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Comparison of baroreflex sensitivity measures for assessing subjects with Obstructive Sleep Apnea

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Abstract—**Baroreflex sensitivity (BRS) is assessed in subjects with and without obstructive sleep apnea (OSA) using the time domain direct sequence technique, the spectral transfer function (TF) technique and the alpha index technique. All three measures showed a significantly depressed BRS value in subjects with severe apnea. The high frequency (HF) component of the spectral measures showed higher correlation with the sequence technique measures than the low frequency (LF) component. The baroreceptor effectiveness index (BEI) showed a strong relationship with the HF coherence value from the spectral measures. All three BRS measures decreased with increasing heart rate. Heart rate correction of the sequence technique estimates to 60 beats per minute did not have a significant impact on the BRS estimates.**

I. Introduction

Reduced baroreflex sensitivity (BRS) has been associated with cardiovascular disorders such as myocardial infarction, hypertension, and chronic heart failure. Traditional invasive methods for assessing BRS have been substituted by more non-invasive measures such as the time domain direct sequence method and frequency domain spectral measures such as the alpha and coherence techniques [1]. These measures have been used in the literature for the assessment of BRS in the normal population and in subjects with obstructive sleep apnea (OSA) with some investigators reporting depressed sensitivity in subjects with OSA [2][3], while others have reported similar levels of sensitivity [4]. Recently however it has been suggested that clinical and anthropometric measures such as age, heart rate (HR), body mass index (BMI), gender, blood pressure (BP) and smoking were independent predictors of BRS with HR accounting for 26% and age accounting for 21% of BRS variability [5]. Moreover Abrahamsson et al. showed that there was a highly significant relationship between BRS and prevailing HR within individuals, a factor, which may have influenced spontaneous BRS measures in previous studies [6]. They showed that BRS decreased exponentially within individuals as HR increased and when a logarithmic scale was applied to the BRS values this relationship was linear. This meant that BRS measures at lower heart rates could be significantly affected by changes in HR by only a few beats and to account for this they suggested normalizing the BRS measures at 60 beats per minute (bpm). Wesseling et al., who showed a similar relationship between BRS and heart rate, further supported these findings although suggesting 100 bpm as a more suitable normalizing value [7].

In this paper we examine non-invasive time and frequency based BRS measures in normal controls and patients with OSA. The direct sequence technique is used to examine spontaneous BRS fluctuations in subjects, which represent the faster moving parasympathetic components of the baroreceptor control loop. Spectral analysis is also implemented using the transfer function (TF) and alpha technique to compare and validate the results obtained from the sequence method. We look at the effects of the prevailing HR on each of these measures and what effect heart rate correction may have on the sequence technique results. Finally we investigate the problems associated with the arbitrarily chosen coherence value in the use of the spectral techniques and examine its relationship with that of the baroreflex effectiveness index (BEI) used in the sequence technique [8].

II. Methodology

A. Measurements

The study consisted of 38 subjects, 14 with severe OSA, 14 with mild to moderate OSA while the remaining 10 were controls. They were examined at St. Vincent's University Hospital Sleep Disorders Clinic, Dublin, Ireland. Inclusion criteria were that subjects must be over 30 years of age, have no known cardiac disease; no known autonomic dysfunction; and not be on medications such as beta-blockers, digoxin, or calcium receptor antagonists known to interfere with heart rate. The protocol was approved by the local Research Ethics board and all subjects provided written informed consent. Full polysomnography (PSG) was performed using the Jaeger-Toennies polysomnography system. Sleep staging was performed using the full polysomnogram by a single experienced sleep technologist. An annotated respiratory event list was also produced which provides onset times, and durations of all sleep-disordered breathing events including obstructive, mixed, and central apneas and hypopneas, and periodic breathing episodes. Obstructive apneas were defined as an interruption of airflow lasting at least 10 seconds accompanied by a decrease of SaO2 of 4% or more. A hypopnea event was defined as a reduction in airflow of at least 50% accompanied by a decrease of SaO2 of 4% or

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more. Central and mixed apneas were not included in the apnea-hypopnea index (AHI). Arterial blood pressure was monitored non-invasively overnight using a Finapres device (Finapres 2300, Ohmeda, Eaglewood, USA). Two cuffs were positioned on the middle phalanx of the index and middle fingers with the device alternating fingers every 30 minutes.

B. Data Processing

BRS was calculated offline using the electrocardiogram (ECG) and BP signals. The ECG was sampled at 128 Hz while the BP signal was resampled from 100 Hz to 128 Hz. The interbeat (RR) intervals were extracted from the ECG signal using a fuzzy logic based QRS peak detector. The blood pressure peaks were obtained using a Hilbert transform based peak detector. Time offsets between the RR intervals and the systolic blood pressure peaks were automatically estimated and then manually verified and corrected. Calibration and finger switching phases of the Finapres device were marked and excluded from all further analysis.

Spontaneous BRS was measured using the direct sequence technique. This involves the scanning of beat to beat series of systolic blood pressure (SBP) and RR intervals in search of spontaneous sequences of three or more consecutive heart beats in which SBP increases and the RR interval progressively lengthens, or vice versa, SBP decreases and RR interval shortens. The slope of the regression line between the SBP and RR intervals is taken as a measure of BRS. SBP and RR interval increases are defined as positive ramps, a measure of baroreceptor activation, and SBP and RR interval decreases are defined as negative ramps, a measure of baroreceptor deactivation. The protocol accepts sequences between 3 and 7 consecutive cardiac cycles in length during which SBP changes by at least 1 mmHg in each beat and the RR interval changes by at least 5 ms with a linear correlation coefficient greater than 0.7 between RR and SBP ramps. A 0 to 2 beat lag range is used in our analysis. The spontaneous BRS measures examined are positive and negative ramp slopes and the BEI.

Spectral investigation of the relationship between RR interval and SBP was examined using the transfer function (TF) coherence technique [9] and the alpha index [10]. The transfer function coherence technique involves assessing the linear coupling between the SBP and RR interval in the frequency domain using the coherence function and calculating the mean modulus or gain of the changes in these two measures across frequency bands where the coherence is greater than or equal to an arbitrary value of 0.5. The BRS estimate is the modulus of the cross spectrum between systolic pressure and RR interval divided by the systolic pressure spectrum [12]. We examine the gain of the change in SBP and RR in two frequency regions. The low frequency (LF) range (0.07 – 0.14 Hz) relating to characteristics of blood pressure control and the high frequency (HF) range (0.14 - 0.45 Hz) corresponding to respiration and parasympathetic activation. The alpha index is similar to the coherence technique. If the coherence at the low and high frequency bands are greater than 0.5, the square root ratio of RR and SBP power spectra are integrated over their respective ranges. The spectra are calculated on linear detrended data sections, 512 points in length using the non-parametric welch periodogram method with 50% overlap. RR and SBP signals were interpolated to 1 Hz using cubic spline interpolation. The TF coherence technique is referred to as TF (LF) for the low frequency component and TF (HF) for the high frequency band. Similarly the alpha index is referred to as α(LF) and α (HF). The sequence techniques are represented by BRS+ for baroreceptor activation ramps and BRS- for deactivation ramps.

C. Heart Rate Correction

Heart rate correction is a technique used to normalize subjects BRS estimates to a fixed heart rate. It was performed independently on both the positive and negative BRS ramps of each subject. The heart rate range for each subject was divided into 5 sections with the natural logarithm of the individual BRS estimates and their corresponding interbeat intervals averaged over this section. The mean intervals were then converted to mean HR and were plotted versus the corresponding averaged logarithmic BRS measures [7]. A straight line was then fitted to the respective data using linear regression analysis. The equation of this regression line was then used to normalize the BRS estimates at 60 bpm for each subject. Heart rate corrected estimates are referred to as BRS60+ and BRS60-.

D. Data Analysis

The 38 subjects were divided into three groups consisting of severe apneic subjects with an AHI > 30, mild to moderate apnea $5 \leq$ AHI ≤ 30 and control subjects with an AHI < 5. Data were averaged for each group with their means and standard deviations calculated. ANOVA was used to test for differences between the three groups. Results were statistically significant at $p < 0.05$. Comparisons between the three BRS measures were made using spearman's rank correlation coefficient.

III. Results

The subject details including BP, HR, AHI and BRS measures of the control, mild and severe apneic subjects are shown in table 1. The groups were matched for age, BMI and blood pressure. The BRS estimates using the coherence, alpha index and sequence techniques are shown in table 2. Only 20 of the 38 (53%) subjects had coherence levels greater than or equal to 0.5 for both the LF and HF bands of the spectral estimations. As stated in [12], low coherence values can be an unavoidable consequence of BRS dysfunction and therefore may preclude subjects in which this method may be of clinical relevance. This is the case in this study as 8 mild/moderate and 10 severe apneics have low coherence values. In these cases we reduced the

accepted coherence threshold to 0.1, 0.2, 0.3 or 0.4 depending on which was the nearest lowest level to the maximum coherence value for that subject in the required frequency band. For example, if a subject's maximum coherence level in the LF band is 0.39, the threshold is set at 0.3 and the mean modulus of the LF frequencies above this threshold is estimated. Figure 3 shows a plot of the maximum coherence values obtained for the LF and HF bands of the 38 subjects. Although there is a difference in the absolute measures for the three groups all three BRS estimates show a significant difference between the groups. Figure 1 shows the three BRS estimates following similar trends for all 38 individual subjects. The correlation values are shown in table 3, which shows a stronger correlation between the HF ranges of the spectral measures and the sequence technique measures than with the LF ranges. A plot of the BRS estimate versus heart rate is shown in figure 2. Subjects with higher heart rates (in this case subjects with severe apnea) tend to have reduced BRS values. This is consistent with the literature in the regard that subjects with severe OSA tend to have impaired BRS and also that HR seems to be an independent predictor of BRS variability with decreasing HR resulting in increased BRS estimates. To determine whether heart rate may account for this difference we normalized the sequence technique values to 60 bpm. The results are shown in table 2. Heart rate correction has little impact on these measures. Finally BEI and the coherence values for each subject are shown in figure 3. The correlation coefficients are shown in table 4 and the measures across each group are shown in table 5. There was a high correlation between the BEI and the coherence of the HF range while the coherence value in the LF range showed a significant difference across the three groups.

TABLE I
PATIENT DETAILS

	Control	Mild/Mod	Severe
Number	10	14	14
Age	38±5	38±7	41±6
Current Smokers	4 (40%)	6 (43%)	7 (50%)
BMI	32.2±2.6	33.8±6.9	34.5±3.3
BP	129/82±12/7	131/82±18/11	138/87±17/14
AHI	0.7±0.9	16.7±7.3	60.1±20.4

TABLE 2
BRS ESTIMATES

BRS (mm/Hg)	Control	Mild/Mod	Severe	p
TF (LF)	9.31±4.18	7.51±2.83	4.82±2.82	0.006
TF (HF)	9.26±3.08	8.53±5.05	4.48±3.60	0.011
α (LF)	12.10±5.02	11.21±3.66	7.49±3.61	0.016
α (HF)	12.08±4.34	11.87±5.67	6.89±5.01	0.020
BRS+	12.53±4.60	12.73±6.16	7.81±5.00	0.038
BRS-	11.96±3.19	11.42±4.66	7.03±4.27	0.009
BRS60+	12.24±3.86	12.15±6.02	7.46±3.85	0.021
BRS60-	11.03±3.47	10.65±3.62	7.01±2.98	0.007

TABLE 3
CORRELATION OF BRS ESTIMATES

Measure 1	Measure 2	Correlation *r*
TF (LF)	BRS+	0.902834
TF (LF)	BRS-	0.870008
TF (HF)	BRS+	0.942007
TF (HF)	BRS-	0.961484
α (LF)	BRS+	0.901521
α (LF)	BRS-	0.874603
α (HF)	BRS+	0.969143
α (HF)	BRS-	0.954481

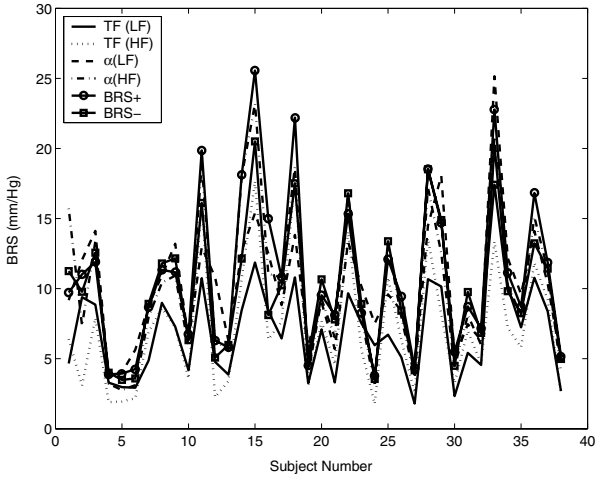

Fig. 1. BRS measures for all 38 subjects

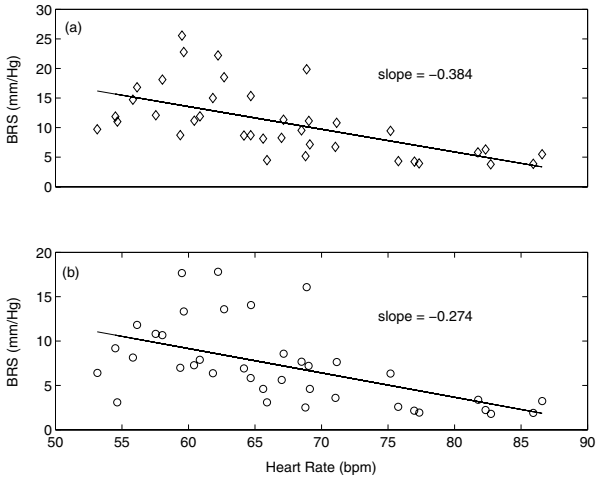

Fig. 2. BRS versus HR for (a) BRS+ and (b) TF (HF) measures

TABLE 4
COHERENCE AND BEI CORRELATIONS

Measure 1	Measure 2	Correlation *r*
Coherence (LF)	BEI+	0.353
Coherence (LF)	BEI-	0.402
Coherence (HF)	BEI+	0.835
Coherence (HF)	BEI-	0.623

TABLE 5
COHERENCE AND BEI MEASURES

	Control	Mild/Mod	Severe	p
BEI+	0.63±0.09	0.54±0.15	0.49±0.14	0.057
BEI-	0.64±0.13	0.61±0.20	0.49±0.15	0.075
Cohere. (LF)	0.67±0.07	0.54±0.12	0.45±0.13	0.0002
Cohere. (HF)	0.75±0.10	0.68±0.20	0.58±0.16	0.041

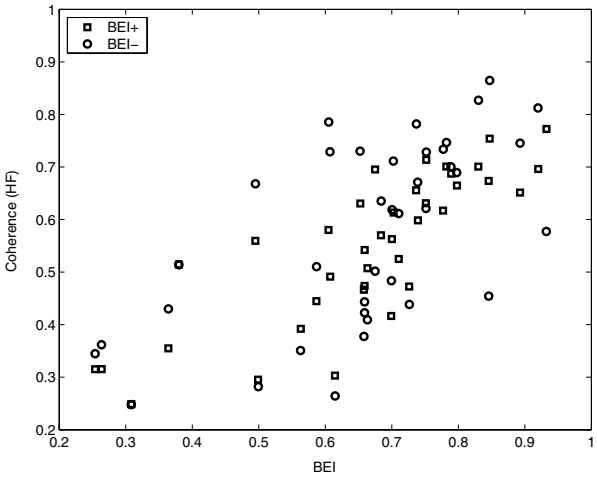

Fig. 3. BEI and Coherence measures for all 38 subjects

IV. Discussion

This study examines three BRS measures in control and apneic subjects. The BRS measures were consistent with previous findings in the literature showing impaired baroreflex sensitivity in subjects with severe OSA [2][3]. It has been suggested that this significantly reduced sensitivity may be due to elevated levels of sympathetic tone, chemoreflex activation due to hypoxia or OSA induced mechanical changes [2][4][11]. The depressed BRS measure was consistent across all techniques and in both the LF and HF bands. There was however a higher correlation between the HF bands for both spectral measures and the spontaneous sequence technique BRS measures. This result is not unexpected as the HF band is associated with respiration and parasympathetic activation while the sequence technique measures the very quick responses of the RR interval to changes in SBP which is a result of the faster moving parasympathetic components of the baroreceptor control loop. One of the disadvantages of the spectral techniques is the requirement of a coherence level of 0.5 to ensure reliable results. This arbitrary parameter has been shown in the literature to preclude subjects who may have BRS dysfunction [12]. This was also true with subjects with OSA as 8 mild to moderate and 10 severe OSA showed a coherence level less than 0.5. To include these datasets back into the analysis we simply ignored the threshold for the alpha index measures and for the transfer function method we reduced the threshold to below the maximum coherence in the frequency band and obtained the mean modulus at frequencies with coherences above this new threshold. This method provided reasonable results as shown in figure 1 and table 1. The reduced coherence and BEI measure in subjects with severe apnea is also evident from table 4 with the LF coherence component showing the largest degree of separation between groups. The HF component and the BEI values showed less significant differences across the three groups but did show strong correlation with each other especially between the HF component and the BRS activation (BEI+) effectiveness index.

The relationship between HR and BRS on an individual basis has been highlighted previously. The methods for heart rate correction of BRS estimates, suggested in [6] and [7], showed that BRS values increased with decreasing heart rate. It is clear from figure 2 that most of the heart rates across all subjects in this study lie in the range of 50–90 bpm with the mean heart rates at 60–70 bpm. This lies outside the linear range suggested by Wesseling et al. and may account for the limited impact on both the positive and negative heart rate corrected BRS estimates we obtained. The limited range of heart rate variation during sleep may result in the subjects regression lines being located on the flatter part of the BRS versus heart rate 'S' curve outlined in [7], which in turn could result in an inaccurate standardized heart rate BRS estimate.

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