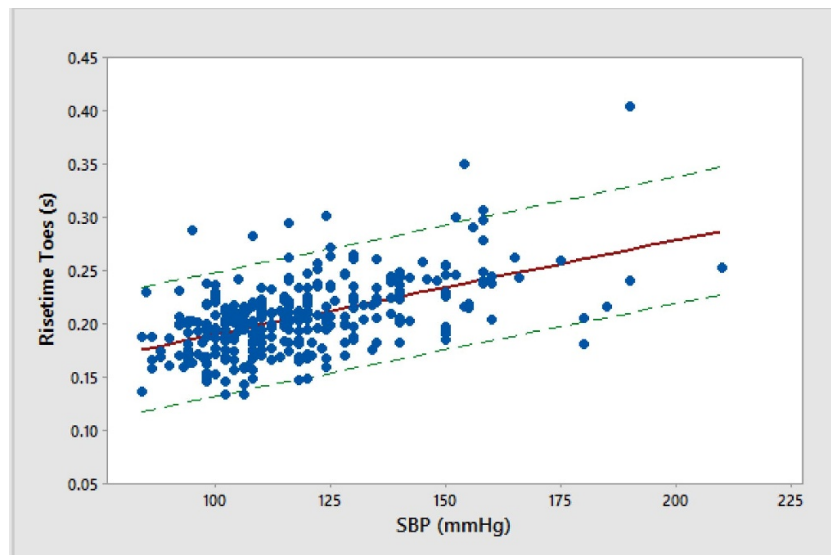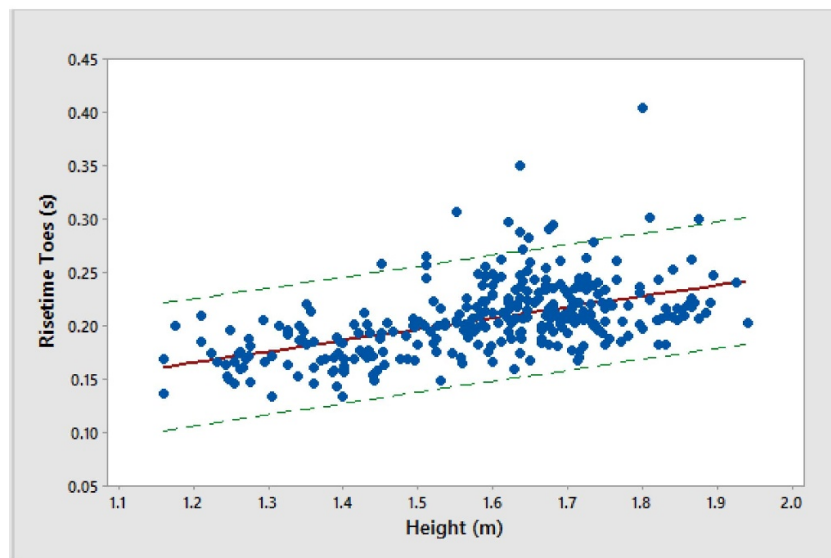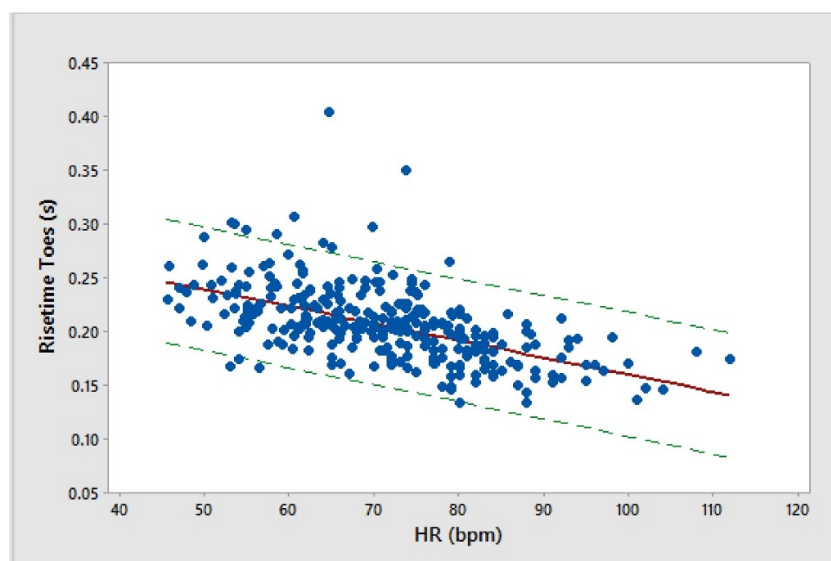
Figure 3. Relationships between Risetime for the toes and (a) SBP, (b) height, and (c) HR. The linear regression lines are shown. The inverse relationship between heart rate and Risetime is clear and holds for all three body sites. The toes site is shown as an example, noting that similar relationships were obtained for the ears and fingers sites.

Table 1. Univariate regression analysis to provide independent regression slopes. Differences in pulse Risetime with subject age, systolic blood pressure, height, and heart rate.

Site	Slope	r^2	P Value
Ears, Risetime change with:			
Age (ms yr^{-1})	+ 0.8	0.25	P < 0.0001
SBP (ms mmHg^{-1})	+ 0.5	0.08	P < 0.0001
Height (ms cm^{-1})	+ 0.5	0.06	P < 0.0001
Heart rate (ms min)	− 1.8	0.40	P < 0.0001
Fingers, Risetime change with:			
Age (ms yr^{-1})	+ 1.9	0.54	P < 0.0001
SBP (ms mmHg^{-1})	+ 1.3	0.25	P < 0.0001
Height (ms cm^{-1})	+ 1.2	0.15	P < 0.0001
Heart rate (ms min)	− 2.5	0.30	P < 0.0001
Toes, Risetime change with:			
Age (ms yr^{-1})	+ 1.1	0.46	P < 0.0001
SBP (ms mmHg^{-1})	+ 0.9	0.28	P < 0.0001
Height (ms cm^{-1})	+ 1.0	0.26	P < 0.0001
Heart rate (ms min)	− 1.6	0.31	P < 0.0001

Table 2. Multivariate regression analysis. Pulse Risetime for predictors of subject age, height, systolic blood pressure, and heart rate.

Site	r^2 value	P value	Predictor	Significance of each predictor
Ears	0.50	P < 0.0001	Age	P < 0.0001
			SBP	NS
			Height	P < 0.0001
			Heart rate	P < 0.0001
Fingers	0.60	P < 0.0001	Age	P < 0.0001
			SBP	NS
			Height	P < 0.0001
			Heart rate	P < 0.0001
Toes	0.54	P < 0.0001	Age	P < 0.0001
			SBP	P < 0.05
			Height	NS
			Heart rate	P < 0.0001

Key: NS; Not Significant.

ear site. Heart rate exerts an important influence and must be considered. Our overall results do highlight the potential of the multi-site PPG technique as a tool to quickly assess patients for possible accelerated vascular changes over time, for example in diabetic and renal patients who are increased risk of blood vessel calcification (Nirala *et al* 2018). Future studies of multisite photoplethysmography could also investigate age-related changes in pulse timing measures and aim to compare these measurements with intimal thickening in the peripheral arteries.

Our results also show the importance of other clinical factors to consider when modeling the pulse characteristics—systolic blood pressure, height, and heart rate differences. The results also show the general trends across the 8 decades studied but that there could be non-linear relationships involved, including that with subject height. We note also that risetime was at best weakly associated with systolic blood pressure and this is important when considering the utility of PPG in SBP tracking for wearable sensor type devices (Chan *et al* 2019).

A range of applications for PPG risetime has already been mentioned. Pulse risetime is an important measure and can be utilized clinically even though we do not fully understand what it might be representing physiologically (Allen and Murray 1999). It is considered there is potentially valuable information on arterial compliance and resistance from works published investigating techniques including Windkessel modeling approaches on PPG waveforms (Zahedi *et al* 2007, Akl *et al* 2014, Lui *et al* 2015). It is accepted peripheral resistance can change with large and small artery disease (Man and Wang 2017) as well as in vasodilatation/vasoconstriction (Cooke *et al* 1985, Kyle *et al* 2017)—having measures that can track changes linked to vascular compliance/resistance demonstrate the significant potential value of MPPG technology in cardiovascular assessments of autonomic function and endothelial function across the ages.

As well as the utility of MPPG risetime in ageing research our group and that of Peltokangas *et al* (2019) are exploring its value for detecting peripheral arterial occlusive disease (PAOD) (Allen *et al* 2005, 2008, McKay *et al* 2017). In Allen and Hedley (2019) it was noted that that some adjustment for very slow or fast heart rates may be needed to improve test accuracy—the regression analysis presented in this study also highlights that heart rate is important when handling risetime measurements. We also recommend that normalized (to pulse period) risetime should be considered in future studies in vascular disease detection.

Limitations of study

We did not specifically measure weight or diastolic blood pressure in all three of the cohorts making up the 304 subjects—these factors could not therefore be considered separately in the univariate modeling or jointly as part of the multivariate modeling. Future wider studies can consider these clinical measurements as well as the potential influence of ethnicity on risetime and characteristic changes.

5. Summary

We have quantified age-related changes in multi-site PPG pulse risetime characteristics in conjunction with showing their association with key clinical variables including subject blood pressure, height and heart rate. The age effect increased linearly between the first and eighth decades demonstrating that the effect of changes in arterial properties and the circulation can be detected non-invasively from an early age at the three main peripheral sites. We have also shown that age and heart rate appear dominant factors in contributing to risetime and also that there can be differences in the pulse characteristics from head to toe. We found no gross differences between body sides and there were no differences overall between male and female subjects. The normative MPPG pulse risetime ranges are available for comparison with cardiovascular patient groups, including those with renal disease, diabetes and/or hypertension.

Acknowledgments

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