ESTIMATION OF BAROREFLEX SENSITIVITY DURING MENTAL STRESS TESTING – A Comparison of Different Methods

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Abstract: We compare three different methods to estimate baroreflex sensitivity (adaptive multivariate, spectral and sequence) on data obtained at rest and during stress (Stroop colour-word interference). Cardiovascular responses during stress are highly individual with rapidly changing heart rate and blood pressure. In most previous methodology studies, baroreflex sensitivity was estimated during periods of cardiovascular stability. Performance during less stable periods might be improved by using shorter epochs of data and recent signal processing methods. We present a novel approach using specific short windows of time located within the five minute rest and stress periods that are commonly used by investigators (first minute of stress task and last four minutes of rest period). Comparisons are made with more conventional average estimates of baroreflex sensitivity using the whole rest and stress periods. The sequence method was found to be unsuitable during mental stress, particularly when applied to the shortened time windows. With other methods, use of the shortened time windows increased estimates of the difference between baroreflex sensitivity at rest and during stress. Greatest discrimination between rest and stress was obtained using the adaptive multivariate method. (183 words)

Introduction

Non-invasive methods for estimation of autonomic activation and baroreflex sensitivity (*BRS*) are increasingly being used to study responses of the cardiovascular system to psychological challenge [1, 2]. The highly dynamic and individual nature of cardiovascular responses during mental and psychosocial stressors presents particular difficulties for existing methods of *BRS* estimation. To our knowledge, previous comparisons [3] of such methods have used data from highly controlled clinical situations that are unlikely to mimic psychological challenge. Furthermore, well established techniques, such as sequence and spectral methods, assume the presence of long periods of time in which the *BRS* of the subject is essentially constant [4]. In practice, these methods are often used to estimate mean *BRS* during periods of stress lasting 15 minutes or more. This may be inappropriate, given that subjects' perceptions of stress, and responses to stress are usually dynamic and may change rapidly within such time periods. Therefore, we propose a novel approach to *BRS* estimation, using specific short windows of time located within the usual periods of time allocated for rest and stress in such studies. Three different algorithms for estimating *BRS* which use either time or frequency domain approaches were compared.

Materials and Methods

Data from a study of Australian adults ($N = 179$, aged 26.3±0.4 years, 57% women) was used [5], which included a rest period (sitting silently) and a stress task (Stroop colour-word interference task), each lasting five minutes, separated by a period of approximately ten minutes. Throughout each session, a continuous recording of finger arterial pressure was made using a Portapres device (FMS BV, Netherlands) which records the data at a sample rate of 100 Hz. Systolic arterial pressure (*SAP*) and heart period (*HP;* the interval between consecutive heart beats) series were extracted from the raw signal using the device's software (Beatscope 1.0). Erroneous samples due to artefacts and ectopic heart beats were removed manually, guided by an automated heart period rejection algorithm [6]. The corrected time series of *SAP* and *HP* were resampled at 4 Hz using linear interpolation.

The arterial baroreflex is a well known cardiovascular control mechanism that modulates heart period when blood pressure changes, limiting blood pressure fluctuations. Both afferent and efferent limbs of the baroreflex form part of the autonomic nervous system which is regulated by multiple brainstem regions. Afferent parasympathetic nerves carry blood pressure information from baroreceptors embedded in major arterial sites such as the carotid body and aortic arch. The efferent limb of the baroreflex then effects changes in heart period through both sympathetic and parasympathetic innervation of the heart. The actions of the parasympathetic and sympathetic nervous system are partially separable in the frequency domain with an upper limit of sympathetic activity around 0.15 Hz whilst parasympathetic neurotransmission is more rapid and, therefore, capable of acting over a wider range of frequencies. *BRS* can be defined as the gain of the control system given by the ratio of the change in heart

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period (ΔHP) over the change in blood pressure (ΔSAP). We considered three, well-established *BRS* estimation approaches: a sequence method (*SEQ*) [3, 7], a spectral method (*SPC*) [3], and an adaptive multivariate autoregressive method (*MV*) [8].

With *SEQ*, the least squares linear relationship between changes in *HP* and the preceding changes in *SAP,* which are assumed to have caused them, is considered as the index of *BRS*. Sequences of consecutive cardiac cycles in which *SAP* increases (by at least 1 mmHg per beat) whilst *HP* increases (by at least 2 ms per beat) are analysed. Similar sequences where *SAP* and *HP* decrease together are also used. Each systolic value is associated with the *HP* terminating at the immediately subsequent heart beat. At resting heart rates, this phase relationship between *HP* and *SAP* is thought to fit best with the inherent delay in the baroreflex. At higher heart rates, such as might occur during stress, we also considered the option of increasing this lag by one further beat, since it may provide a better phase match to the underlying baroreflex characteristics. Only sequences of three beats or longer are considered suitable for *BRS* estimation. For each suitable sequence, the slope of the regression line is computed and used as the index of *BRS* [9].

With *SPC*, the transfer function between *SAP* and *HP* is estimated using an open-loop fast Fourier transform approach and *BRS* is estimated as a weighted mean of the transfer function gain in specific frequency bands: low frequency (*LF*: 0.05 – 0.15 Hz, SPC_{LF}) and high frequency (*HF*: 0.15 – 0.5 Hz, SPC_{HF}). The weight $w(f)$ corresponding to each frequency is defined as:

$$w(f) = \begin{cases} \gamma(f) & if\ \gamma(f) \geq 0.5 \\ 0 & if\ \gamma(f) < 0.5 \end{cases}$$

where γ is the estimated coherence between *SAP* and *HP* at each frequency.

For *MV*, the method presented in [8] was adopted. With this method, a closed-loop multivariate adaptive approach is used to model the reciprocal interaction between *SAP* and *HP*. The transfer function and the coherence between *SAP* and *HP* are computed from the model coefficients and *BRS* is estimated as a weighted mean of the transfer function gain. This approach was used to provide sample-by-sample estimates of *BRS* in both frequency bands (MV_{LF} and MV_{HF}). We used an order 16, autoregressive model, as suggested in [10], which was initialised with the first 120 seconds of data from each recording.

For each method, *BRS* was estimated in the conventional manner, using all five minutes of the rest period (*R*5), and all five minutes of the stress task (*S*5). In earlier work using the *MV* approach (in preparation), it became clear that there is a transient at the onset of rest before *BRS* settles to a more constant value. We also found that during stress, *BRS* falls rapidly to a minimum in the first minute with recovery commencing within the duration of the stress task (Figure 1).

Therefore, we have estimated *BRS* using the last four minutes of rest (*R*4) and just the first minute of the stress task (*S*1) and compared these results to those from *R*5 and *S*5.

Paired *t*-tests were carried out on log transformed estimates of *BRS* to detect differences between values during stress and at rest for each method. Log transformation was necessary due to the highly skewed distribution of *BRS* values. All statistical tests were considered significant for $p < 0.05$.

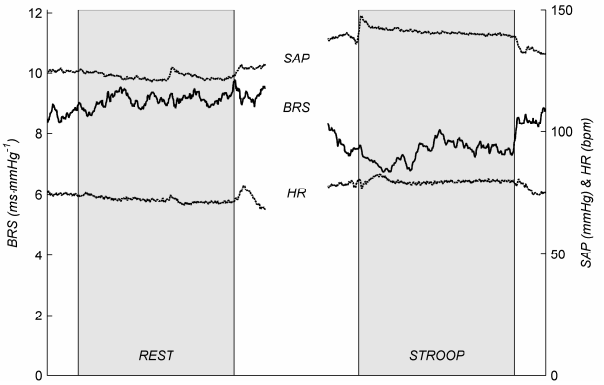

Figure 1: Mean systolic arterial pressure (*SAP*) and heart rate (*HR*) and geometric mean baroreceptor sensitivity (*BRS*) estimated using the low-frequency multivariate method, at rest (5 minutes) and during stress (Stroop; 5 minutes) in 179 subjects.

Results

In order to provide *BRS* estimates using *SEQ*, suitable sequences of increasing or decreasing *SAP* and *HP* are required which are not always found in short segments of data. We found that these requirements were not met in a considerable number of subjects, particularly during stress, for whom a useful estimate of *BRS* using *SEQ* was not obtainable (Table 1).

Table 1: Number (%) of subjects with suitable sequences to estimate baroreceptor sensitivity using the sequence (*SEQ*) method (*N* = 179).

	Number (%) of subjects with at least:		
Time Window	1 sequence	2 sequences	3 sequences
*R*4	164 (92%)	150 (84%)	138 (77%)
*S*1	110 (61%)	51 (28%)	22 (12%)
*R*5	169 (94%)	157 (88%)	152 (85%)
*S*5	166 (93%)	143 (80%)	120 (67%)

*R*4, last four minutes of five minute rest period; *S*1, first minute of stress period; *R*5, five minute rest period; *S*5, five minute stress period.

For example, using *S*1, 39% of the subjects had no suitable sequences. Given that a single estimate for a whole test period is unlikely to yield accurate estimates, Table 1 shows the degree of further attrition to be expected if higher numbers of sequences are required. For *R*4, the problem is similar. Even using five minute data segments, there were a considerable number of subjects with very few suitable sequences for estimating *BRS* with *SEQ*. For these reasons, data on *S*1 and *R*4 using the *SEQ* method are not presented. To rule out the possibility that using a lag between *HP* and *SAP* that

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was not optimal caused the poor performance of the *SEQ* method during stress, where higher heart rates are generally found, we repeated this analysis using a range of beat lags. Results were not significantly improved compared to those presented.

Figure 2 shows mean *BRS* estimates for each method. As expected, the decrease in *BRS* caused by stress is evident for all methods. Furthermore, the *SPC* (open-loop approach) estimates are higher than the *MV* (closed-loop approach) estimates which is consistent with previous findings [11], and *HF* estimates are greater than *LF* estimates for both approaches as found in the EuroBavar study [3]. Use of the shorter epochs increased the estimated difference between rest and stress *BRS* for the MV_{LF} method by 0.71 ms.mmHg^{-1} ($p = 0.001$) and the SPC_{LF} method by 1.47 ms.mmHg^{-1} ($p < 0.0001$). Comparisons of rest to stress differences made between the methods revealed that, when using the full windows, the MV_{LF} estimates were 0.78 ms.mmHg^{-1} greater than those produced by the SPC_{LF} method ($p = 0.007$), but no significant difference between these methods was found using the shorter windows ($p = 0.98$), or for comparisons of MV_{LF} with SEQ ($p = 0.61$) and $SPC_{LF}$with SEQ ($p = 0.19$).

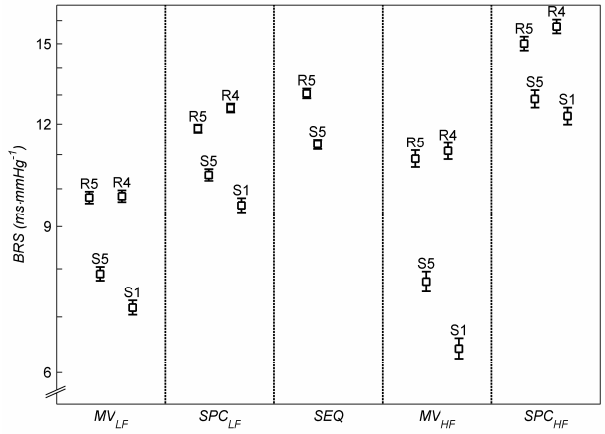

Figure 2: Mean (± s.e.) estimates of baroreceptor sensitivity (*BRS*) for the whole rest (*R*5) and stress (*S*5) time windows and the shortened rest (*R*4) and stress (*S*1) time windows using different methods (*N* = 179). *SPC*, spectral (FFT) method; *MV*, adaptive multivariate method; *SEQ*, sequence method; *LF*, low-frequency band (0.05 – 0.15 Hz); *HF*, high-frequency band (0.15 – 0.5 Hz).

Discussion

In any study investigating non-invasive methods of *BRS* estimation, the lack of an accepted gold standard, either invasive or non-invasive, must be broached. Many authors consider a pharmacological approach to *BRS* estimation to be a gold standard [12]. However, this issue is highly contentious due to the impact that pharmacological intervention has on the normal functioning of the baroreceptors [13, 14]. Unfortunately, the lack of an accepted gold standard has led to the appearance of a wide variety of non-invasive methods without the means to assess their true performance. Large-scale comparisons of these methods have been published where majority agreement has been substituted for a measure of good performance [3]. However, it remains entirely possible that estimates produced by the majority of methods are in agreement but less accurate than those produced by less frequently used methods. In this study, we have taken a pragmatic approach. Given that the aim of many studies of *BRS* is to demonstrate a difference between two or more physiological conditions, rather than accurately determine an absolute value, it might be argued that any method which tends to maximise this should be preferred. In this regard, our novel approach uses the last 4 minutes of the rest period and just the first minute of the stress task to estimate *BRS.*

The increased estimate of the difference between rest and stress *BRS* which results from using the shortened time windows has a simple possible explanation: *S*1 uses the initial part of the stress task, in which *BRS* reaches a minimum, whereas *S*5 includes the rest of the stress task, during which most subjects show a consistent recovery to higher values resulting in a much higher estimate of *BRS* and, therefore, an underestimate of the stress effect (Figure 1). Furthermore, *R*4 avoids the first minute of the rest task where a transient in *BRS*, which may represent a minor stress response to the onset of the task, causes underestimation of resting *BRS*. Hence, if the aim is to estimate the maximum *BRS* change caused by the stress stimuli, *S*1 and *R*4 are to be preferred. On the other hand, one may question if *S*1 alone represents the most important aspect of the response during stress (in psychophysiological terms). For example, it is conceivable that for some clinical and physiological problems, the speed of recovery from the initial minimum in *BRS* may be more important than the early drop in *BRS*. Further work is required to explore this aspect.

In previous work (in preparation), we observed very similar patterns of *BRS* response to mirror-tracing tasks and a simulated defence against an accusation of shoplifting. This suggests that a pattern of early reaction to a stress task followed by a steady recovery, whilst the stressor continues, may occur commonly. The use of the adaptive multivariate (*MV*) method in future studies would allow investigators to examine the pattern of response (Figure 1) to their chosen stress stimulus and make an appropriate choice of time window for analysis. Analysis with the other methods does not give this option as their temporal resolution is relatively poor.

The *MV* method appears to be the best choice for analysis of *BRS* during periods of relative cardiovascular instability as it provides sample-by-sample estimates of *BRS,* allowing researchers to examine short-term patterns of cardiovascular activity and thereby, improve estimates of difference from a resting condition. It also appears to maximise estimates of the difference in *BRS* between rest and stress, although without a gold standard, one should be cautious in interpreting this as a definite improvement over other methods. We have presented data on high-frequency band estimates of transfer function gain using MV and SPC methods for comparison with those

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presented in previous studies such as the EuroBavar study [3]. Although there is good evidence to suggest that low-frequency oscillations of *SAP* originate from sympathetically induced fluctuations of peripheral vascular tone, resulting in similar oscillations of *HP* through the cardiac vagal efferents of the baroreflex, the opposite is true for high-frequency oscillations [15]. These oscillations appear to originate in higher CNS centres and therefore interpretation of transfer function gain in the high-frequency band as a measure of baroreflex function remains controversial. For this reason, most of our analysis is focused on results obtained for the low-frequency band.

The *SEQ* method proved to be unsuitable for the analysis of the first minute of the stress task as it provided an insufficient number of suitable sequences (Table 1).

It might be argued that use of Portapres-derived *HP* series is not ideal despite several published reports of their successful use for *BRS* estimation [1, 2]. Published comparisons between Portapres-derived and ECG-derived *HP* series show reduced correlations between these methods during stressors such as the Stroop task compared to correlations made at rest and greater estimates of power in both *LF* and *HF* bands for Portapres-derived *HP* series [16]. Nevertheless, there are no conclusive findings supporting the idea that the use of Portapres-derived *HP* series produces misleading estimates of *BRS* [16].

Conclusions

Studies where rapid changes in *BRS* might be expected such as those we found during mental stress may benefit from a more focused analysis looking at specific short epochs of data. We found that such an approach significantly increased estimates of a rest-stress difference in *BRS* using several methods. Choosing the appropriate region of data for such an analysis requires a method which is able to discriminate short-term variations in *BRS*. The *MV* method which we used and other such ARMA-type methods are most appropriate for this task.

The *SEQ* method was the least useful method for analysis of short periods of data and was found to be unsuitable in this typical mental stress study. Therefore, alternative methods should be sought when cardiovascular stability is not expected. If the aim of future studies is to understand how disease develops from individual differences in cardiovascular function, it might be argued that a greater understanding of cardiovascular adaptations to environmental challenge is more valuable than exploring cardiovascular function only in the resting condition. Given that there appear to be few disadvantages to the other methods we have explored in this study, continued use of the *SEQ* method in future studies of *BRS* might be questionable. Use of the *SPC* and *MV* methods yielded similar results. In future work, the pattern of *BRS* response to various stressors will be investigated in order to evaluate the use of other descriptors of the response to stress (e.g. recovery time).

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