Improved BRS Assessment Using the Global Approach in the Sequences Technique

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Abstract

The sequences technique, the most used time domain method for the assessment of arterial baroreceptor reflex sensitivity (BRS), is based in the linear regression of systolic blood pressure (SBP) and heart period (RR) values in baroreflex sequences (BRSseqs). In a previous study, a global estimator was compared with the traditional estimator: global is less biased, presents lower variance and the use of SBPramps in BRS estimation, instead of BRSseqs, turns both estimators unbiased. In this work, the replacement of BRSseqs for SBPramps in BRS analysis is further evaluated. Also, it is introduced a robust global (total) approach and compared with the traditional and the global approaches. The results showed that BRS global estimator with BRSseqs has lower bias, lower variability and present increased power to discriminate between Lying and Standing situations in the EuroBaVar dataset. It is expected that the robust properties of the total estimator can be fully enhanced in clinical practice.

1. Introduction

The sequences technique is a standard method for BRS estimation which consists in time domain analysis of SBP and RR beat-to-beat spontaneous variability. This method is based on the identification of *valid* baroreflex sequences (BRSseqs), i.e. simultaneous ramps in SBP and RR, and in a local linear regression over the correspondent SBP and RR values [3]. An overall estimate is obtained by averaging the regression slopes obtained for each BRSseq, during the recording period (this method is referred in this work as the *local approach* BRS_{local}).

A previous work [1] described an alternative estimator: instead of taking the mean of the slopes, BRS is quantified by the slope obtained from all SBP and RR values, in the set of all BRSseqs (*global approach* with estimator BRS_{global}). Experimental and simulation results showed that BRS_{local} and BRS_{global} values are highly correlated and present the systematic relation $BRS_{local} > BRS_{global}$. Also, it was found that BRS_{global} is less biased and has lower variance. Finally, it was shown that the use of SBPramps in the BRS estimation, instead of BRSseqs, turns both estimators unbiased.

As illustrated in figure 1, the beats identified in BRSseqs are also identified in SBPramps, but not vice-versa. In this way, BRS studies can benefit with the use of SBPramps: the more data available allows a quantitative BRS assessment in cases of BRSseq absence, such as in cardiac BRS failure and may improve the BRS characterization in normal conditions. However, the correspondent RR values in SBPramps and not in BRSseqs also present more variability and some outliers, when compared to the RR values in BRSseqs, as a consequence of less restrictive thresholds for valid SBPramps. It is known that least squares procedures can be strongly influenced by outliers, since a single observation can have excessive effect on the fitted model [5]. In this work, the global approach was improved to achieve more robustness to outliers using a rejection rule combined with a method for slope estimation accounting for errors both in SBP and RR values (*total* approach with estimator BRS_{total}). Also, the replacement of BRSseqs for SBPramps in BRS analysis is further evaluated and it is discussed the use of *local*, *global* or *total* approach in BRS assessement with the EuroBaVar dataset [2].

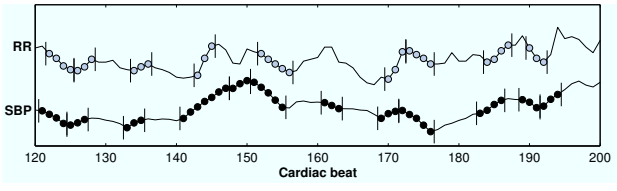
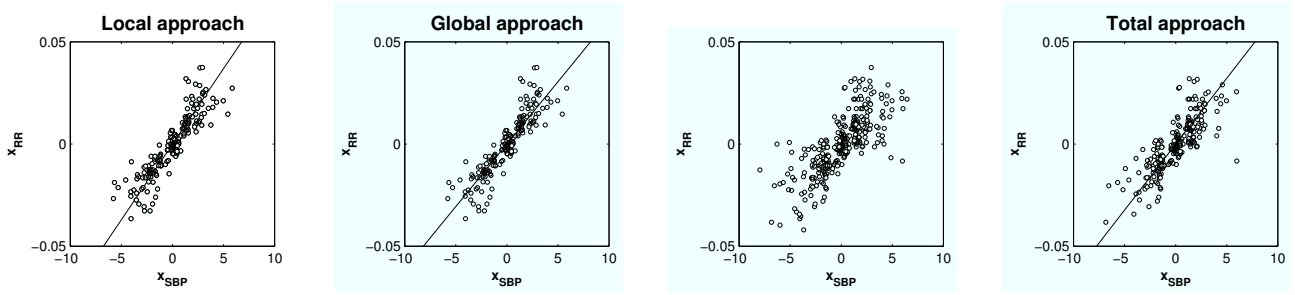


Figure 1. Examples of valid BRSseqs (●) and SBPramps (●) in the file "A001LB.txt" from EuroBaVar dataset [2].



(a) (b) (c) (d)

Figure 2. Dispersion diagrams of SBP and RR mean detrended values for BRS analysis. Values found in BRSseqs together with the line with slope BRS_{local} (a) and the global regression line with slope BRS_{global} (b). Values found in SBPramps (c) and after outliers removal superimposed with the total regression line with slope BRS_{total} (d). First segment of 512 beats from "A001LB.txt" file in EuroBaVar dataset [2].

2. Methods

The method used for BRS estimation is detailed elsewhere [1] and it consists in (1) the identification of the SBP and RR values in valid BRSseqs, (2) local mean detrend of the data in each BRSseq and (3) BRS computation from the slopes of the regression lines. The *local* (traditional) approach provides a BRS measure associated to each BRSseq [3], and an overall estimate BRS_{local} is obtained from the mean of the local slopes. Alternatively, a *global* BRS measure can be considered as the slope BRS_{global} obtained from all the x_{RR} and x_{SBP} values in the set of all BRSseqs [1]. In this work, both BRSseqs and SBPramps are identified if they satisfy 3 beats minimum length and 1 mmHg minimum step-wise changes in SBP. Additionaly, a valid BRSseq must satisfy 5 msec minimum RR changes and present a minimum correlation coefficient of 0.8.

The comparison between figure 2(c) and 2(a or b) shows that with the use of SBPramps in BRS analysis there is a higher number of beats available and the correspondent SBP and RR values also present more variability. The estimate based on SBPramps is unbiased at the expense of a higher variability, as a consequence of less restrictive thresholds for valid SBPramps. To overcome this higher variability, the global approach was improved to achieve more robustness using an outlier rejection rule combined with the slope estimation by total least squares minimization (*total* approach with estimator BRS_{total}).

In the *total* approach, the regression slope was estimated by total least squares (TLS), minimizing the sum of orthogonal direction errors [4] and, therefore, accounting for errors in both SBP and RR values. This approach differs from the classical least squares estimation where only the observation vector x_{RR} is subjected to errors. In this way, the total approach also allows a better characterization of the SBP/RR relationship, since errors in both SBP and RR can occur due to ECG and ABP signals acquisition errors and abnormal physiologies or due to SBP and RR pre-processing. As TLS estimation is sensitive to scale changes [4], x_{SBP} and x_{RR} were normalized by the step-wise changes of 1 mmHg and 5 msec, respectively.

To reduce sensitivity to outliers, influential SBPramps were removed from BRS analysis by an outlier rejection criteria, as follows. The influence of each SBP ramp was evaluated as the ratio (*TLS slope when that SBP ramp was ommited from the analysis*)/(*TLS slope when all data was used*). An influence value near 1 indicates no significant effect on the BRS estimation. A natural approach for outlier identification would be to find SBPramps with higher influence, with a reasonable threshold being two standard deviations from the mean. For a robust identification, the mean and the standard deviation were replaced by robust measures of location and dispersion, such as the median and the median absolute deviation from the median divided by the normalization factor 0.6745 [5]. As illustrated in figure 3, the criteria introduced allows the identification of outlier events. The extreme points of these outlier events are typically out of the linear mass center of the data and were excluded from BRS analysis, as can be seen from the comparison between figures 2(c) and 2(d).

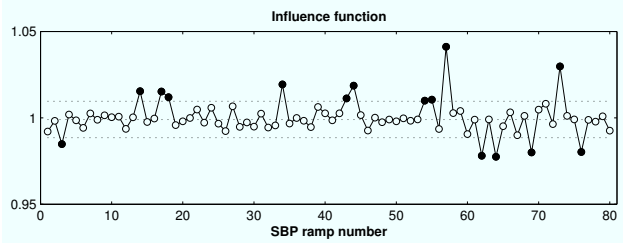
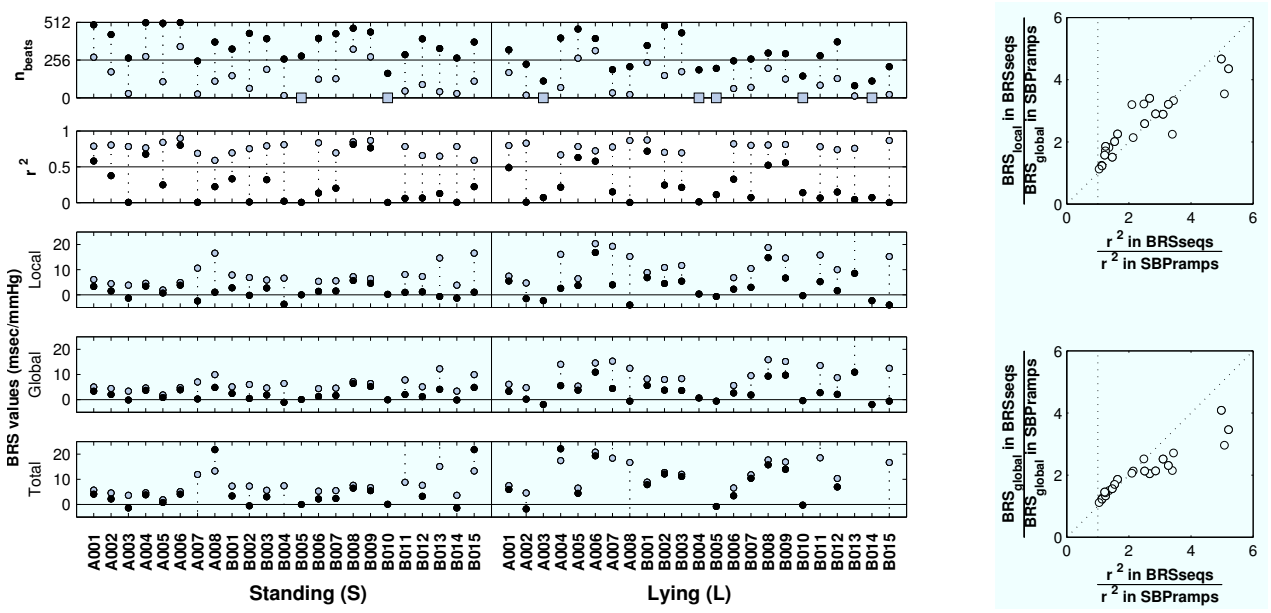


Figure 3. Influence function for the SBPramps with 95% robust acceptance region [5]. Black circles indicate the identified outlier SBPramps. Same data as in figure 2.



(a) (b)

Figure 4. Results of the BRS analysis using BRSseqs (●) and SBPramps (●), for the 46 files in the EuroBaVar dataset. The gray squares indicate the 7 files without BRSseqs. All of the 46 files from the dataset present SBPramps. (a) Number of beats for BRS analysis (n_{beats}), quantification of SBP/RR linear inter-dependence (by the coefficient of determination r^2) and BRS values estimated by *local*, *lobal* and *total* approach. (b) Comparison between *local* versus *global* approach.

3. Results

The experimental data used is the EuroBaVar dataset, composed by 46 paired records of simultaneous SBP and RR, acquired from 21 subjects in lying (L) and standing (S) positions. Two of the 21 subjects were classified as cardiac baroreflex failure patients by the Ewing's score [2]. In this study, the first 512 beats of each record were analysed considering one-beat delay between SBP and RR, that is, SBP values matching the following RR intervals.

Figure 4(a) summarizes the results for the 46 analysed files of the EuroBavar dataset. It was found that the number of beats (n_{beats}) in SBPramps is highly correlated with the n_{beats} in BRSseqs (r=0.73, n=39 files). Also, n_{beats} in SBPramps is always higher, because SBPramps are in higher number and are longer events than BRSseqs. For the 46 analysed files, there were found 5134 (22%) beats in BRSseqs and 15004 (64%) in SBPramps, in a total of 23552 (512 beats times 46 files). For L and S positions, it was found that n_{beats} is always smaller for L, in accordance with [2].

Concerning the quantification of SBP/RR linear interdependence (r^2), higher values with BRSseqs were found. The lower r^2 values with SBPramps are explained by the lower homogeneity in the correspondent SBP/RR values. Also, it was not found significant statistical evidence that the r^2 values both in BRSseq and in SBPramps differ with L and S positions (p>0.3, n=18 subjects, in a hypothesis testing for zero mean paired differences). In the 7 files marked with gray squares, it was not possible to identify BRSseqs and, therefore, no correspondent BRS values can be estimated using BRSseq. From these 7 cases, 4 were paired evaluations of patients B005 and B010 (both for S and L). In these cases, the n_{beats} in SBPramps for S(L) positions identified in these records were respectively 283(200) and 166(148). Also, small BRS values were obtained with SBPramps, as expected in BRS failure cases. However, as r^2 values were very low (<0.15), the small BRS values obtained can be a consequence of poor fit of the linear model and may not be associated with the physiological conditions of the subjects.

With the use of BRSseqs, the BRS values obtained showed large interindividual differences. For S position, the mean(sd) values were 7.4(4.0) for *local*, 5.9(2.5) for *global* and 7.2(3.5) for *total* approach. For L position, the BRS values were higher: 13.9(7.7) for *local*, 11.7(6.5) for *global* and 14.8(8.6) for *total*. All approaches provided estimates with pairwise correlations higher than 0.97 (n=39 files). The results confirm the relation $BRS_{local} > BRS_{global}$ [1] and it was found that $BRS_{local} > BRS_{total} > BRS_{global}$ (p<0.05, n=39).

With the use of SBPramps, the correlation coefficient

between *local* and *global* estimates is 0.87 and between *local* and *total* estimates is 0.40 (n=39 files). As illustrated in figure 4(b), when the ratio of r^2 in BRSseqs and r^2 in SBPramps is low, the similarity between *local* estimates with BRSseq (traditional) and *global* estimates with SBPramps is evident. The same behaviour, but more clear, was observed for the *global* approach with BRSseq and with SBPramps. When r^2 value in SBPramps is close to r^2 value in BRSseqs (few cases), the *total* approach with BRSseq and with SBPramps gives even more similar estimates than the *global* approach.

For the discrimination between L and S positions, it is expected the L/S BRS values ratio to be above 1 [2]. For the subjects with BRSseqs in both positions (18), L/S BRS values obtained with the *local*, *global* and *total* estimates were above 1 respectively in 16, 18 and 17 of the 18 subjects. All subjects present SBPramps and with the use of SBPramps in BRS analysis the power to discriminate L and S is lower: the L/S BRS values obtained with the *local*, *global* and *total* estimates were above 1 respectively in 13, 18 and 14 of the 23 subjects. As illustrated in figure 5, the *global* approach with BRSseqs is able to discriminate 75% (18/23) of the cases. In the 18 subjects that present BRSseqs, the L/S BRS ratio estimated with SBPramps above 1 was respectively 11, 14 and 12 for *local*, *global* and *total* approach.

The boxplot notches (for the medians) and the confidence intervals for the mean illustrated in figure 5 show no significant statistical differences between the means and the medians. With the use of BRSseqs, the confidence intervals indicate significant statistical evidence that the medians and means values are higher than 1 and therefore, when BRSseqs are available, all approaches are able to distinguish L and S with superior results with the *total* approach.

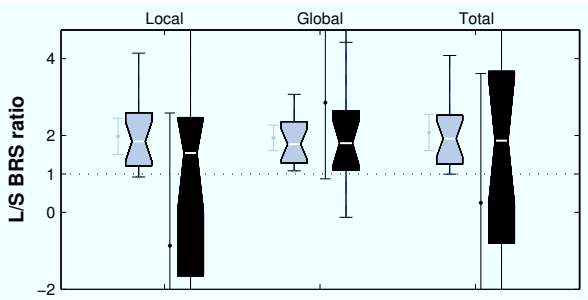


Figure 5. Boxplots of the BRS values ratio for L/S positions, showing the lower quartile, median, and upper quartile BRS values, with BRSseqs (●) and SBPramps (●) and using *local*, *global* or *total* approach. Outliers are not represented in this axis. The 95% confidence intervals for the median and mean are respectively represented by the notch and by the interval at the left of each boxplot.

4. Conclusions

In this work, the use of *local*, *global* and *total* approaches obtained with BRSseqs or SBPramps in BRS analysis is further evaluated. The number of beats in SBPramps is highly correlated with the number of beats in BRSseqs and is higher in SBPramps, because SBPramps are in higher number and are longer events. However, the SBP/RR inter-dependence in SBPramps is much lower. In the EuroBaVar dataset, the previous results were corraborated [1]: $BRS_{local} > BRS_{global}$ and estimates using BRSseqs higher than estimates using SBPramps. It is clear that, when BRSseqs are available, spontaneous *BRS studies should use the global approach with BRSseqs rather than with SBPramps*. Althought a biased estimator, the *global* approach with BRSseqs is less biased and has lower variance than the *local* approach with BRSseqs. Furthermore, the discrimination between S and L is the highest, probably because of the lowest variance of the global estimator with BRSseqs. *Global* and *total* approaches provide similar results only for high SBP/RR inter-dependence values and alternatives have to be found for lower values and for absence of BRSseqs. *Total* estimates present higher power to discriminate L and S, considering the median values. Therefore, in more diversified situations corresponding to clinical practice, it is expected that the robust properties underlying the *total* approach can be fully enhanced.

Acknowledgements

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