Assessment of baroreflex sensitivity by continuous noninvasive monitoring of peripheral and central aortic pressure

Zahra Kouchaki, Mark Butlin, Ahmed Qasem, and Alberto P Avolio

Abstract— **Noninvasive assessment of baroreceptor sensitivity (BRS) facilitates clinical investigation of autonomic function. The spontaneous sequence method estimates BRS using the continuous measurement of arterial pressure in the finger. Since the baroreceptors are centrally located (aortic arch, carotid arteries), this study assessed the use of a continuous aortic pressure signal derived from the peripheral pressure pulse to compute the BRS from changes in systolic pressure (SBP) and pulse interval (PI). BRS computed from central aortic (cBRS) and peripheral pressure (pBRS) was calculated in 12 healthy subjects (25-62 years, 7 females). The difference between pBRS and cBRS was calculated for four levels of pulse lags between changes in SBP and PI. For each lag and for the pooled data for all lags, cBRS was significantly correlated with pBRS (r^2=0.82). The within subject difference ranged from -41.2% to 59.2%. This difference was not related to age, gender of hemodynamic parameters (systolic or diastolic pressure, heart rate, aortic pulse wave velocity). However 18.2% of the variance was due to the difference in the number of spontaneous pulse sequences used to determine values of cBRS and pBRS. The differences between pBRS and cBRS are in the range of values of BRS as those found, in other studies, to discriminate between patient groups with different levels of autonomic function. Findings of this study suggest that, given the heart rate dependent amplification of the arterial pressure pulse between the central aorta and the peripheral limbs, BRS determined from central aortic pressure derived from the peripheral pulse may provide an improved method for noninvasive assessment of baroreceptor function**

I. INTRODUCTION

The implementation of the Peňáz technique involving the principle of vascular unloading and servo-controlled pumps led to the development of finger cuff devices for the continuous measurement of arterial pressure [1]–[4]. The ability for continuous monitoring of arterial pressure [5] enabled investigations assessing blood pressure variability in short (beat-to beat) and long (minutes, hours) time scales [6], [7]. In combination with beat-to-beat changes in pulse interval (PI), techniques were developed that facilitated the assessment of baroreceptor function, specifically the cardio-vagal arc of the baroreceptor control system [8], [9].

Baroreflex sensitivity (BRS) is determined by affecting a rapid change in arterial pressure by intra-venous injection of a vasoactive agent (e.g. bolus injection of phenylephrine) and measuring the concomitant change in heart rate (or PI) [10]. This, however, involves invasive intra-arterial monitoring of blood pressure, although recordings are taken over a relatively short period. With recordings over longer periods, BRS can be determined from spontaneous changes in systolic blood pressure (SBP) and PI. Thus, concomitant variations of SBP and PI can be analysed as time varying functions. BRS is then quantified as the ratio of spectral estimates of PI and SBP [7], [10]. BRS can also be determined from a relatively more simple analysis of the time-related changes in SBP and PI, where the changes occur in contiguous cardiac cycles. It has been shown that concomitant changes that occur in sequences of cardiac cycles are related to spontaneous activity of baroreceptors [8], [9]. BRS can be quantified from the slopes of the regression lines obtained between changes in PI and SBP. With the ability for continuous long-term monitoring of finger SBP, the sequence technique of BRS estimation has been employed in clinical studies of baroreceptor function in a range of cardiovascular conditions [6], [11]–[13].

However, although peripheral locations (e.g. finger) greatly facilitate the continuous non-invasive recording of SBP, the baroreceptors are located centrally (carotid arteries, aortic arch), a considerable distance from the site of measurement. Importantly, there can be significant difference between central and peripheral SBP due to pressure pulse amplification [14]–[16]. In addition, the frequency characteristics of the transfer function between the aorta and peripheral locations makes the amplification heart rate dependent [17]. Hence, comparison of BRS estimated from central SBP and heart rate (or PI) and peripheral SBP would involve a non-linear effect due to the heart rate depended relationship between central and peripheral SBP.

This comparison can now be assessed using technology that allows non-invasive estimation of central aortic pressure from the peripheral arterial pulse [14], [15]. These techniques are used in this study, which investigates BRS determined using the sequence technique from a series of cardiac cycles showing spontaneous changes in PI and SBP obtained from the peripheral pulse and from the estimated central aortic pulse.

II. EXPERIMENTAL PROCEDURES

A. Human subjects

This study was conducted in 12 healthy adult subjects (age 25-62 years, 7 women). The study was approved by the University Human Ethics Committee and all subjects participated with informed consent. Measurements were taken in

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the morning between 8 am and 12 noon and subjects were requested to take only a light breakfast and to refrain from intake of caffeine.

B. Data acquisition and analysis

Continuous finger pressure and ECG signals were acquired with the subject in supine position for a period of 15 minutes. Finger pressure was recorded using the Peňáz technique (Finometer Pro, Finapres Medical Systems, Amsterdam). The close proximity and similarity between radial and finger sites [17] enables the application of the finger aortic pressure to derive central pressure signals using a radial to central aortic generalized transfer function [14], [18]. The generalised transfer function was used as it is a commercially available option for clinical implementation (SphygmoCor, AtCor Medical), has been shown to track central aortic pressure over a large range of pressure and heart rate changes as produced by valsalva manoeuvre [14] and individualized transfer functions offer only marginal improvements [14]. The finger pressure and derived central pressure from finger pressure were applied for calculation of pBRS and cBRS respectively.

The spontaneous sequence technique was applied for computation of BRS using PI and SBP signals [19]. BRS was determined from the slopes of linear relationships of PI and SBP of contiguous cardiac cycles, where SBP and PI change in the same direction. BRS was computed for a lag of 0,1,2,3 cardiac cycles between PI and SBP. Computations were performed for sequences with at least 3 pulse exhibiting concomitant changes in PI and SBP using thresholds of 1ms for PI, 1 mmHg for SBP and correlation coefficient of 0.8 for the linear regression between PI and SBP [19]. BRS was determined as the average of the magnitude of positive and negative slopes of the regression lines of PI and SBP in the sequences found for the complete recording. BRS was computed for a range of lags (L0, L1, L2 L3) between pulse changes in PI and SBP. L0 refers to changes in PI and SBP for the same cardiac cycle, L1 for a change in SBP associated with change in PI for the next beat; similarly for L2 and L3. The BRS computed from the central and peripheral pressure signals is designated cBRS and pBRS.

Aortic pulse wave velocity was measured between the carotid and femoral artery using tonometry with the SphygmoCor device using standard methodology of foot-to-foot pulse delay and linear distance between the sites [20].

III. RESULTS

A. Differences in BRS computed from peripheral and central aortic pressure

For all lags there was a significant correlation between cBRS and pBRS. A typical scatter plot is shown in Fig. 1 for L0 and for the pooled data for all lags. The Bland-Altman plot (Fig. 2) shows a broad scatter of the differences (pBRS-cBRS) being spread around zero, where in some subjects cBRS is higher than pBRS and in others lower.

When pooling all measurements for all lags (total of 48 observations) the percentage difference between cBRS and

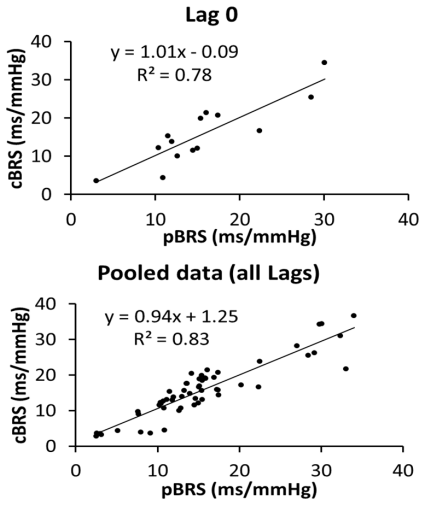

Fig. 1. Regression between cBRS (y) determined from central aortic pressure and pBRS (x) from peripheral (finger) pressure for Lag 0 (Top) and for the polled data from all lags (bottom).

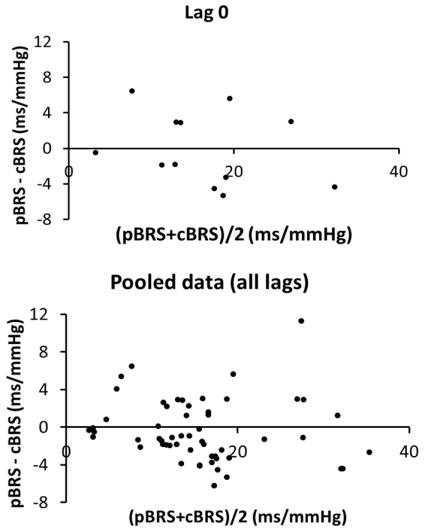

Fig. 2. Bland-Altman plots for differences between pBRS and cBRS as a function of average BRS values for Lag 0 (top) and pooled data (bottom). Mean differences: Lag 0:-0.16±3.98 ms/mmHg; Pooled data: -0.4±3.1 ms/mmHg.

pBRS ranges from 59.2% to -41.2% with a skewed distribution towards the negative values, that is, where cBRS>pBRS. Overall, the differences are distributed in the following manner (Fig. 3):

1) 60.4% of recordings had negative differences (ie cBRS>pBRS)
2) 39.6% of recordings had positive differences (ie cBPR<pBRS)
3) Positive differences are consistent for all lags in 25% (3/12) of subjects and for >2 lags in 33.3% (4/12)
4) Negative differences are consistent for all lags in 42% (5/12) of subjects and for >2 lags in 58% (7/12).
5) Positive difference range: 0.93% to 59.2%; Negative difference range: -1.5% to -41.2%

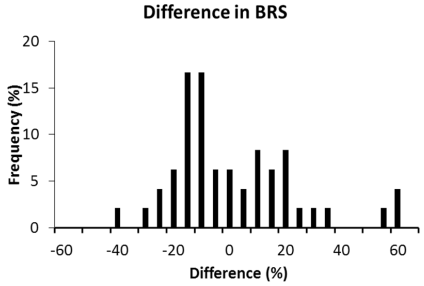

Fig. 3. Distribution of percentage differences between pBRS and cBRS for all lags (L0, L1, L2, L3). Total number of measurements=48; kurtosis=0.93; skewness=0.98.

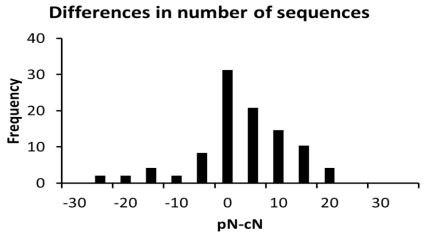

Fig. 4. Distribution of differences between number of sequences for pBRS (pN) and cBRS (cN) for all lags (L0, L1, L2, L3). Total number of measurements=48; median= 0; kurtosis = .03; skewness = -0.72.

B. Number of sequences

The number of sequences calculated as the number of contiguous pulse sequences detected where a change (increase or decrease) in systolic pressure parallels a change in pulse interval. However, due to the particular relationship of amplification between central and peripheral pressures, and also heart rate in an individual subject, the number of sequences included in calculation necessarily differs. For a pulse sequence that shows an increase in PI) with an increase in systolic blood pressure, a particular amplification factor can cause a decrease or no change in central systolic pressure. This results in a different number of sequences used for estimation of BRS from peripheral and central aortic pressure signals.

The number of sequences ranged between 5 and 143 for pBRS and 9 and 162 for cBRS calculations across all subjects. There was a high correlation between the number of sequences for cBPR (cN) and for pBRS (pN) (cN = 0.98pN +0.17 ; r^2=0.91). There was also consistency between the mean values of cN and pN for different lags, although with substantial variation about the mean [cBRS : L0: 36±27; L1: 20±16; L2: 36±16; L3: 38±29; pBRS : L0: 37±26; L1:20±14; L2: 36±17 L3: 36±25].

The distribution of the differences in the number of sequences is skewed towards positive differences (Fig. 4), that is, the mean number of sequences for the computation of cBRS is lower than that for pBRS.

The skewed distribution from the pooled data from all lags is consistent with a general reciprocal relation between the difference of the computed BRS values (pBRS-cBRS) and the difference between the associated number of sequences (pN-cN). For negative BRS differences, 79.3% of values have positive sequence differences; for positive BRS differences 68.4% of values have negative sequence differences. The regression relation between the BRS and sequence differences is shown in Fig. 5. The relation indicates that 18.7% of the variance of the difference in BRS is explained by the difference in the number of sequences used for the computation of the BRS values (r^2=0.187).

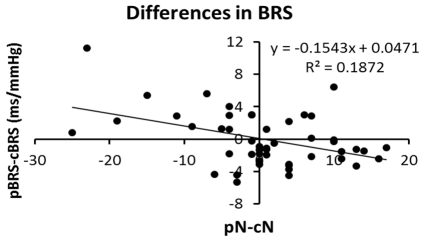

Fig. 5. Relation between differences between pBRS and cBRS and associated difference number of sequence difference (pN-cN.) The difference in number of sequences explained 18.7% of the variance in the BRS differences.

C. BRS differences and other parameters

In an attempt to explore possible correlates to explain the differences in BRS determined from peripheral and central aortic pressure, univariate analysis was performed on the pooled data between the difference of pBRS and cBRS and heart rate, systolic and diastolic blood pressure, age, aortic pulse wave velocity and gender. No statistical correlation was found with any of these parameters.

IV. DISCUSSION

This study addresses the difference between BRS computed from central and peripheral arterial blood pressure signals employing the sequence technique. The principle finding is that while there is a significant correlation between the values of cBRS and pBRS in a cohort of healthy adult subjects, there is a large spread of the differences within individual subjects. In this group of subjects the differences were generally consistent within subjects for all lags. However, the magnitude or direction of differences were not associated with age, gender or any hemodynamic parameters parameter (level of blood pressure, heart rate, pulse wave velocity). This may be due to the age range of subjects not having a wide spread. However, even with this age range it has been shown that the pulse amplification between peripheral and central pressure is age-dependant, with decrease amplification as age advances [21]. The age dependent amplification will necessarily affect the parameters used in the BRS calculation (eg the number of sequences and calculation of slopes), but for this cohort, it does not appear to translate to age dependent differences in the oveall comparison of BRS. A greater number of subjects over a wider age range is required to show this relationship.

Findings shows that the BRS computed using SBP from peripheral and central aorta, for an identical series of cardiac cycles, can vary markedly among individual subjects, with differences spanning a range of -40% to + 60%. Although

small changes for small values of BRS can yield high percentage differences, values as high as 34% difference are obtained for high BRS values of 27ms/mmHg. Since low values of BRS indicate pathological conditions of loss of cardiovascular control of blood pressure, differences in the low range become clinically relevant. Importantly, significant differences are found in the range of BRS values that can differentiate autonomic function between normotensive and hypertensive patients. Values of BRS using the sequence technique and finger pressure have been found to be in the range 7-15 ms/mmHg and differences in the order of 2 ms/mmHg (10-15%) can distinguish between high and low salt intake [11]. This is the range of BRS where large positive and negative differences are found between cBRS and pBRS (Fig. 2). The implication is that changes in BRS that may not be detected using the peripheral pulse may be detected using the central pulse in the same subject. Indeed, some studies suggest that BRS calculated from peripheral pressure measurement of arterial pressure does not detect age-related impairment of baroreceptor function associated with exercise [13].

This study was conducted in healthy subjects to illustrate the concept that using central and peripheral pressure for BRS estimation can give differing results. Further studies in specific groups with known autonomic dysfunction will be required to assess the sensitivity and specificity of cBRS compared to pBRS and to ascertain whether the use of changes in central aortic SBP can provide a more reliable method for non-invasive assessment of baroreceptor function.

V. CONCLUSIONS

Continuous non-invasive beat-to-beat changes in arterial pressure, as measured in a peripheral location (finger), facilitates assessment of baroreceptor function. However, the baroreptors sense pressure in central locations (carotid arteries, aortic arch). The use of changes of systolic pressure from non-invasive estimation of central aortic pressure from the peripheral pulse gives substantial differences for calculated BRS values using the spontaneous sequence technique. The difference can only partially be explained by methodological factors such as difference in number of spontaneous pulse sequences. These studies suggest a possible role of continuous monitoring of non-invasive central aortic pressure for improved assessment of baroreceptor function.

REFERENCES

[1] P. Gizdulich, B. P. Imholz, A. H. van den Meiracker, G. Parati, and K. H. Wesseling, "Finapres tracking of systolic pressure and baroreflex sensitivity improved by waveform filtering." *J Hypertens*, vol. 14, no. 2, pp. 243–250, Feb. 1996.

[2] B. P. Imholz, W. Wieling, G. A. van Montfrans, and K. H. Wesseling, "Fifteen years experience with finger arterial pressure monitoring: assessment of the technology." *Cardiovasc Res*, vol. 38, no. 3, pp. 605–616, Jun. 1998.

[3] J. Penáz, "Criteria for set point estimation in the volume clamp method of blood pressure measurement." *Physiol Res*, vol. 41, no. 1, pp. 5–10, 1992.

[4] K. H. Wesseling, "Finger arterial pressure measurement with finapres." *Z Kardiol*, vol. 85 Suppl 3, pp. 38–44, 1996.

[5] G. P. Molhoek, K. H. Wesseling, J. J. Settels, E. van Vollenhoven, H. W. Weeda, B. de Wit, and A. C. Arntzenius, "Evaluation of the penàz servo-plethysmo-manometer for the continuous, non-invasive measurement of finger blood pressure." *Basic Res Cardiol*, vol. 79, no. 5, pp. 598–609, 1984.

[6] E. Finta, D. Laude, S. Alföldi, C. Farsang, and J.-L. Elghozi, "Effects of rilmenidine on 24-h rhythmicity of blood pressure and spontaneous baroreflex sensitivity in essential hypertensive subjects." *J Hypertens*, vol. 24, no. 8, pp. 1619–1625, Aug. 2006.

[7] P. Castiglioni, G. Parati, S. Omboni, G. Mancia, B. P. Imholz, K. H. Wesseling, and M. Di Rienzo, "Broad-band spectral analysis of 24 h continuous finger blood pressure: comparison with intra-arterial recordings." *Clin Sci (Lond)*, vol. 97, no. 2, pp. 129–139, Aug. 1999.

[8] G. Bertinieri, M. Di Rienzo, A. Cavallazzi, A. U. Ferrari, A. Pedotti, and G. Mancia, "Evaluation of baroreceptor reflex by blood pressure monitoring in unanesthetized cats." *Am J Physiol*, vol. 254, no. 2 Pt 2, pp. H377–H383, Feb. 1988.

[9] A. Frattola, G. Parati, P. Gamba, F. Paleari, G. Mauri, M. Di Rienzo, P. Castiglioni, and G. Mancia, "Time and frequency domain estimates of spontaneous baroreflex sensitivity provide early detection of autonomic dysfunction in diabetes mellitus." *Diabetologia*, vol. 40, no. 12, pp. 1470–1475, Dec. 1997.

[10] H. S. Smyth, P. Sleight, and G. W. Pickering, "Reflex regulation of arterial pressure during sleep in man. a quantitative method of assessing baroreflex sensitivity." *Circ Res*, vol. 24, no. 1, pp. 109–121, Jan. 1969.

[11] P. Coruzzi, G. Parati, L. Brambilla, V. Brambilla, M. Gualerzi, A. Novarini, P. Castiglioni, and M. Di Rienzo, "Effects of salt sensitivity on neural cardiovascular regulation in essential hypertension." *Hypertension*, vol. 46, no. 6, pp. 1321–1326, Dec. 2005.

[12] M. Di Rienzo, G. Parati, P. Castiglioni, R. Tordi, G. Mancia, and A. Pedotti, "Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life." *Am J Physiol Regul Integr Comp Physiol*, vol. 280, no. 3, pp. R744–R751, Mar. 2001.

[13] J. P. Fisher, S. Ogoh, C. Junor, A. Khaja, M. Northrup, and P. J. Fadel, "Spontaneous baroreflex measures are unable to detect age-related impairments in cardiac baroreflex function during dynamic exercise in humans." *Exp Physiol*, vol. 94, no. 4, pp. 447–458, Apr. 2009.

[14] C. H. Chen, E. Nevo, B. Fetics, P. H. Pak, F. C. Yin, W. L. Maughan, and D. A. Kass, "Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function," *Circulation*, vol. 95, no. 7, pp. 1827–36., 1997.

[15] M. Karamanoglu, M. F. O'Rourke, A. P. Avolio, and R. P. Kelly, "An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man," *Eur Heart J*, vol. 14, no. 2, pp. 160–7., 1993.

[16] a. Pauca, S. Wallenhaupt, N. Kon, and W. Tucker, "Does radial artery pressure accurately reflect aortic pressure?" *Chest*, vol. 102, no. 4, pp. 1193–1198, Oct. 1992.

[17] A. P. Avolio, A. Qasem, and Y. J. Park, "Noninvasive estimation of baroreflex sensitivity using pressure pulse amplification," *IEEE Eng Med Biol Mag*, vol. 20, no. 2, pp. 53–8, 2001.

[18] A. L. Pauca, M. F. O'Rourke, and N. D. Kon, "Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform." *Hypertension*, vol. 38, no. 4, pp. 932–7, Oct. 2001.

[19] D. Laude, J.-L. Elghozi, A. Girard, E. Bellard, M. Bouhaddi, P. Castiglioni, C. Cerutti, A. Cividjian, M. Di Rienzo, J.-O. Fortrat, B. Janssen, J. M. Karemaker, G. Lefthériotis, G. Parati, P. B. Persson, A. Porta, L. Quintin, J. Regnard, H. Rüdiger, and H. M. Stauss, "Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the eurobavar study)." *Am J Physiol Regul Integr Comp Physiol*, vol. 286, no. 1, pp. R226–R231, Jan. 2004.

[20] B. M. Pannier, A. P. Avolio, A. Hoeks, G. Mancia, and K. Takazawa, "Methods and devices for measuring arterial compliance in humans." *Am J Hypertens*, vol. 15, no. 8, pp. 743–753, Aug. 2002.

[21] R. Kelly, C. Hayward, A. Avolio, and M. O'Rourke, "Noninvasive determination of age-related changes in the human arterial pulse," *Circulation*, vol. 80, no. 6, pp. 1652–1659, 1989.