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Estimation of pressure pulse amplification between aorta and brachial artery using stepwise multiple regression models

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Abstract

The pressure pulse is amplified between the aorta and peripheral sites. This study compares two methods to estimate pressure pulse amplification (PPA) between the aorta and the brachial artery. *Method 1*: PPA was determined from a multi-parameter linear regression of subject parameters (gender, age, height, weight, heart rate (HR), brachial systolic pressure (BSP), diastolic pressure (BDP), mean pressure (MP)). *Method 2*: PPA was calculated from central aortic pressure waveforms (CW) estimated from the same subject parameters. The sample population (1421 male, 992 female) was selected from a database where aortic pressure was estimated by mathematical transformation of a peripheral (radial) pulse calibrated to sphygmomanometric BSP and BDP. The two methods were consistent in showing HR and MP as the most important parameters to estimate PPA. Correlation coefficients (R^2) of 0.48 (method 1) and 0.44 (method 2) were obtained using height, weight, HR, BSP, BDP and age. Inclusion of MP increased R^2 to 0.77 (method 1) and 0.71 (method 2). This study shows that databases containing peripheral and central aortic pressure waveforms can be used to construct multiple regression models for PPA estimation. These models could be applied to studies of similar subject groups where peripheral waveforms may not be available.

Keywords: pulse pressure amplification, linear regression model, central aortic blood pressure

1. Introduction

Since the introduction of the cuff sphygmomanometer in the late 19th century, it has been possible to measure arterial systolic and diastolic blood pressures non-invasively. With oscillometric techniques it is now also possible to measure mean arterial pressure accurately (Yamakoshi *et al* 1982, Lehmann *et al* 1998). Non-invasive measurements of blood pressure are obtained most commonly in the arm. In contrast to the arterial mean pressure that varies very little throughout the large arterial vasculature, systolic pressure can vary significantly at different locations due to the haemodynamic characteristics of the subject (Nichols *et al* 1998). Diastolic pressure may also vary but to a much lesser extent. Since the introduction of a generalized transfer function between the aorta and radial artery (Karamanoglu *et al* 1993, Chen *et al* 1997), it has been possible to estimate central aortic pressures with reasonable accuracy from the radial pulse (Pauca *et al* 2001). Pressure pulse amplification (PPA) is defined as the ratio between brachial pulse pressure and central pulse pressure. PPA is not always available because the recording of the peripheral (brachial or radial) waveform is not a common practice and previous blood pressure studies did not measure the radial waveform. To make a retrospective analysis of previous studies from a central pressure perspective possible we propose the estimation of PPA from parameters more readily available.

This study compares two methods to estimate PPA when the radial blood pressure waveform is not available, by utilizing parameters estimated from databases containing both measured radial and derived aortic pressure waveforms. The two estimation methods are based on subject parameters—gender, age, height, weight, heart rate (HR), brachial systolic pressure (BSP), brachial diastolic pressure (BDP) and mean arterial pressure (MP). These (and other) abbreviations are listed in table 1.

2. Methods

The analysis was performed in three consecutive stages. Initially, a database of central aortic blood pressure waveform (CW) measurements was established from measurements where the central blood pressure was estimated from the peripheral (radial) pulse using a mathematical transfer function (Karamanoglu *et al* 1993, Chen *et al* 1997) (SphygmoCor, AtCor, Australia). Secondly the PPA predictor parameters were orthogonalized using the Gram–Smith algorithm (Draper and Smith 1981). Finally two regression models were created to estimate PPA. The first method was a direct multiparameter linear regression. In the second method, PPA was calculated from the CWs, which were estimated by linear regression of the Fourier components of the waveform and the subject parameters. Both methods were validated using a 16 fold cross validation technique (Hastie *et al* 2001).

2.1. Centralized database

A centralized and integrated database was created. Data were collected from seven different studies of central pressure conducted in different sites in Australia. The population includes both healthy and diseased subjects. The complete range of conditions for the diseased subjects is not known. These data included subjects' gender, height, weight, HR, age, BSP, BDP, MP, central systolic pressure (CSP), central diastolic pressure (CDP), radial pulse wave (RW) and CW, along with other parameters not used in this study. A total of 2413 (1421 males aged 20 to 101 yr, mean 59.5 yr; 992 females aged 20 to 100 yr, mean 58.8 yr) measurements were available after the selection made on the following criteria: (i) age $>$ 20 yr and (ii) for subjects with multiple measurements the record that corresponded to the median heart rate was used.

Table 1. Listing of abbreviations.

Term	Abbreviation
Pressure pulse amplification	PPA
Brachial systolic pressure	BSP
Brachial diastolic pressure	BDP
Radial blood pressure waveform	RW
Brachial form factor	BFF
Central systolic pressure	CSP
Central diastolic pressure	CDP
Central aortic blood pressure waveform	CW
Arterial mean pressure	MP
Heart rate	HR
Orthogonalized age	age+
Orthogonalized height	height+
Orthogonalized weight	weight+
Orthogonalized heart rate	HR+
Orthogonalized brachial systolic pressure	BSP+
Orthogonalized brachial diastolic pressure	BDP+
Orthogonalized brachial form factor	BFF+
Error deviation from zero	err0
Error standard deviation	errSD
Correlation coefficient	R^2

Table 2. Sample population characteristics. All values are shown as mean ± SD.

	Males	Females	Total
Subjects	1421	992	2413
Age (yr)	59.5 (15.2)	58.8 (15.9)	59.2 (15.5)
BSP (mmHg)	138.7 (21.3)	137.8 (22.3)	138.3 (21.7)
BDP (mmHg)	76.2 (11.4)	76.7 (11.7)	76.4 (11.5)
HR (bpm)	68.4 (12.3)	68.6 (12.4)	68.5 (12.3)

The age criterion was necessary because the brachial to central general transfer function was determined for adults only (Karamanoglu *et al* 1993, Chen *et al* 1997).

Figure 1 and table 2 present the characteristics of the final sample used for this study. The data were imported into Matlab (Mathworks, Inc., USA), into Stata 6.0 (Stata Corporation, TX, USA), and into Mathematica 5.0.1 (Wolfram Research, Inc.) for analysis.

2.2. Orthogonalization of predictor parameters

The parameters used for estimation were gender, age, height, weight, BSP, BDP, HR and brachial form factor (BFF) calculated as $\mathrm{BFF} = (\mathrm{MP} - \mathrm{BDP})/(\mathrm{BSP} - \mathrm{BDP})$.

BFF was used instead of MP because it is an indicator of the average of the waveform independent of absolute blood pressure values.

All parameters except gender were orthogonalized before being used as predictor parameters to eliminate their cross correlation and to make their contribution to the estimation mutually independent. The orthogonalization process was done using the Gram–Smith algorithm (Draper and Smith 1981). The order proposed for orthogonalization was as follows: height, weight, HR, BSP, BDP, age and BFF. Orthogonal predictor parameters are referred to

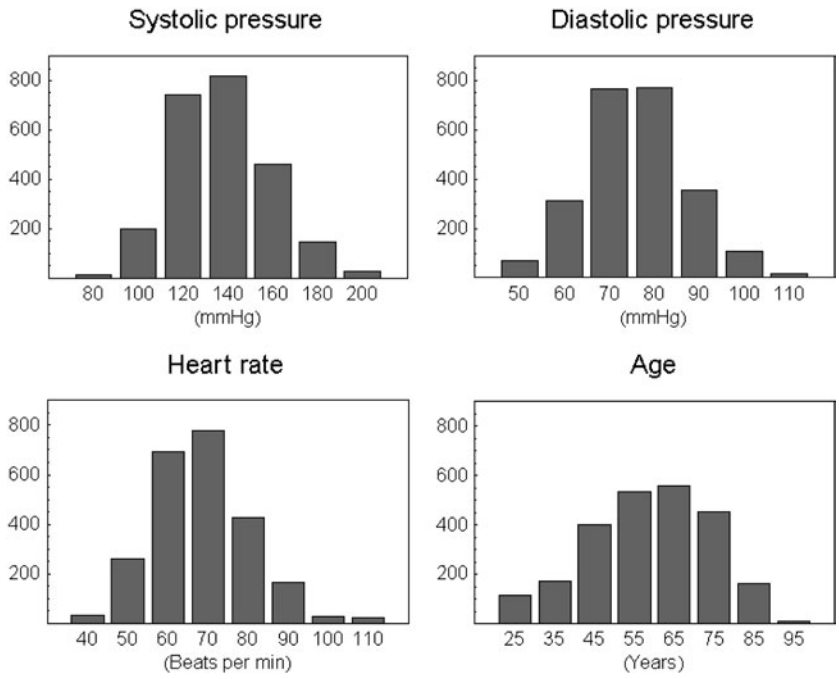

Figure 1. Sample population characteristics. Histograms are given for the distribution of systolic pressure, diastolic pressure, heart rate and age. Vertical axis represents the count of subjects for each category.

as height+, weight+, HR+, BSP+, BDP+, age+ and BFF+. Gender was not included in the orthogonalization process as it is a categorical variable. BFF was the last parameter to be orthogonalized because it was not always available (in many studies, true MP is not always measured). Its contribution after accounting for all the previous parameters is of interest because it indicates the importance of including MP for the estimation of PPA. Age was the second last variable in order to determine its contribution in the estimation of PPA after accounting for all previous parameters. As with the parameters previously mentioned the order is such as to present the effect of a certain parameter after accounting for the effect of the previous ones. The order of the parameters does not affect the estimation process or the final estimation. However, it does affect the contribution of each individual orthogonal parameter because the order determines the other parameters against which it is orthogonalized.

2.3. Regression models

PPA is defined as

$$\mathrm{PPA} = (\mathrm{BSP} - \mathrm{BDP})/(\mathrm{CSP} - \mathrm{CDP}).$$

Two multi-parameter linear regression models were created to estimate PPA from all orthogonal predictor parameters and gender.

The first model was a multi-parameter linear regression (method 1) where PPA was of the form

$$\mathrm{PPA} = a + b_1\mathrm{height} + b_2\mathrm{weight} + b_3\mathrm{HR} + \cdots \quad \text{where } a, b_1, b_2, b_3, \ldots, \text{are constants.}$$

The model was implemented using Stata 6.0. The regression was initially done only for height, weight and HR, and then repeated including a new additional predictor parameter each time. The correlation coefficient (R^2) was calculated for each regression.

The second approach was to calculate PPA from estimated CW (method 2). Estimation of CWs from predictor parameters is a multi-step process in which each of the first 12 Fourier components is predicted using a linear regression model of the subject parameters. Initially, CWs were normalized with BSP and BDP corresponding to 1 and 0 respectively. The first twelve Fourier components of CW were obtained by fast Fourier transformation (FFT). A model for each FFT component of the CW was constructed by multi-parameter linear regressions implemented using Stata 6.0. Normalized waveforms were obtained by inverse Fourier transformation on the twelve estimated components. Finally the waves were denormalized to absolute values. CW is estimated from a number of frequency components less than the number of sample points of the wave. This is possible as the high-frequency information is low (Nichols *et al* 1998). Two indicators were used to assess the quality of the estimated CW: deviation from zero (err0) and error standard deviation (errSD). Both are time-dependent functions. err0 was calculated as

$$\text{err0}(k) = \Sigma(\text{CWi}(k) - \text{estimated CWi}(k))/N; \quad \text{where } 1 \leqslant i \leqslant N, N$$

is the number of measurements and $1 \leqslant k \leqslant M$, M is the number of sampling points and errSD was calculated as

$$\text{errSD}^2(k) = [\Sigma(\text{CWi}(k) - \text{estimated CWi}(k))^2]/(N-1)^2$$

PPA was calculated from the estimated CWs:

$$\text{PPA} = (\text{BSP} - \text{BDP})/(\text{central systolic from estimated CW} - \text{central diastolic from estimated CW}).$$

The method was repeated including a new additional predictor parameter each time and the correlation coefficient (R^2) was calculated for each regression.

Each model was validated using a 16-fold cross validation in which the initial data are divided into sixteen similar size datasets. Fifteen of the sets are used to estimate the model and the remaining set is used as testing set. The process is repeated for each of the sixteen sets. A 16-fold partition was selected as the most appropriate for our data set of size 2413. The analysis of errors was based on the cross validated data.

3. Results

Both methods were consistent in showing the dependency of PPA with height, weight, HR, BSP, BDP, age and BFF; although, estimations vary depending on the regression method used. The results obtained by direct linear regression (method 1) will be presented followed by the results obtained by calculation of PPA from the estimated CW (method 2).

The multi-parameter linear regression model based on orthogonalized subject parameters shows a significant dependency of PPA on height+, weight+, HR+, BSP+, BDP+, BFF+ and age+. Table 3 shows the coefficients for the regression where all parameters are significant at the $p < 0.05$ level. Table 4 shows how R^2 (which indicates how well PPA can be predicted) increases by the inclusion of each of the predictor parameters. As the predictor parameters are orthogonal, it is possible to sum each individual R^2. Age, after accounting for height, weight, HR, BSP and BDP, is a significant contributor to R^2, therefore to the estimation of PPA. R^2 increases by 0.29 by including BFF, after accounting for all the previous parameters. It is important to note that $R^2 = 0.475$ for prediction without the need of the waveform or

Table 3. Coefficients for linear regression of orthogonal predictor parameters height+, weight+, HR+, BSP+, BDP+, age+ and BFF+. 'Mean' is the average value of PPA.

PPA	Coefficient	Standard error	p	(95% confidence interval)	
Height+	0.001 8388	0.000 1625	0.000	0.001 5201	0.002 1575
Weight+	−0.000 2568	0.000 1138	0.024	−0.000 4800	−0.000 0335
HR+	0.007 8545	0.000 1469	0.000	0.007 5665	0.008 1424
BSP+	−0.002 5296	0.000 0827	0.000	−0.002 6918	−0.002 3675
BDP+	−0.000 5212	0.000 1838	0.005	−0.000 8817	−0.000 1608
Age+	−0.003 9847	0.000 1300	0.000	−0.004 2397	−0.003 7297
BFF+	−2.236 4920	0.040 9840	0.000	−2.316 8600	−2.156 1240
Mean	1.324 7960	0.001 7867	0.000	1.321 2920	1.328 2990

Table 4. Comparison of correlation coefficients (R^2) for the two regression methods and for the inclusion of new predictor parameters. Cumulative R^2 is the sum of R^2 for each additional parameter.

	Method 1		Method 2	
Predictor	R^2	Cumulative R^2	R^2	Cumulative R^2
Height+	0.0125	0.0125	0.0151	0.0151
Weight+	0.0005	0.0130	0.0008	0.0159
HR+	0.2788	0.2918	0.2366	0.2525
BSP+	0.0912	0.3830	0.0933	0.3458
BDP+	0.0008	0.3838	−0.0018	0.3440
Age+	0.0915	0.4753	0.0952	0.4392
BFF+	0.2903	0.7656	0.2714	0.7106
Gender	0.0001	0.7657	0.0001	0.7107

BFF. Gender was not significant, with a $p = 0.357$, when included in a regression with all predictors. R^2 increased only by 0.0001 when gender was included in the regression with all other predictors.

The coefficients of a regression based on the original predictor parameters (not orthogonalized) are shown in table 5. There is a marked difference in significance of the parameters. This is due to the fact that cross-correlation between predictor parameters is eliminated during the orthogonalization process. The total R^2 and the $p > F$ (seven degrees of freedom, 2405 samples) (F distribution) for regressions using orthogonal and non-orthogonal predictor parameters are identical, as the predictor parameters have not been changed, only linearly transformed.

The second method to estimate PPA is based on the estimated CW. CWs could be reconstructed from twelve Fourier components estimated by linear regressions using orthogonal predictor parameters. The analysis of the estimation of CW is presented initially followed by the analysis of the calculated PPA. The CWs prediction errors decrease with the inclusion of predictor parameters. Figure 2 shows the errors for predictions using the first 3 (height+, weight+, HR+), 4 (height+, weight+, HR+, BSP+), 5 (height+, weight+, HR+, BSP+, BDP+) and 6 (height+, weight+, HR+, BSP+, BDP+, age+) parameters. The errors for predictions using the first six parameters (as before) and BFF+ are shown in figure 3. By introducing BFF+ there is a marked reduction in error after 0.1 s corresponding to the first systolic inflection. The error reduction at 0.27 s (corresponding to systolic peak) is of the

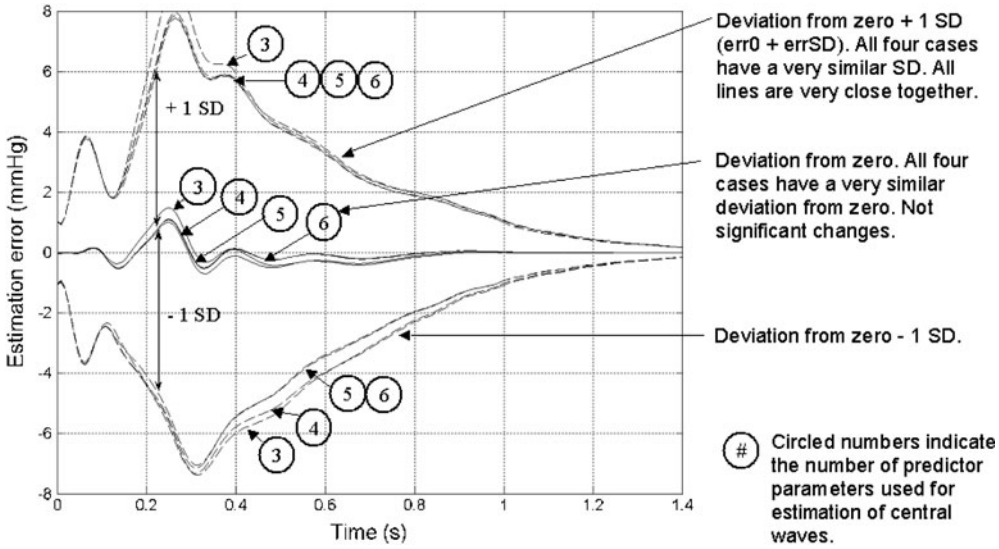

Figure 2. CW estimation error: deviation from zero (err0) ± standard deviation (errSD). The different graphs correspond to four estimations using sets of 3, 4, 5 and 6 predictor parameters. 1: height+, weight+, HR+; 2: height+, weight+, HR+, BSP; 3: height+, weight+, HR+, BSP+, BDP+; 4: height+, weight+, HR+, BSP+, BDP+, age+. Circled numbers indicate the numbers of predictor parameters used for estimation of central waves. The error reduces with the inclusion of each new predictor parameter.

Table 5. Comparison of regression coefficients when orthogonal and original (non-orthogonal) predictor parameters are used. The total correlation coefficients (R^2) for both regressions are identical: 0.48. The predictor parameters are transformed, not changed.

PPA	Coefficient	Standard error	p	(95% confidence interval)	
		Orthogonal predictor parameters			
Height+	0.001 839	0.000 243	0.000	0.0014	0.0023
Weight+	−0.000 257	0.000 170	0.132	−0.0006	0.0001
HR+	0.007 855	0.000 220	0.000	0.0074	0.0083
BSP+	−0.002 530	0.000 124	0.000	−0.0028	−0.0023
BDP+	−0.000 521	0.000 275	0.058	−0.0011	0.0000
Age+	−0.003 985	0.000 195	0.000	−0.0044	−0.0036
Mean	1.324 796	0.002 672	0.000	1.3196	1.3300
		Original			
Height	0.002 943	0.000 324	0.000	0.0023	0.0036
Weight	0.000 376	0.000 172	0.029	0.0000	0.0007
HR	0.007 877	0.000 221	0.000	0.0074	0.0083
BSP	−0.001 075	0.000 159	0.000	−0.0014	−0.0008
BDP	−0.003 077	0.000 302	0.000	−0.0037	−0.0025
Age	−0.003 985	0.000 195	0.000	−0.0044	−0.0036
Mean	0.874 264	0.057 453	0.000	0.7616	0.9869

order of 3 mmHg. Deviation from zero (err0) is almost constant with variation of less than 1 mmHg. Figure 4 shows the space of probable central waves, as well as two typical central pressure waveforms. Systolic pressure lies between 0.2 and 0.3 s from the foot of the wave, which coincides with the area of maximum errSD and err0.

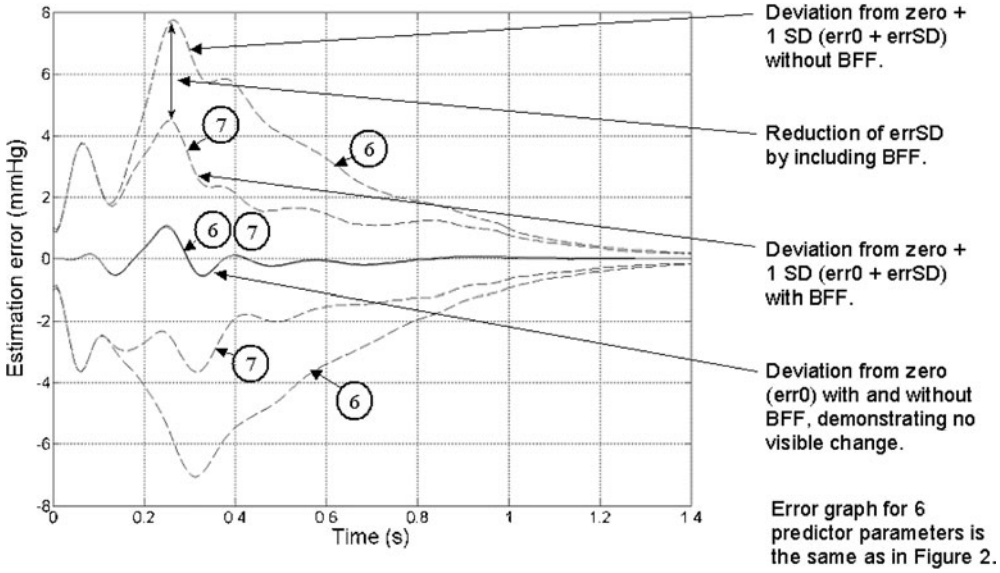

Figure 3. CW estimation error: deviation from zero (err0) ± standard deviation (errSD). The different graphs correspond to two estimations using (1) the same sets of six parameters used in figure 1 (height+, weight+, HR+, BSP+, BDP+, age+) and (2) including BFF+ (height+, weight+, HR+, BSP+, BDP+, age+, BFF+). Circled numbers indicate the numbers of prediction parameters used for estimation of central waves. Note the significant decrease in standard deviation when BFF+ is included.

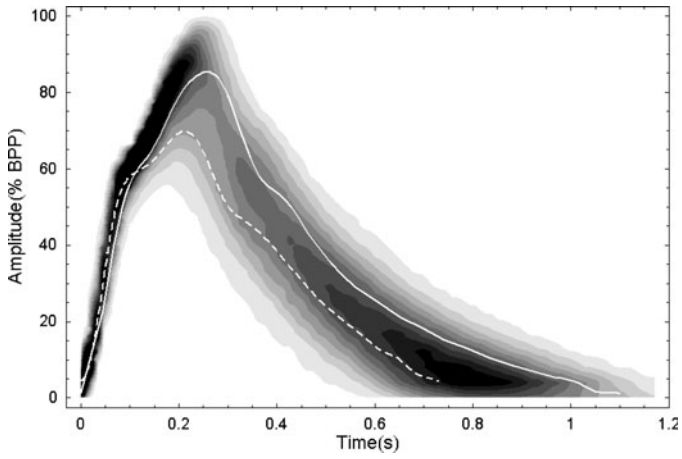

Figure 4. Space of normalized central aortic waves represented as a density plot. Darker areas represent higher probability of a wave in that area. Two typical sample waves are shown on top of the density plot. CWs are normalized to the difference between systolic and diastolic brachial pressures. Space for all subjects in the study ($N = 2413$). BPP: Brachial pulse pressure.

PPA was calculated from the estimated CWs. In a similar way to method 1, the inclusion of each new predictor improves the estimation of PPA. The increment in R^2 for method 2 compared with method 1, for each of the orthogonal predictor parameters, is shown in table 4. Figure 5 shows the error mean and standard error of the estimation for both methods, where method 2 is shown to be a biased estimator of PPA.

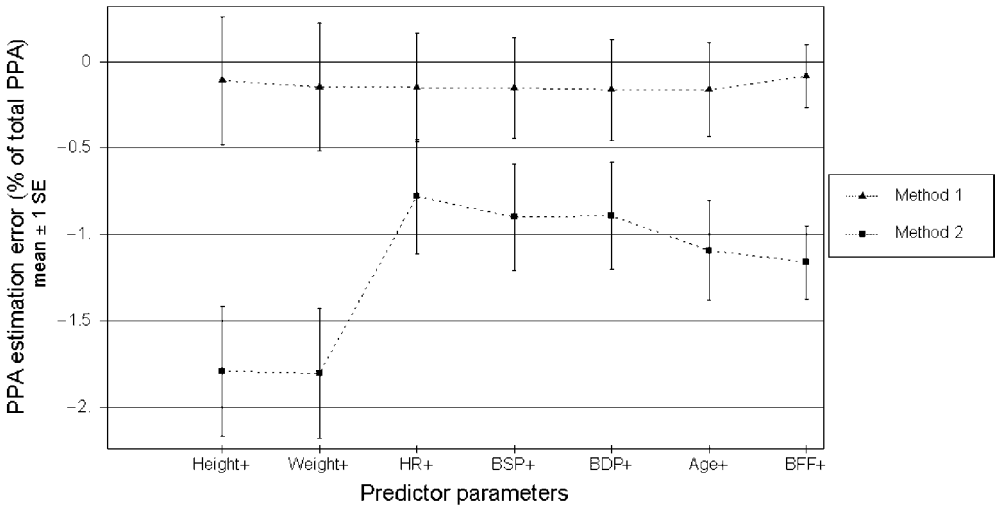

Figure 5. Estimation comparison. Mean ± 1 standard error. Method 2 is a biased estimator of PPA. Method 1: multiparameter linear regression. Method 2: calculation based on estimated central aortic waves. Values estimated from cross-validated data.

4. Discussion

The methodology described in this study provides an analysis of the graded importance, for a specific sequence of parameters, of height, weight, HR, BSP, BDP, age and BFF as predictor parameters for estimating PPA. Although results from the two methods are not identical, they consistently show the importance of HR and BFF as the most significant predictor parameters. The marked dependency of PPA on age agrees with the results from other investigations (Chemla *et al* 2002) where PPA can be derived from the brachial pulse pressure (BPP) as

$$\text{PPA} = \text{BPP}/(\text{BPP} - 15), \text{ where BPP is measured in mmHg.}$$

Because BPP increases with age (Kesteloot and Joossens 1980), PPA will decrease with age and approach unity. This is consistent with our results. The relationship between PPA with BFF has not been previously reported.

The use of orthogonal predictor parameters facilitates the understanding of the importance of each parameter individually. The main difficulties in applying this method are the need of transforming the original parameters—using the Gram–Smith algorithm—and the arbitrary selection of the parameter's order. The Gram–Smith algorithm, although simple, is computationally heavy, making it impractical to use with large datasets. The orthogonalization order of the predictor parameters could change their relative importance, but overall does not change the final estimation characteristics. Therefore, a specific order could 'favour' certain parameters presenting it as more important. That is, it is up to the investigator to decide if parameter *X1* depends on *X2* or vice versa, where *X1* and *X2* are any of the regression parameters. In this study the order was so as to emphasize the important of age accounting for height, weight, HR, BSP and BDP. It is important to note that for estimation of PPA, not for analysis of predictor's importance, it is not necessary to use orthogonal parameters, as the total regression characteristics remain unchanged.

From the two methods presented, the direct linear regression method is easier to implement with better predictions. It is also easier to estimate PPA once the regression is known because

there is no need for inverse Fourier transformation. It can also be implemented in commercially available statistic packages directly.

For this specific study, the linear regression method was a better estimator of PPA, although this is not necessarily always the case. The estimation of other parameters, for example, augmentation index (amount of late systolic pressure augmentation) or mean systolic pressure, could be better estimated using method 2. The characteristics of the population can also affect the models. Models targeted to specific populations, for example, diabetics, pregnant women, or young healthy adults, could generate better estimation of central parameters or reveal relationships between the different parameters specific for each subpopulation. This is still to be studied, as well as estimation using other methodologies such as non-linear regression.

Although linear regression is a simple approach to estimate PPA, the correlation coefficient of the estimation is high, with an R^2 of approximately 0.48 without including BFF and over 0.77 when BFF was included. These are estimations of PPA, not of central systolic pressures, which will be much more closely correlated ($R^2 = 0.95$ without BFF and $R^2 = 0.99$ with BFF − values calculated for the same data). These high correlation values suggest that the only additional requirement to estimate central systolic and central diastolic pressures is a measure of BFF, in addition to the current measurements of BSP, BDP and the patient's characteristics. This could provide a reasonable first-order approximate estimation of central aortic pressure when only systolic and diastolic pressure are required. It does not, however, replace the recording of the radial artery waveform when waveform features are required.

The estimation of PPA and central pressures from subject parameters when no waveform is available can enable retrospective analysis of epidemiological data from existing studies. Blood pressure, measured in the arm, is one of the most important indicators of cardiovascular risk (Gerova *et al* 1999, Blacher *et al* 2000, Sesso *et al* 2000, Asmar *et al* 2001, Glynn *et al* 2002), but the estimation of the risk is still to be analysed from a central aortic pressure perspective.

Although the optimum way to estimate central aortic pressure non-invasively is still by the use of a peripheral (radial) waveform; in its absence, there may be advantages in using estimated central pressures rather than not accounting for the marked differences in systolic and pulse pressure between measured pressures in the arm and pressures in the ascending aorta.

5. Conclusion

As the use of central aortic blood pressure becomes more accepted, the need to understand its significance in terms of cardiovascular risk will also increase. We have proposed two methods to estimate PPA using linear regressions based on subject parameters. This approach may provide a new perspective to understand the importance of central blood pressure as a cardiovascular risk indicator in blood pressure studies where pulse waveform data are not available. Furthermore, the non-invasive data on central aortic blood pressure estimated from the peripheral (radial) pulse available for large groups can enable multi-regression models to be tailored to specific subpopulations where age-related arterial properties may become modified (e.g. hypertension, diabetes, heart failure, pre-eclampsia in pregnancy).

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