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A New First-Derivative Related Index to Assess Pulse Wave Transit Time from a Photoplethysmographic Waveform: Age Dependence and Agreement with Normative Data

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Abstract

To potentiate the diagnostic capacity of photoplethysmographic (PPG) signals is a major challenge for both researchers and clinicians. We introduced the “waveform transit time” (TT_W) as a new first derivative related index to assess pulse wave transit time on the basis of the analysis of a PPG waveform. Numerical simulation revealed that that TT_W is a good proxy for the delay between incident and reflected waves in a model PPG waveform. A study was conducted on a sample of 230 PPG recordings obtained from presumably healthy subjects (8 to 89 years of age). TT_W analysis revealed that TT_W linearly decreases with age (TT_W = -1.5773*age+207.26; R = -0.82). Lumped data regression confirmed the linear trend, but also revealed heteroskedasticity, with standard deviation decreasing from 25 ms at the age of 20 down to 15 ms at the age of 60. Assuming that the reflected wave traveled an additional pathway of 1 meter as average in an adult population, an attempt was made to predict “normative” data for pulse wave velocity (PWV) based on our results. The obtained prediction for different age groups was in excellent agreement with published normative data for PWV. The plausibility of our results and the fact that TT_W estimation requires minimal expertise, provide further support to the idea of PPG as a promising source for PWV assessment not only in research laboratories but also in primary health care facilities.

Keywords

Photoplethysmographic Signal, Transit Time, Pulse Wave Velocity, Cardiovascular Ageing

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1. Introduction

One of the strategies in present-day medicine is to increase the diagnostic capacity of available methods and devices [1]. This is in line with the goal of reducing health care expenses, increase health care delivery efficiency and offer the best care possible without threatening the wellbeing of the patient. In this sense, a special place corresponds to photoplethysmography (PPG), a low-cost technique routinely used for assessment of cardiovascular health. Thus the PPG signal has been proven as an excellent surrogate for electrocardiogram in heart rate variability studies.

Among markers of arterial disease, arterial stiffness has proven to be an important aspect in the assessment of cardiovascular risk [2]. From the different options to evaluate arterial stiffness, carotid to femoral pulse wave velocity (PWV) has emerged as the gold standard method because of its relative ease in determination, its perceived reliability, and

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growing evidence demonstrating its association with cardiovascular disease in various populations [3].

Arterial stiffness measures and PWV in particular, are being increasingly recommended for routine clinical assessment of patients as well as part of large-scale clinical studies. Thus PWV has been included in the 2007 guidelines from the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) for the management of hypertension [4].

With available commercial systems for PWV estimation some disadvantages are indeed present associated to difficulties in reliably obtaining the required data as well as affordability aspects. Certainly, assessing PWV through standard techniques, is yet out of the reach for most health facilities worldwide (a SphygmoCor system for PWV analysis costs more than 10 000 US dollars, compared to less than 40 US dollars for a portable oximeter).

Attempts to obtain surrogates for PWV from PPG signals are not new [5]. This possibility arises from assuming that the PPG signal can be the result of a superposition of at least two waves: a direct pressure wave coming from the heart and a second, reflected wave coming from abdominal aorta bifurcation [6-7] (Figures 1 & 2).

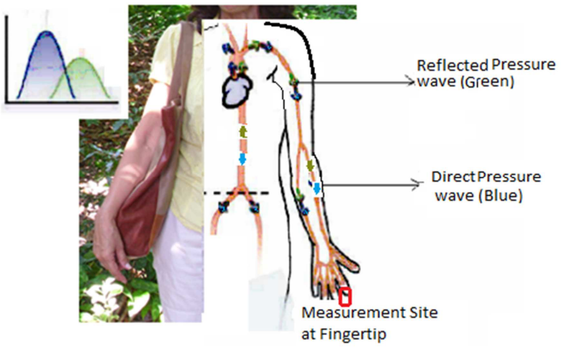

Figure 1. Schematic interpretation of the PPG signal as a superposition of incident and reflected pressure waves.

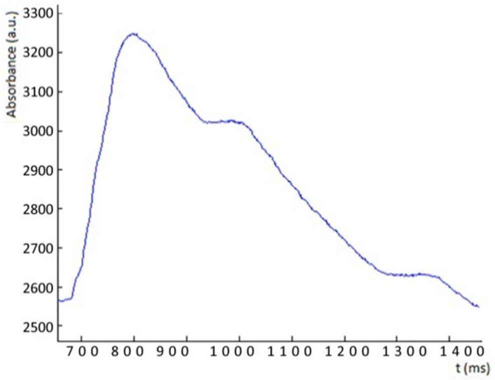

Figure 2. PPG waveform from a 10-year-old female subject.

However this is far from being the common situation for all PPG waveforms (see figure 3).

Moreover, the waveform in figure 2 suggests the presence of more than one reflected wave, and the inflection in the rising phase adds further difficulty to any attempt to find a reasonable explanation to the nature of this signal. These known facts add difficulties to current attempts to extract physiologically-meaning information from PPG signals [7].

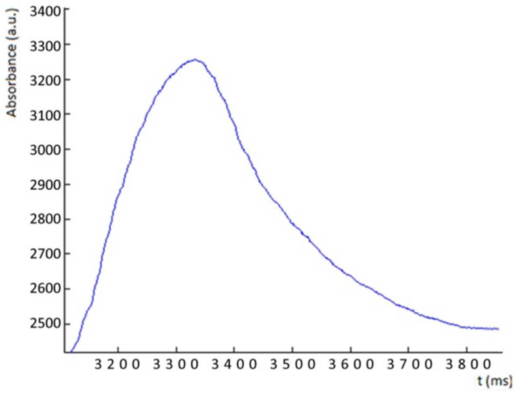

Figure 3. PPG waveform from a 56-year-old female subject.

Ideas from local extremes and inflexion point finding through the estimation of first and second derivatives of the waveform have been proposed for detecting the peaks of direct and reflected waves in the time axis [8]. A major drawback of this approach is the tradeoff between a signal that preserves all of its components and a noiseless derivative [9].

An additional complication arises from paucity of normative data. In spite of being recognized as the gold standard method for the assessment of arterial stiffness, a broader implementation of PWV into clinical practice is hindered by the absence of established reference values. In this regard it is noteworthy that normative values were proposed in 2010 on the basis of PWV studies conducted in 13 different European Centers [10].

Indices related to transit-time obtained from PPG analytical procedures have not yet been standardized and population studies are usually constrained in both sample size and age range.

Our goal is to introduce an easy to implement algorithm for transit time estimation from the PPG waveform. Accordingly, here we are introducing the “waveform transit time” (TT_W) as a new first-derivative related index to assess pulse wave transit time from a PPG waveform. The study was conducted on a sample of 230 presumably healthy subjects (8 to 89 years of age). Our results suggest a good correspondence with previously reported normative data for PWV. This and the fact that TT_W estimation requires minimal training, provides further support to the idea of PPG as a promising source for PWV estimation not only in research laboratories but in primary medical services.

2. Methods

2.1. Subjects

A total of 230 subjects were involved in the study, with their ages ranging from 8 to 89 years; 134 subjects were male. The demographic data of the subjects are as summarized in Table I.

Table I. Demographic data of the subjects are as shown.

Age range (years)	Female	Male	Total
6 to 20	7	11	18
21 to 30	17	23	40
31 to 40	24	25	49
41 to 50	12	30	42
51 to 60	11	18	29
61 to 70	12	12	24
71 to 80	10	14	24
81 to 89	3	1	4
	96	134	230

Recordings were obtained in Orense, Spain, and more than 95% of subjects were original from Galicia. The inclusion criteria were: no clinically apparent arterial disease or physical abnormality and not observantly obese or on any medication. Approval was obtained from the local research ethics committee, and each subject's verbal consent was taken before the recordings were made. Peripheral (pointer finger of the right arm) pulse measurements were recorded for 5 min, using a validated oximeter (Nellcor 395, USA), with the subject sitting on a chair and the arm positioned at heart level with the forearm resting on a table in a temperature controlled room (24±1.5°C). Care was taken to see that the effect of motion artifact was the lowest possible. The subjects were also asked not to undergo strenuous exercise, avoid consuming hot drinks or those containing caffeine, and refrain from smoking for 2 hours prior to recording. It was also ensured that the subjects were relaxed and breathing regularly and gently. Signals were digitized at 1000 Hz and saved as ASCII files

2.2. Signal Processing

No wave averaging or additional filtering was performed in this study. A segment containing between two and three subsequent PPG waves (usually 2500 data points) was randomly picked from the original 5-min recording. As an approximation to the first derivative, a vector of differences was estimated. This "first derivative" signal was then approximated to a 40-degree polynomial using Scilab, and the obtained fit was superimposed on the original "first derivative". The TT_W index was estimated manually as the difference between the first local minimum and the subsequent local maximum of the first derivative. Even when estimation from the fitted polynomial is straightforward and can easily be obtained with an automated algorithm, visual control was required, and the polynomial fitted curve was used in case that the local minimum and maximum corresponded to the trend seen in the "derivative" signal, otherwise it served as eye guidance for TT_W estimation. TT_W was obtained as the average of at least two observations. An example of the method's application is summarized in figures 4 & 5. Figure 4.1, 4.2 & 4.3 are illustrations for TT_W estimation of a male subject, age 37.

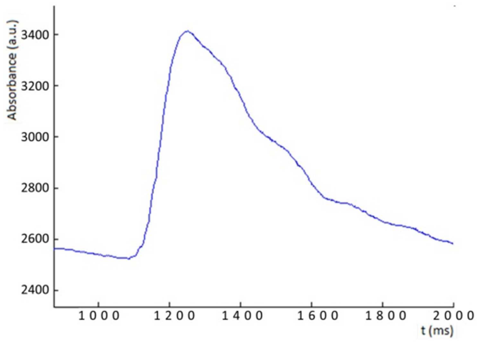

Figure 4.1. An original PPG signal.

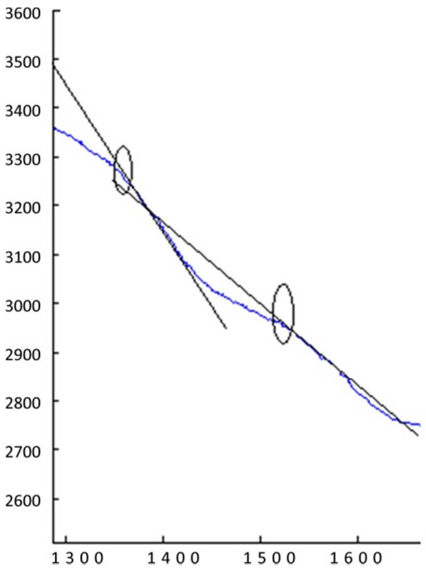

Figure 4.2. Enlarged display of the diastolic phase from the waveform at figure 4.1. Sharp changes in the negative slope can be noticed at points around 1380 and 1510 ms, respectively.

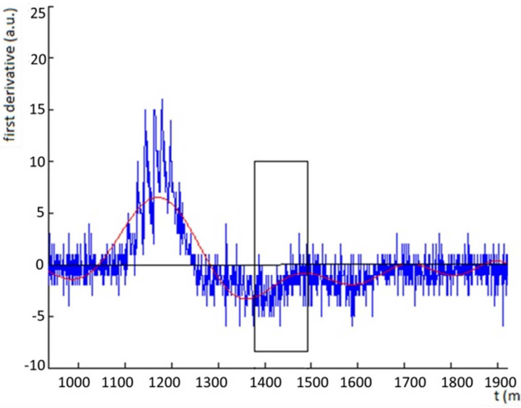

Figure 4.3. The "first derivative" signal (blue trace) and its approximation to a 40-degree polynomial (red line). Same PPG wave as in figures 4.1 & 4.2.

As observed from figure 4.3, the first local minimum appears around 1375 and the subsequent local maximum is around 1495, in apparent correspondence with the breakpoints seen in the middle graph. The vertical parallel sides of the inserted rectangle yield a TT_W = 120 ms, in good accordance with the graph at figure 4.2. It should be noted that the fitted polynomial is being used mainly for eye guidance.

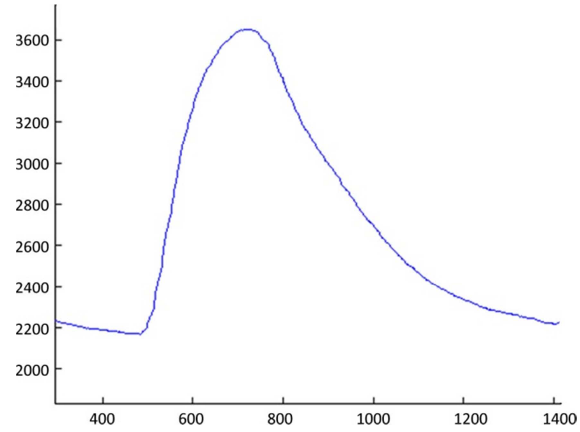

Figure 4.4. PPG signal of an 82-year old subject.

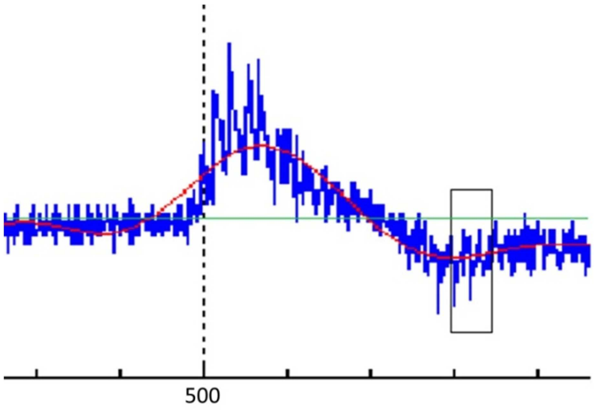

Figure 4.5. Representation of a TT_W estimation with a PPG waveform from an 82-year old female subject. TT_W = 83ms.

2.3. Attempt to Correlate TTW with Real Transit Time through a Simulation Approach

Due to the complex nature of the PPG signal, it is risky to determine *a priori* what is being measured with one or another index, unless the real nature of the signal is uncovered [6-7]. We attempted to clarify this question using a very simple model for the PPG waveform. The PPG waveform (y) as a function of time (t) was modeled with the product of two simple exponentials. Reflected wave had the same shape; its amplitude was at 90% of the incident wave and was shifted in the time axis in ΔT units. Thus,

$$y=\left(1-e^{-t/40}\right)*e^{-t/180}+0.9*\left(1-e^{-(t-\Delta T)/40}\right)*e^{-(t-\Delta T)/180} \quad (1)$$

We used numerical simulations in an attempt to find a relationship between TT_W and ΔT.

In figure 5, a simulated PPG signal is represented (ΔT=200 ms) and we estimated TT_W from it. The obtained TT_W was 170 ms, suggesting a 15% departure from the "true" value of 200 ms.

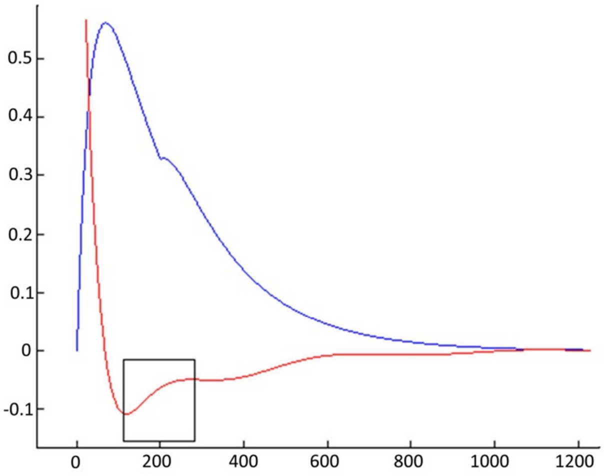

Figure 5. Estimating TT_W from a simulated PPG signal. The time lag between the two components was ΔT=200ms, whereas the estimated TT_W was 170 ms.

This procedure was repeated for a sample of 23 simulated curves with ΔT values changing from 50 ms to 430 ms. For the association between TTw and ΔT, we obtained a slope of 0.95 (TT_W = 0.9532* ΔT; R = 0.964). Thus these results suggest that TT_W is a creditable proxy for estimating the time shift between incident and reflected wave in the PPG signal.

2.4. Statistical Methods

SciLab was used for correlation estimation as well as for high degree polynomial approximation.

2.5. Limitations of Present Study

Studied subjects belong to a relatively large sample and are presumably healthy; however there are no clinical confirming data for cardiovascular health (e. g. ECG, blood pressure, lipid profile, etc.). The proposed algorithm for TT_W includes a component that depends on the researchers' subjective criterion. Even when relatively easy to be learnt by others, a fully automatic version of the algorithm still remains as a challenge for future research. However, the plausibility of obtained results points to the virtue of TT_W.

Another limitation is related to sample size. This study uses a much smaller sample than published PWV reports. However, it is larger compared to most PPG transit time publications thus far.

3. Results

3.1. Search for Age Differences

With an age-paired male-female sample, age dependence of TT_W estimation did not bring any gender differences. Regression lines for age were $TT_W = -1.5277*age + 196.61$ ($R = -0.87$) for female and $TT_W = -1.5005*age + 197.46$ ($R = -0.84$) for male subjects. This result is summarized in figure 6.

3.2. Age Dependence of the Whole Population

Figure 7 illustrates the age dependence of TT_W for the totality of the studied sample. As observable, TT_W linearly decreases with age ($TT_W= -1.5773*age + 207.26$; $R = -0.82$).

The obtained correlation between TT_W and age ($R = -0.82$) is one of the highest reported for a cardiovascular index in this age range and with comparable sample size.

3.3. Attempt to Obtain Normative Data

A moving average lumping data in an age range of ±3 years was estimated as an attempt to obtain a “developmental equation” for TT_W For the mean, the obtained result is represented in figure 8.

Lumped estimates for standard deviation suggest the presence of heteroskedasticity, with standard deviation falling from 25 ms at the age of 20 down to 15 ms at the age of 60 (figure 9).

Data from figures 7 & 8 makes it possible to obtain normative equations.

3.4. Attempt to Compare Present Results with PWV Normative Data

If TT_W corresponds to the time delay associated to the reflection in the lower aortic branch, we may assume that the reflected wave traveled an additional pathway of 1 meter as average in an adult population (twice 0.5 m), and this distance of 1m seems to be plausible for adults. With this presumed value, a surrogate for pulse wave velocity can be proposed as the inverse of TT_W expressed in seconds. We compared our surrogate PWV values with those published [10]. As it can be seen from Table II, there is a good agreement between predictions from present study and reported PWV normative data.

Regression analysis revealed an excellent agreement between both estimates:

$$PWV_{Predicted} = 0.9777*PWV_{Observed};\ R = 0.99.$$

Table II. Normative data for PWV reported for a normal population and surrogat e values for PWV [10] compared to those obtained from present study. Values are expressed in m/s.

Age	Normative PWV(mean)	Normative PWV(Range)	Estimated Mean PWV (This Study)	Estimated Range for PWV (This Study)
10 to 19	-	-	5.514	3.9 to 5.7
20 to 30	6.6	4.9 to 8.2	6.031	4.44 to 8.85
30 to 39	6.8	4.2 to 9.4	6.654	5.56to10.8
40 to 49	7.5	5.1 to 10	7.422	6.71to 9.17
50 to 59	8.4	5.1 5 to 11.7	8.390	6.62to10.53
60 to 69	9.7	5.7 to 13.6	9.648	7.09to12.35
70 to 79	11.7	6.0 to 17.5	11.351	8.06 to 18.52

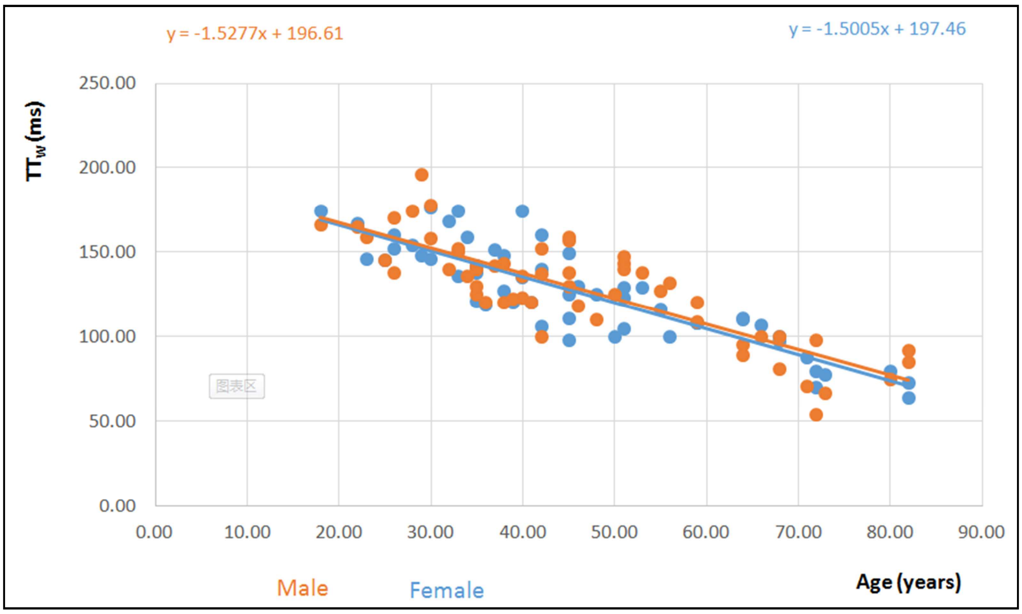

Figure 6. Comparison of male and female subjects as per TT_W age dependence.

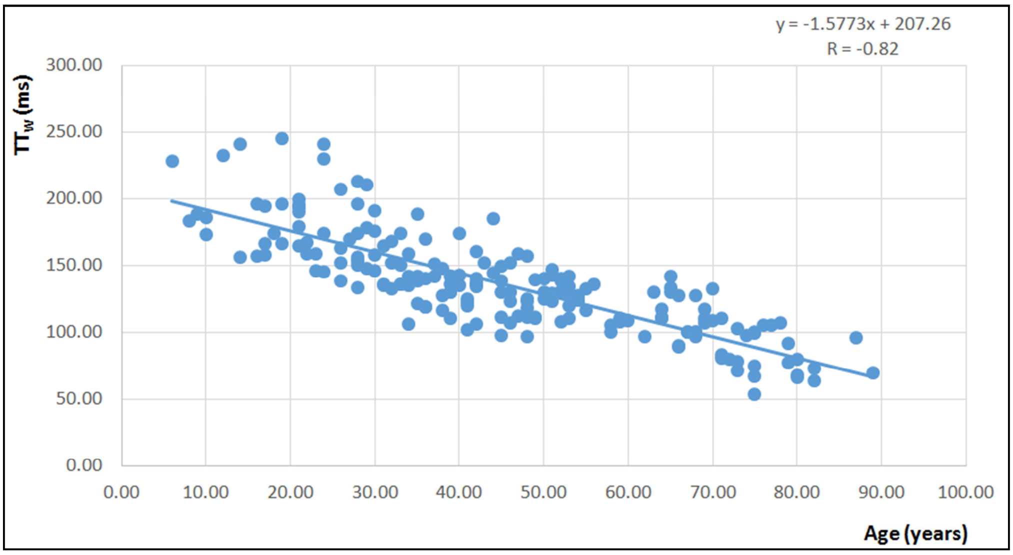

Figure 7. TT_W age dependence for the whole sample.

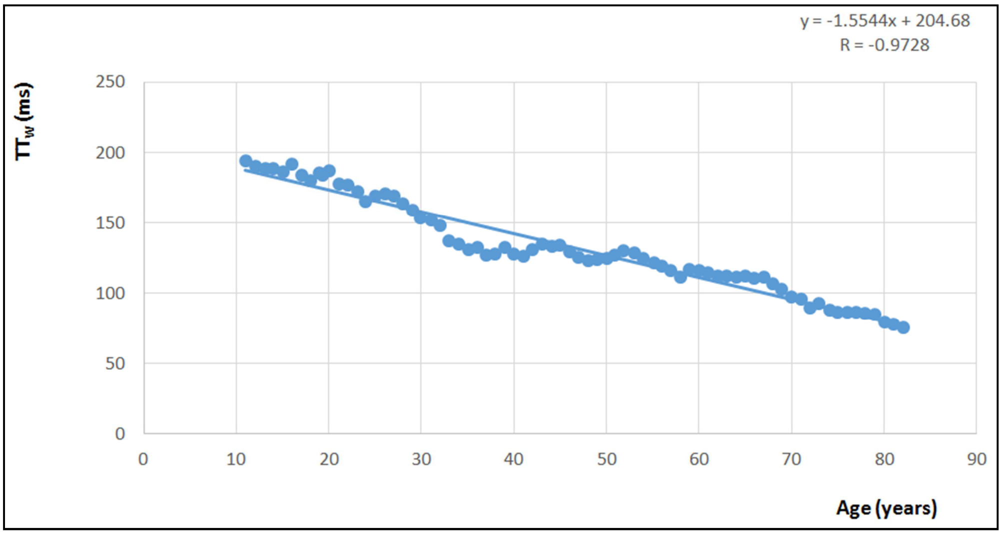

Figure 8. Moving average regression for age dependence of TT_W.

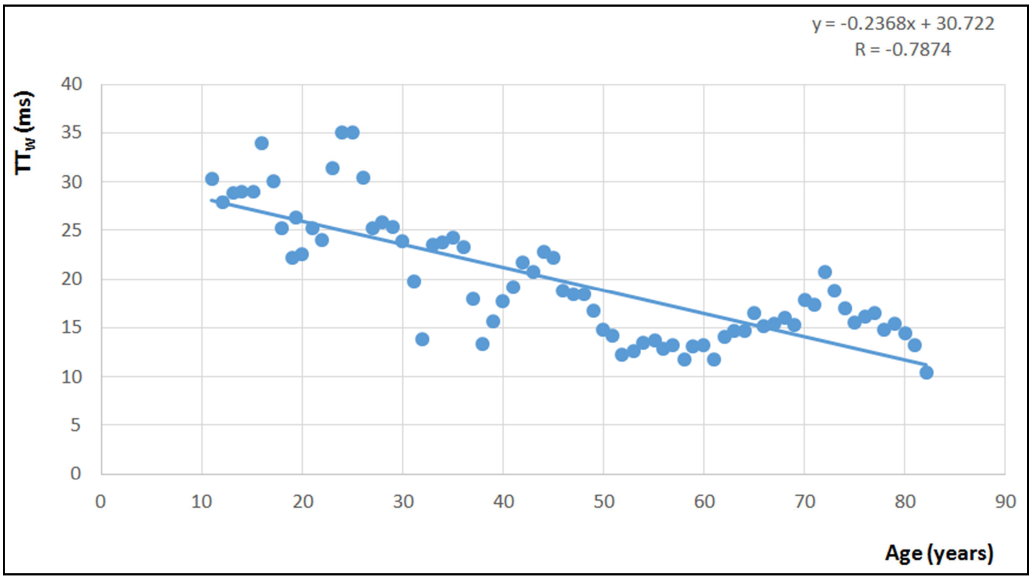

Figure 9. Lumped standard deviation for TT_W as a function of age.

4. Discussion

A common view among health services providers is that the introduction of scientific advances is linked to the deployment of sophisticated and necessarily costly technology. Nowadays, however, the vast majority of humankind lives under serious economic constrains, and an assumption might be that what is needed is not more technology but rather more public health interventions. Contrary to this pessimistic view, an endeavor aimed at boosting information extraction from available techniques appears as a new approach that combines sustainability with sound scientific bases.

Recommended guidelines for arterial stiffness estimation are based on the recording of continuous blood pressure [4]. Available systems for continuous blood pressure monitoring are prohibitive for medical institutions in most developing countries. The PPG signal has proven to be linearly associated to the pressure signal [9], and this justifies its use as a reliable proxy for satisfying most of the requirements stated in published guidelines.

Several indices have been proposed for cardiovascular age estimation. Statements of the type “patient’s chronological age is 45 years whereas her cardiovascular age is 57”, may look intuitively very informative and easy to interpret. However in this statement information about dispersion in age dependence of values is not considered. This explains why in this investigation we studied the age dependence of the proposed index, assessed the quality of fit for this age dependence through the correlation coefficient, and additionally estimated the value of standard deviation corresponding to each lumped age value. This allowed not only estimating the “cardiovascular age”, but also to express the probability for an individual to belong in the normal population according to their age.

In this context, our research was aimed at implementing a new algorithm for transit time estimation from the PPG waveform. Perhaps the best virtue of our algorithm is that, being easy to implement it can be applied to the great diversity of PPG waveforms found in real recordings. For us it was important to clarify the reliability of TT_W. for assessing age related cardiovascular changes. In this connection the first support for the proposed index arose from the high quality of fit of the TT_W regression with respect to age.

The second support originated from the satisfactory correspondence between our predicted values for normative values of PWV based on TT_W and those obtained from a large database from European Laboratories.

We also tried to understand to which extent TT_W might reflect a time delay between primary and reflected pulse waves. For that, a consistent model of the PPG wave is requisite [6-7]. Here, the proposed PPG model is based on a quite intuitive idea, and the comparison of TT_W with time delays defined by construction is satisfactory.

Thus, TT_W was introduced as a way to estimate transit time from peripheral PPG waveform. The proposed algorithm combines ideas from local extremes and inflexion point analysis with a minimal part of visual pattern recognition. The analysis of the 230 recordings provided in this study suggests that by doing this we accommodate our algorithm to the great diversity of PPG wave patterns reported [11] while avoiding the drawbacks associated to filtering of signals [9]. We hope that in the near future a completely automated version could be created for this index.

One of the interesting results from our study is that TT_W does not seem to be gender-sensitive. The implication of this result is that since male adults are about 10% taller than their female counterparts (respective averages of 1.77 m vs. 1.61 m for our data sample), pulse wave velocity is expected to be lower among females. Indeed, a 10% difference has been reported for PWV when genders are compared (7.4 m/s for female subjects vs. 8.2 m/s for males [10]).

5. Summary and Conclusions

The proposed index, TT_W is an easy to estimate PPG index that exhibits a strong correlation with age and is congruent with published results about PWV. Due to its relatively easy determination, it could boost the potentialities of PPG recordings.

In the methods section the algorithm for estimating TT_W is described, and it also provides the result of a numerical simulation suggesting that TT_W really measures the delay between incident and reflected waves in a PPG signal. The results section includes gender comparison, age dependence of TT_W as well as comparison between theoretically expected mean values for PWV derived from TT_W, with published normative data for PWV. The discussion refers to the main findings of our study as well as its relevance for boosting the diagnostic capability of the PPG signal.

Research Significance: The introduction of a new index for transit time estimation allowed to find a strong association ($R = -0.82$; $n = 230$, ages from 8 to 89 years) between estimated transit time and subject’s age. Predicted values for pulse wave velocity revealed an excellent agreement with published normative values. All this together support the idea about the PPG signal as an important source of clinically relevant information.

Acknowledgements

We would like to extend our gratitude to unknown referees for their valuable comments.

Notations, Definitions, and Symbols

PPG	Photoplethysmographic signal
PWV	Pulse wave velocity
TT_W	Waveform transit time
R	Correlation coefficient
ESH	European Society of Hypertension
ESC	European Society of Cardiology

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