Applying the 3-element windkessel model to photoplethysmographic signals. Gender differences and age correlation

Aplicación a señales fotopletismográficas del modelo de "Cámara de aire con tres elementos". Diferencias en cuanto a género y correlación con la edad

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ABSTRACT

Automatically averaged photoplethysmographic (PPG) signals were fit to a 3-element windkessel model using a Gauss-Newton optimization algorithm. Data corresponded to 78 healthy subjects (ages from 8 to 87 years). Unlike other reports, two phase velocities are also estimated from the model. Gender differences were found, particularly respect to individual parameters correlation with age. When a nonlinear model was fit to the two first principal components, a high correlation with age was found for both females ($r=0.69$) and male subjects ($r=0.77$). Our results further support the idea that the PPG signal is a valuable source of information about the cardiovascular system, comparable to the much more expensive continuous pressure signal.

Key words: photoplethysmographic signal, windkessel model, cardiovascular age, mathematical model.

RESUMEN

Señales fotopletismográficas automáticamente promediadas fueron ajustadas a un modelo de "bomba hidráulica" de tres elementos. Para ello se utilizó un algoritmo de optimización del tipio "Gauss-Newton". Los datos fueron obtenidos de 78 individuos sanos con edades entre 8 y 87 años. A diferencia de otros reportes, en el presente trabajo se estimaron dos velocidades de fase a partir del modelo. Al aplicar un modelo no lineal respecto los dos primeros componentes principales, se

obtuvo una elevada correlación con la edad tanto para los sujetos femeninos (r=0.69) como para los masculinos (r=0.77). Nuestros resultados ofrecen un apoyo adicional a la idea de que la señal fotopletismográfica es una fuente importante de información acerca del sistema cardiovascular, comparable a la señal de presión continua, aun cuando esta última es mucho más costosa.

Palabras clave: señal fotopletismográfica, modelo de cámara de aire, edad cardiovascular, modelo matemático.

INTRODUCTION

The first cardiovascular model that considered pulsatile flow was suggested by Otto Frank in 1899.[1,2] Frank hypothesized that the arterial tree functions as a compression chamber or "windkessel" in a fire pump. The first half of 20th century saw very little application of Frank's model to cardiovascular function, limited mainly by scarce knowledge about vessel's dynamics as well as poor technological resources for continuous pulse pressure recordings.[3] Recently this state of affairs has changed for the better, and small modifications introduced to the lumped model are leading to the extraction of clinically sound information. From a practical viewpoint, the most important part of the analysis with a 3-elements' variant of the Frank's model includes the approximation of the systolic component of the waveform to the following nonlinear function with 6 parameters ($A_1 \ldots A_6$).

$$P(t) = A_1 e^{-A_2 t} + A_3 e^{-A_4 t} Cos\ (A_5 t + A_6) \quad (1)$$

Where $P(t)$ denotes the continuous pressure as a function of time.[4]

If systemic vascular resistance can be estimated, then two compliance components ("resistive compliance" C_1 and "oscillatory compliance" C_2) can be obtained, since[4]

$$C_1 R = \frac{2A_1 \left\{ (A_2 + A_4)^2 + A_5^2 \right\}}{A_2 (A_2 + A_4)(A_4^2 + A_5^2)} \quad (2)$$

$$C_2 R = \frac{1}{2A_4 + A_2} \quad (3)$$

$$\frac{L}{R} = \frac{(2A_4 + A_2)^2}{2A_4 \left\{ (A_2 + A_4)^2 + A_5^2 \right\}} \quad (4)$$

In particular, oscillatory compliance (C_2) has reported the strongest correlation with age thus far[5] (r=-0.66, n=210).

Widespread application of these results in primary care settings meets at least two drawbacks. The first limitation is related to the need to record pulse pressure continuously. This is possible only in specialized laboratories, and public health facilities in many countries lack them. On the other hand, obtaining a compliance estimate requires measuring peripheral resistance, but peripheral resistance can be obtained either from cardiac output or from a nonlinear function of age, mean heart rate, mean systolic and mean diastolic blood pressure. Such estimation can add substantial error (due to individual's variability) to the estimated compliance.

The use of the photoplethysmographic signal (PPG) as a proxy for continuous pulse recordings has been proposed.[6,7] Theoretical models suggest that pulse pressure and volume changes are linearly proportional.[4] Even when the "plethysmographic" signal is not purely about volume changes, an important part of it is associated to volume dynamics. On the other hand, PPG signals can be acquired at a high sampling frequency, 1000 Hz being a typical value. Compared to the 128Hz sampling frequency reported in most studies with continuous pressure recordings, PPG signal can add a larger number of data points thus improving the time resolution. It seems that the low temporal resolution of continuous pressure signals can be the cause of errors in compliance estimation.[5,8]

Theoretical elaborations, however, suggest that another important parameter can be estimated from the 6-parameter model without the need of estimating peripheral resistance.

In particular, phase space velocity may be deduced from:[9]

$$\vartheta = \frac{1}{\sqrt{LC}}$$

(5)

Hopefully these two velocities can be somehow related to propagation velocity, a measurable entity highly correlated with age.[10-15]

Here, we approximate the diastolic component of the PPG signal with function (1). Besides parameters A_1-A_6, we calculate C_1R, C_2R as well as two phase velocities: "resistive phase velocity" $\vartheta 1$ and "oscillatory phase velocity" $\vartheta 2$.

All these are submitted to multivariate analysis focused on association with age.

METHODS

Subjects. Seventy eight volunteers (47 males with ages from 12 y to 87 y, and 31 females with ages from 8 y to 89 y) were recruited in the city of Orense (Spain). They were free of clinical cardiovascular disease and medication, and Body Mass Index never surpassed 31 kgxm-2. Approval was obtained from the local research ethics committee, and written informed consent was obtained from all participants. Five-min-duration photoplethysmographic signals were obtained from the pointer finger of the right arm with the subject in supine position, using a validated

oximeter (Nellcor 395, USA). Signals were digitized at 1000 Hz and saved as ASCII files.

Wave averaging. For wave averaging, a pattern vector of length L (usually about 90 data points) was picked by visual inspection. Correlations were measured between the pattern vector and each individual vector of length L starting at the point I of the original signal. The obtained vector of correlations (corresponding to about 100 seconds of recording) was then submitted to further analysis. Those vectors signal having a correlation higher than a certain threshold "Th" and corresponding to a local correlation maximum were picked as individual waves and entered as rows of the matrix M of the waveforms. From M the average waveform was obtained via averaging over all rows. The main virtue of the method is that a representative wave is obtained without the need to rely on subjective opinions of experts.

Fitting of data into the model. Averaged waves were fit to equation (1) by using a Gauss-Newton optimization algorithm.[16] Only solutions whose correlation coefficients exceeded 0.99 were accepted.

Statistical methods: Correlation matrices and multiple regression analysis (forward stepwise variant) were performed.

Multivariate analysis included principal component determination and nonlinear regression respect to PC1 and PC2. For nonlinear estimation, the following 4th degree function was fitted to age data.

$$Age = a + b(PC1) + c(PC1)^2 + d(PC2) + e(PC2)^2 + f(pc1)(pc2) + g(PC1)^3$$
$$+ h(PC1)^2(PC2) + i(PC1)(PC2)^2 + j(PC1)^4 + K(PC2)^4 + m(PC1)(PC2)^3 + N(PC1)^3(PC2)$$
(6)

Limitations of present study. Using PPG signal as a proxy for continuous pulse wave recordings seems to be justified for the case when both signals are proportionally dependent. Evidence from the literature supports this assumption.[7] At the same time, the surrogate variables obtained ("compliance", "phase velocity", etc.) can be approximated to the real variables with the precision of a linear factor. Since the PPG signal is expressed in units of absorbance, it is very difficult to express these variables in their real units without a shrewd calibration experiment. Thus the words "compliance", velocity, etc. cannot be taken at face value.

The second limitation is related to the sample size. This study uses a smaller sample than other reports. Some of the differences obtained here between male and female subjects may vanish with increased sample size.

RESULTS

Evidences from the literature suggest marked differences between women and men in their compliance values.[4] Thus the analysis was conducted separately for each gender.

Male subjects. The correlation matrix for all variables appears represented in Table 1. As can be seen, significant correlations with age were obtained for both phase velocities and "L/R". At the same time, $\vartheta 2$ is highly correlated with $\vartheta 1$ whereas for $\vartheta 2$ a significant correlation was found with "L/R".

Table 1. Linear correlations among all variables obtained from the 3-element windkessel model for PPG recordings from male subjects. Number of valid cases N=47.Correlations highlighted in red are significant al p<0.05

Variable	Age	A1	A2	A3	A4	A5	A6	C1R	C2R	L/R	ϑ1	ϑ2
Age	1	.02	.16	-26	-12	.02	.02	-.29	-.04	.44	.38	.48
A1	.02	1	.36	-04	.08	-18	-08	-.10	-.35	.34	.31	.30
A2	.16	.36	1	-25	-04	-09	-01	-.23	.04	.21	.48	.07
A3	-26	-04	-25	1	-25	.18	-25	.97	-.06	-10	-18	-16
A4	-12	.08	-04	-25	1	-88	-36	-.03	-.10	-14	-13	-15
A5	.02	-18	-09	.18	-88	1	.25	.36	.05	.02	.01	.01
A6	.02	-08	-01	-25	-36	.25	1	-.17	-.03	.04	.04	.05
C1R	-29	-10	-23	.97	-03	.36	-17	1	-.01	-13	-21	-22
C2R	-04	-35	.04	-06	-10	.05	-03	-.01	1	.01	-39	-44
L/R	.44	.34	.21	-10	-14	.02	.04	-.13	.01	1	.44	.58
ϑ1	.38	.31	.48	-18	-13	.01	.04	-.21	-.39	.44	1	.83
ϑ2,	.48	.30	.07	-16	-15	.01	.05	-.22	-.44	.58	.83	1

Unexpected is the very high correlation between C_1R and A_3 even when no explicit theoretical association is perceived (see equations 1-4).

Since there are significant univariate correlations with age, it is to be expected that a multivariate linear regression could yield a correlation with age stronger than any of the individual variables does.

Regression summary (Fig.1) accounts for a strong presence of "oscillatory phase velocity" in the regression model. Overall, the strength of association increased to 0.58. In terms of significance an improvement from p= 0.0080 to p=0.00152 took place when passing from univariate to multivariate regression.

Regression Summary for Dependent Variable: Age						
R= .57893663 R²= .33516762						
F(4,42)=5.2935 p<.00152 Std.Error of estimate						
	BETA	St. Err. of BETA	B	St. Err. of B	t(42)	p-level
Intercpt			58.60	14.83	3.95	0.00
υ2	0.3256	0.2	8.91	4.34	2.05	0.05
C2R	0.2906	0.2	0.05	0.03	1.83	0.07
L/R	-0.1955	0.1	0.00	0.00	-1.51	0.14
A1	-0.1941	0.1	-7.97	5.55	-1.44	0.16

Fig. 1. Regression summary for multivariate linear regression of all variables vs. age. Male subjects. Forward stepwise analysis

Multivariate analysis including principal component determination and nonlinear regression of age respect to PC1 and PC2 (equation 6). Led to a further improvement in prediction quality (r=0.77; figure 2).
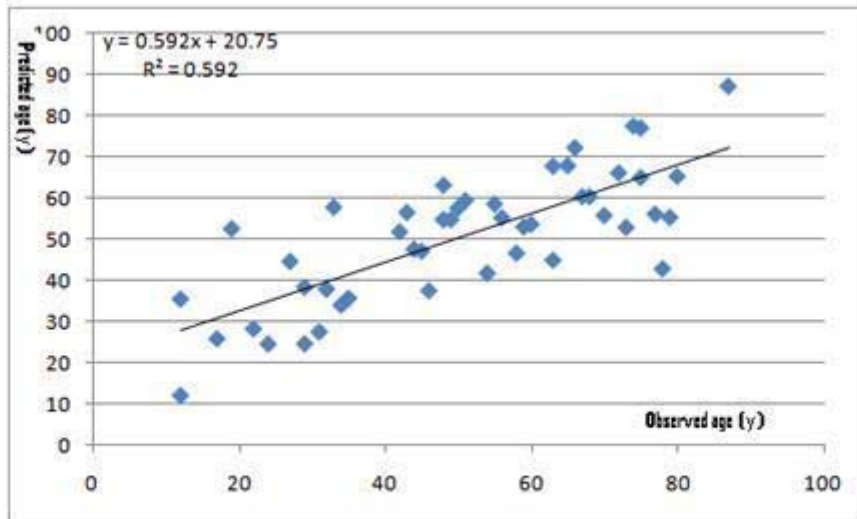
Fig. 2. Scatterplot with observed vs. predicted ages obtained from the nonlinear model with principal components PC1 and PC2. Male subjects

Female subjects. Table 2 represents the correlation matrix for all variables. In this case, several differences with male subjects appeared. As can be noticed, a significant correlation with age was obtained for parameter A2 only. At the same time, similar to male subjects, θ_2 is highly correlated with θ_1.

Table 2. Linear correlations among all variables obtained from the 3-element windkessel model for PPG recordings from female subjects. Number of valid cases N=30. Correlations highlighted in red are significant al $p<0.05$

Variable	Age	A1	A2	A3	A4	A5	A6	C1R	C2R	L/R	θ_1	θ_2
Age	1	.30	.44	.14	.22	.00	-.05	.07	-.11	-.26	.35	.14
A1	.30	1	-.05	.05	-.07	.03	.19	-.07	.08	-.03	-.13	.03
A2	.44	-.05	1	.25	-.04	-.13	.69	-.24	-.09	-.04	.57	.13
A3	.14	.05	.25	1	-.11	.63	-.43	.93	-.03	-.03	-.25	-.25
A4	.22	-.07	-.04	-.11	1	-.13	.36	-.11	-.44	-.21	.47	.47
A5	.00	.03	-.13	.63	-.13	1	-.45	.63	-.05	-.03	-.38	-.45
A6	-.05	.19	.69	-.43	.36	-.45	1	-.43	-.08	.00	.09	.22
C1R	0.07	-.07	-.24	.93	-.11	.63	-.43	1	-.04	.05	-.26	-.31
C2R	-.11	.08	-.09	-.03	-.44	-.05	-.08	-.04	1	.65	-.35	-.22
L/R	-.26	-.03	-.04	-.03	-.21	-.03	.00	.05	.65	1	.03	.27
θ_1	.35	-.13	.57	-.25	.47	-.38	.09	-.26	-.35	.03	1	.82
θ_2	.14	.03	.13	-.25	.47	-.45	.22	-.31	-.22	.27	.82	1

The high correlation between C_1R and A_3 observed for male subjects is still present among female subjects.

The results of multivariate analysis for female subjects are summarized in figure 3.

Regression Summary for Dependent Variable: VAR1 (uy.sta) R= .83733341 R²= .70112723 Adjusted R²= .60603135 F(7,22)=7.3728 p<.00013 Std.Error of estimate: 15.303		St. Err.		St. Err.		
	BETA	of BETA	B	of B	t(22)	p-level
Intercpt			22.86	10.19	2.24	0.04
A2	0.6	0.12	39619.95	8045.56	4.92	0.00
A3	-0.3	0.20	-5.03	3.34	-1.50	0.15
A6	0.3	0.13	806.15	331.20	2.43	0.02
A5	5.0	1.26	7.13	1.79	3.99	0.00
C1R	-4.7	1.26	0.00	0.00	-3.77	0.00
C2R	-0.5	0.16	-0.01	0.00	-3.31	0.00
L/R	0.4	0.17	0.02	0.01	2.42	0.02

Fig. 3. Regression summary for multivariate linear regression of all variables vs. age. Female subjects. Forward stepwise analysis

As observed, both the two compliances and 4 coefficients from model (1) are contributing to the linear multivariate model. Salient here is the sharp improvement obtained with the multivariate regression. In terms of probability it changed from $p=0.0441$ to $p=0.00013$ when passing from univariate to multivariate regression.

Multivariate analysis including principal component determination and nonlinear regression of age with respect to PC1 and PC2 (equation 6) led to a similarly high prediction quality (r=0.69; figure 4).
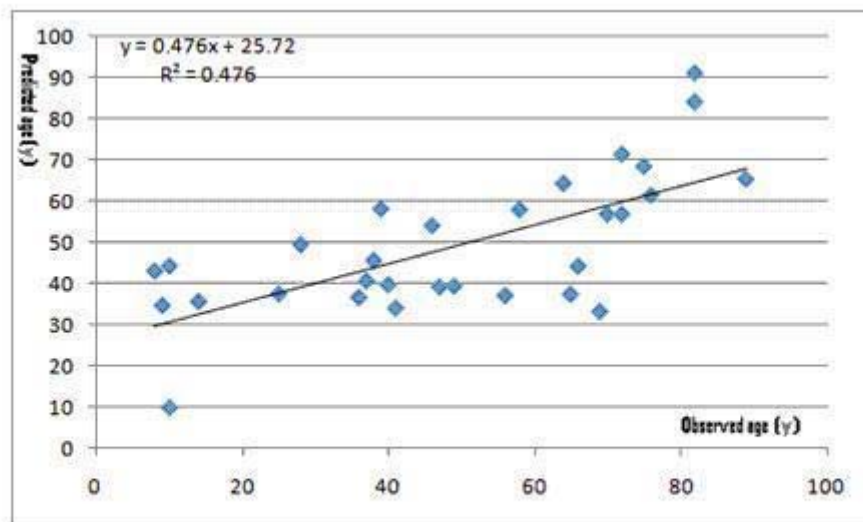

Fig. 4. Scatterplot with observed vs. predicted ages obtained from the nonlinear model with principal components PC1 and PC2. Female subjects

DISCUSSION

In this work, we tried to get an answer to the rather naïve question of what information can be obtained if we apply the 3-element windkessel model to a

sample of PPG recordings with no possibility of recording other variables such as peripheral resistance. According to our results the answer heavily depends on the gender of recorded subjects: More variables retain a strong univariate association with age among male subjects whereas a surprisingly high correlation can be obtained in a linear multiple regression for female subjects. Nonlinear regression of age against PC1 and PC2 leads to comparable results for both genders.

In this study based on the 3-elements windkessel model, versions of both resistive and oscillatory phase velocities are introduced. Since these do not depend upon peripheral resistance, a certain advantage respect to oscillatory compliance. Our results showed that both velocities (resistive and oscillatory) were highly correlated to each other among both female and male subjects. It reached significant values with age among male subjects.

That strong associations are found, especially in multivariate analysis with female subjects, as well as in nonlinear analysis, is noteworthy. We do not exclude the possibility that some differences will be erased as the sample size is increased. However, at this stage results remain encouraging, especially because they illustrated other potentialities of the 3-element windkessel model.

Even when the structure of the correlation matrices differed among genders, the introduction of two phase velocities into the model, as well as he application of nonlinear multivariate regression respect to principal components clearly suggests that the 3-element windkessel model is a promising platform for further analysis of PPG signals.

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