A New Approach for Noninvasive Baroreflex Sensitivity Assessment: Preliminary Results

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Abstract

This paper presents a new method for noninvasive assessment of baroreceptor sensitivity (BRS). Using this new method, BRS is estimated by linear regression analysis of the instantaneous values of BRS reorder in a logical ascending sequence. The performance of the new method was compared with measurements of BRS by the traditional bolus phenylephrine method, and other well known noninvasive BRS assessment techniques such as the "spontaneous sequences" and "the correlated modulus" methods in 19 subjects. The BRS of the entire population was 8.31 ± 3.90 ms/mmHg for the phenylephrine method, 8.39 ± 4.21 ms/mmHg for the new method, and 12.6 ± 6.72 ms/mmHg for the spontaneous sequences method. However estimation of BRS using the modulus method was only valid for 5 subjects (weighted coherence >0.5) with BRS of 10.41± 4.18 ms/mmHg. The estimates of BRS derived from the four methods were significantly correlated for these 5 subjects. This result suggests that with further refinements, the new method may be used for reliable noninvasive estimation of BRS.

1. Introduction

Baroreceptor Reflex Sensitivity (BRS) has been traditionally measured by provoking changes in heart rate by manipulation of blood pressure using bolus doses of phenylephrine +/- sodium nitropusside. BRS has shown to be the most sensitive marker of risk of sudden cardiac death in the year after a heart attack [1]. However, this measurement of BRS requires patients to have a needle placed in the main artery in the wrist to measure the blood pressure and to be given drugs to momentarily raise the blood pressure to cause changes in the heart rate. This is normally very safe but is potentially dangerous after heart attacks and for this reason has not become widely used. Alternative noninvasive techniques for BRS estimation have also emerged in recent years to avoid the need for drugs and intravenous cannulation of patients.

For instance, the "spontaneous sequences" method [2] estimates BRS by linear regression analysis of spontaneous sequences of three or more consecutive beats, where changes in systolic blood pressure and the associated next RR intervals have the same direction of change, either up or down. For each valid sequence, the regression coefficient between systolic blood pressure (SBP) and the next pulse beat is calculated as an estimate of the BRS for the sequence. Then the total BRS for the individual is estimated as the mean of the regression coefficients of all the valid sequences.

Other methods for non-invasive BRS estimation are the so-called "spectral analysis" methods, which use power spectral analysis to quantify the relationship between heart rate and arterial blood pressure. Spectral analysis methods can be subdivided into the "modulus" and the "bivariate parametric spectral analysis" methods. The "modulus method" [3] uses the correlated modulus of the transfer function between variations in systolic blood pressure and heart rate in the mid-frequency band (0.07-0.14 Hz) as an estimation of BRS. A variation of this technique is the called "bivariate parametric spectral analysis" method. It is a more complex model of estimation of BRS based on a closed loop feedback system model [4] coupling the fluctuation in heart rate and arterial blood pressure.

Recently, other methods for BRS estimation based on parametric identification [5] obtained using autoregressive moving-average (ARMA) analysis have also been introduced. However, these methods of analysis are mathematically more complex and have several limitations, as described in [5].

This paper presents a new approach for noninvasive estimation of spontaneous BRS. Its performance is compared with measurement of BRS by the traditional bolus phenylephrine method and other well-known noninvasive unprovoked techniques such as the spontaneous sequences and the modulus methods.

2. The new approach to BRS estimation: the logical instantaneous sequence

In this new method, the instantaneous value of BRS is determined for each beat-to-beat as the spontaneous change of systolic blood pressure and its associated change in the next RR interval both having the same

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direction of change either up or down. Then each pair wise of changes in SBP and in RR are plotted in rearranged logical ascending order from lower to higher value having the changes in SBP as the x-axis. The value of BRS is estimated as the slope of the linear regression line of the points of the logical sequence formed, only regression lines with correlation coefficient (r) at least equal to 0.5 were accepted as valid BRS estimates. Figure 1 shows the BRS logical instantaneous sequence. The beat-to-beat changes in SBP and the corresponding beat-to-beat changes in RR intervals are displayed in the first and second graphs.

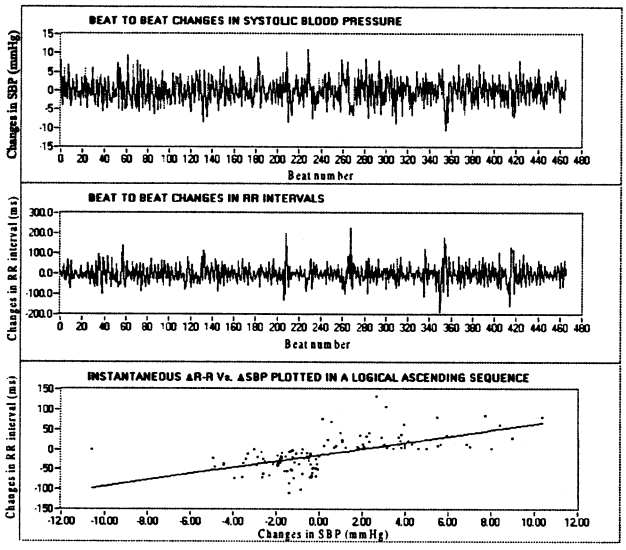

Figure 1. Instantaneous beat-to-beat changes in SBP and their corresponding beat-to-beat changes in the associated next RR intervals plotted in a rearranged logical ascending sequence. BRS is estimated as the slope of the regression line of this logical sequence.

3. Subjects and methods

19 subjects (11 male, mean age 51.5 ± 7.1) were used in the study. All the subjects were day-case admission patients for routine coronary angiography at the Manchester Royal Infirmary. Patients with ages less than 18 years or older than 65 years, sufferers of diabetes mellitus, left ventricular ejection fraction < 40%, Coronary stenoses > 70 % or unable to give informed consent were excluded of the study. Approval from the Central Manchester Local Research Ethics Committee was obtained prior to the study.

3.1. Instrumentation, data recording and protocol

For each subject, data was acquired at 1 kHz using a 16-bit data acquisition card and a dedicated computer program [6]. This followed elective coronary angiography utilizing an attached continuous electrocardiographic (ECG) and monitoring the arterial pressure trace from the subject's right femoral artery sheath, whilst they remained in the catheter laboratory. BRS was measured according to the technique used by Farrel et al [7]. Following an initial dose of 0.2 mg, incremental boluses of Phenylephrine were given intravenously at 15-second intervals until a rise in SBP of 15-40 mmHg was obtained. After a return to the ward, 30 minutes later the BRS was reassessed unprovoked using noninvasive "Portapres" measurements of spontaneous blood pressure changes at rest, combined with a single ECG lead recording of RR intervals over at least ten minute period of quiet breathing. After this, the femoral arterial sheath was removed and the subject was discharged as normal on the same day.

3.2. Assessment of baroreflex control

BRS was estimated invasively by pharmacological manipulation of blood pressure using phenylephrine and by non-pharmacological manipulation of blood pressure using the noninvasive methods previously mentioned using a special purpose computer program [6] written in Labview. Pulse intervals were calculated for each heartbeat using an efficient QRS detection algorithm [8]. Any ectopic beats were identified and removed from the analysis of BRS. For the traditional method of pharmacological manipulation of blood pressure, the resulting changes in systolic blood pressure were plotted against their corresponding changes in the succeeding RR intervals. BRS was then calculated by linear regression analysis, as the slope of the regression line of the plot. Only regression lines with correlation coefficients greater than 0.8 [1] were accepted and the final BRS result was the average of at least 3 consecutive estimations.

BRS was then estimated for each one of the non-invasive methods using the noninvasive portapres measurements of blood pressure. In the spontaneous sequences method, BRS was estimated by linear regression analysis of spontaneous sequences of three or more consecutive beats where changes in systolic blood pressure and the associated next RR intervals have the same direction of change, either up or down. Only sequences in which BP rose or decreased at least 1 mmHg and the RR interval increased or decreased at least 4 ms were considered valid. For each valid sequence, the regression coefficient between changes in SBP and the next pulse beats was calculated as an estimate of the BRS for the sequence. Then the total BRS was estimated as the mean of the regression coefficients of all the valid sequences.

Similarly, the correlated modulus of the transfer function between variations in systolic blood pressure and heart rate in the mid-frequency band (0.07-0.14 Hz) was also used as an estimation of BRS. The magnitude-

squared coherence (MSC) was calculated via overlapped Fast Fourier Transform (FFT) processing [9]. In the case of the modulus method, the modulus value becomes unreliable if the weighted coherence is low, therefore the values of BRS were only accepted for those patients where the weighted coherence was at lest 0.5.

4. Results and discussion

For the 19 subjects the BRS estimated was 8.31±3.90 ms/mmHg for the traditional method of pharmacological manipulation of blood pressure, 8.39±4.21 ms/mmHg for the new method and 12.6±6.72 ms/mmHg for the spontaneous sequences method. Regression analysis for the total population (n=19) showed a significant correlation value between the invasive method of BRS estimation and the new method (r=0.72, p=0.001). The limits of agreement between traditional method and the new method are further evidenced by the Bland-Altman plot [10] of Figure 2. Two-tail student's t-test for paired observations analysis also showed that the differences between the estimations of BRS by methods did not achieve statistical significance. (t=-0.12, p=0.91).

Estimation of BRS using the modulus method, however, was only valid for 5 subjects (weighted coherence >0.5) with a BRS 10.41 ± 4.18 ms/mmHg. Therefore, comparative analysis between the different methods implemented for BRS estimation was performed for this 5 subject only. All the estimations of BRS (the proposed new method, the spontaneous sequences method and the correlated modulus) correlate very well with the phenylephrine invasive method and high values of correlation were obtained between the methods as shown by the pair-wise correlation values of Table 1. The similarity of the methods was confirmed using regression analysis as shown in Figures 3 to 5. Diagonal lines represent the regression line and r^2 represents the regression coefficient between the values obtained.

Method	Phenyle-phrine	New method	Spontaneous sequences
New method	0.96 (p=0.01)		
Spontaneous sequences	0.87 (p=0.057)	0.97 (p=0.007)	
Correlated modulus	0.99 (p=0.001)	0.94 (p=0.016)	0.83 (p=0.08)

Table 1. Correlation (r) between the pharmacological invasive and noninvasive methods of BRS estimation

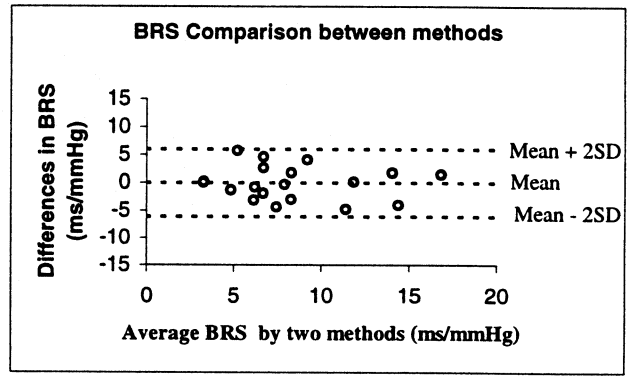

Figure 2. Difference against mean for BRS measurements obtained using the Phenylephrine and Logical Sequence methods (n=19).

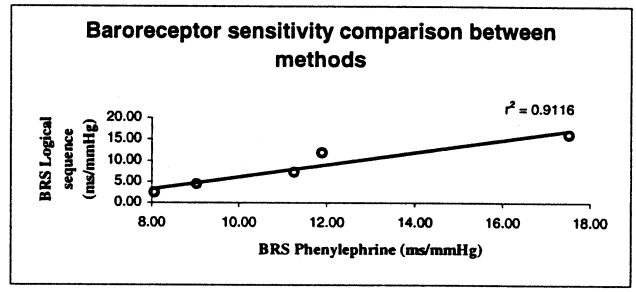

Figure 3. Comparison between BRS estimation using the Phenylephrine and Logical Sequence methods (n=5).

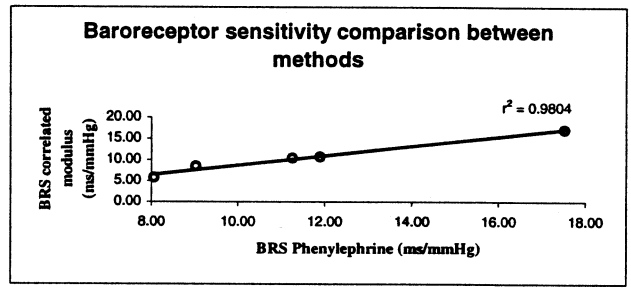

Figure 4. Comparison between BRS estimation using the phenylephrine and correlated modulus methods (n=5).

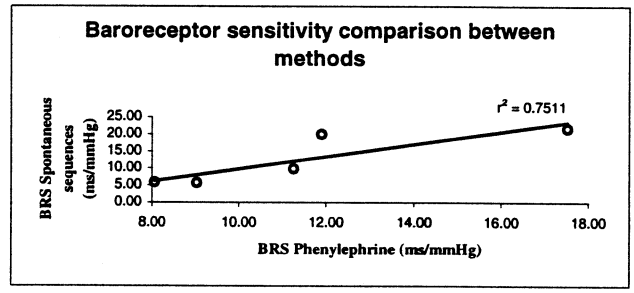

Figure 5. Comparison between BRS estimation using the phenylephrine and spontaneous sequences methods (n=5).

It is important to note that the use of intra-arterial blood pressure measurements for the estimation of invasive BRS and finger blood pressure measurements for the noninvasive estimation of BRS may introduce errors in the comparison, since although both methods are highly correlated, measurements may differ in the absolute magnitude of the SBP [11]. This could be solved in future studies by measuring the BP for the invasive and non-invasive methods of BRS estimation with the same device. The noninvasive method of BP measurement using the "portapres" device appears to be the most suitable method for this purpose, since due to the non-invasiveness and low associated risks, it is most likely to be accepted by the patient. The major limitation of the BRS estimation using the "correlated modulus" is that the coherence confidence interval depends on data length; it requires at least 5 minutes of stationary data for a correct computation of the coherence. Recent work [12] points out that in disabled and older patients, the value of coherence tends to decrease, and the question arises whether leaving out low coherence values introduces BRS bias.

On the other hand, the estimation of BRS using spontaneous sequences is limited by the amount of data (number of sequences) satisfying the conditions required for a sequence to be considered valid. The percentage of data used in the estimation of BRS by the proposed new method (logical sequence) was much higher than the percentage of data used by the spontaneous sequences method. The results obtained in this study indicate that with future refinements the logical sequence method of BRS estimation described in this paper could be used as a non-invasive technique for BRS estimation. Nonetheless, further studies involving control patients are required in order to quantify the limitations and stability of this new method.

5. Conclusion

A new noninvasive method for BRS estimation, which could be a major advance in preventing deaths after heart attacks, was described in this paper. It was compared with measurements of BRS by the traditional bolus phenylephrine method and other well known non-invasive nonpharmacologically derived BRS assessment techniques such as the "spontaneous sequences" and "the correlated modulus" methods. The results obtained in this preliminary study suggest that with further refinements, the method developed could be used as a reliable noninvasive method for BRS estimation. Further studies involving control patients are at present being carried out to quantify the limitations and stability of this method.

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