# Correlation Between Time Domain Baroreflex Sensitivity and Sympathetic Nerve Activity

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## Abstract

*Autonomic nervous system (ANS) dysfunction is evidenced by reduced baroreflex sensitivity (BRS), which can be quantified as the slope between SBP and RR values in baroreflex events (BEs). BEs can be either of short or of long length, so they are likely to be associated with fast/parasympathetic as well as with slow/sympathetic ANS modulations. Under sympathetic inhibition, LF power in Muscle Sympathetic Nerve Activity (MSNA) decreases and HF power dominates. Therefore, it is suggested that LF and HF powers of MSNA are related with sympathetic neural excitation and inhibition, respectively.*

*In this work, MSNA powers are associated with BRS from short/long BEs, defined from a cutoff length estimated from the respiratory frequency of each subject. The results indicate that BRS from short(long) BEs are correlated with HF(LF), while not significantly correlated with LF(HF) powers. Therefore, short and long BEs may carry different information on ANS modulations in baroreflex regulation.*

## 1. Introduction

Dysfunction of the autonomic nervous system (ANS) is evidenced by reduced baroreflex sensitivity (BRS) indices [1]. The BRS is assessed by measuring RR changes in response to changes in systolic blood pressure (SBP). Time domain BRS methods are frequently used, thanks to their ease of interpretation and implementation [2]. In particular, the sequences technique is based on the identification of baroreflex sequences (BSs), i.e. three or more consecutive beats exhibiting minimum SBP and RR beat-to-beat changes and a minimum SBP–RR correlation [3]. Our previous work evidences that the use of beat-to-beat SBP and RR changes thresholds is redundant, if the minimum correlation is set to 0.8 [4]. This simplification leads to the identification of baroreflex events (BEs), which are not constrained to be monotone segments. Therefore, BEs can be longer than BSs and occur more frequently. The higher number of beats in BEs was shown advantageous in cases of reduced BRS or when BS are not identified [2]. Other studies indicated that baroreflex changes, associated with posture changes [2] or drug induced BRS stimulation [5, 6], can be better detected using the events technique.

Time domain BRS estimates account for both parasympathetic and sympathetic ANS modulations. It is reported that sympathetic ANS branch exhibits oscillations with lower frequency than the parasympathetic branch [7]. As the sequences technique provides a slope based on short segments of data (typically of 3-beats length), it is accepted that BRS estimates based on BSs essentially reflect the parasympathetic ANS activity [8]. As the events technique is able to provide longer BEs, besides the BEs of the same length as BSs, BEs are more likely to also capture the sympathetic ANS modulation [2].

The Muscle Sympathetic Nerve Activity (MSNA) signal has been used to directly investigate ANS modulations and better understand SBP and RR oscillations. Therefore, the observation that the MSNA beat-to-beat series exhibits power in both LF ($[0.04,0.15]Hz$) and HF ($[0.15,0.4]Hz$) bands has been an issue of debate [9]. The RR oscillations around the respiratory frequency (Respiratory Sinus Arrhythmia, RSA) are primarily mediated by the parasympathetic ANS activity and, therefore, increased RSA indicates increased parasympathetic activity. Since respiration also induces mechanical effects on SBP, the HF oscillations in MSNA can be due to the respiratory modulation in SBP and, by this reason, due to increased parasympathetic activity. Other studies corroborate this hypothesis: under a sympathetic inhibition (by continuous administration of phenylephrine) the MSNA power in the LF band decreases and the MSNA power in the HF band dominates over that evaluated for LF band [7]. Therefore, it is suggested that MSNA LF and HF power are related to sympathetic neural

excitation and inhibition, respectively.

In this work, BRS estimates from short/long BEs are associated with MSNA powers, to test if the events technique is able to distinguish the parasympathetic/sympathetic ANS modulations in baroreflex regulation.

## 2. Material and Methods

### 2.1. Data acquisition

The data was acquired from 15 healthy males (20–36 years) in supine rest condition and spontaneous breathing [10]. The experiments were carried out in the Erasme University Hospital, Belgium, in the scope of a protocol approved by the Ethics Committee of the hospital.

For each subject, simultaneous ECG, non invasive ABP, respiration and continuous MSNA signals were recorded during 5 minutes, using a sampling rate of $1000Hz$. MSNA was obtained from multiunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head [10]. Electric activity was measured with the use of tungsten microelectrodes (shaft diameter 200 $\mu$m, tapering to a non-insulated tip of 1 to 5 $\mu$m). A subcutaneous reference electrode was inserted 2 to 3 cm away from the recording electrode, which was inserted into the nerve fascicle. The neural signals were amplified, filtered, rectified and integrated to obtain a mean voltage display of sympathetic nerve activity.

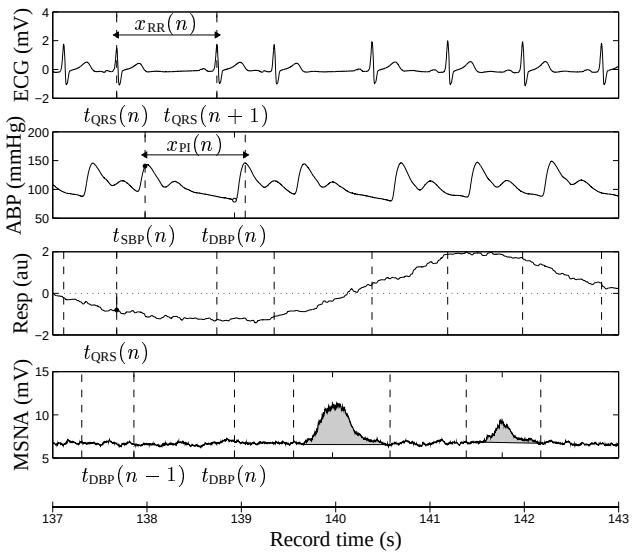


Figure 1. Reference marks in the acquired signals, associated with the $n^{th}$ heartbeat. Data showing a long RR interval and evidencing the ECG, ABP and MSNA phase dependencies. Notation in accordance with [7].

### 2.2. Extraction of variability series

Figure 1 illustrates the procedure to extract the beat-to-beat variability series from the acquired signals. The $x_{RR}(n)$ series was obtained after automatic QRS detection on the ECG signal [11]. The $x_{SBP}(n)$ values correspond to the maxima of the ABP signal in each cardiac cycle, delimited by two consecutive QRS complexes.

Figure 1 also illustrates that the respiratory and continuous MSNA signals do not exhibit variability on a beat-to-beat basis. Therefore, the corresponding beat-to-beat series were extracted with the use of ECG and ABP heartbeat reference marks, respectively. The respirogram $x_{RESP}(n)$ was obtained by sampling the respiratory signal at the time of the QRS occurrence. The MSNA beat-to-beat series $x_{MSNA}(n)$ was obtained through integration of the continuous MSNA signal over the time window between two consecutive diastolic blood pressure (DBP) values. This procedure allowed to obtain variability series synchronous on a beat-to-beat basis that reproduce the phase beat dependencies observed in the acquired signals.

### 2.3. Time domain BRS estimation

Figure 2 illustrates the stages for BRS estimation from the events technique [2]. BRS estimation is performed over the $x_{SBP}(n-1)$ and $x_{RR}(n)$ series, with $n$ indicating the beat number. As illustrated in Fig. 2(a), each baroreflex event $BE_k$, $k = 1, 2, \ldots, K$ is identified as a segment with $N_k$ pairs of values $(\mathbf{x}^k_{SBP}, \mathbf{x}^k_{RR})$ that exhibit a minimum beat length ($N_k \geq 3$) and a minimum correlation between the $x_{SBP}$ and $x_{RR}$ values in that segment ($r_k \geq 0.8$).

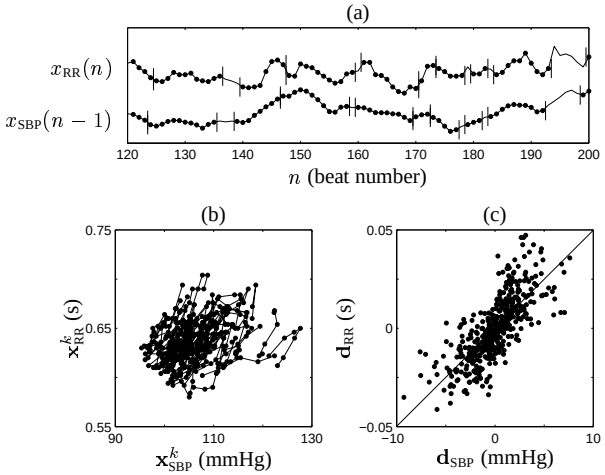


Figure 2. BEs are identified imposing a minimum SBP and RR correlation of 0.8 (a), and the SBP and RR pairs can be displayed (b). After, the data is local mean detrended for slope computation (c). Full line has slope $\hat{\beta}$.

After, the data is locally mean detrended by performing $\mathbf{d}_\vartheta^k = \mathbf{x}_\vartheta^k - \bar{x}_\vartheta^k \, \mathbf{1}_{N_k}$, where $\vartheta \in \{\text{SBP,RR}\}$, $\bar{x}_\vartheta^k$ is the mean of $\mathbf{x}_\vartheta^k$ values and $\mathbf{1}_{N_k}$ is a vector of ones with length $N_k$. This transformation is of major importance because it puts together the SBP and RR pairs identified in BEs at different operating points and enhances the global linear SBP and RR relation (Figs. 2(b–c)).

Before slope estimation, the detrended values from all segments are concatenated in $\mathbf{d}_\vartheta = \left[\mathbf{d}_\vartheta^1 \;\; \mathbf{d}_\vartheta^2 \;\; \ldots \;\; \mathbf{d}_\vartheta^K\right]$ vectors, respectively. Finally, the BRS estimate is the least squares slope $\hat{\beta}$, obtained considering the regression model $\mathbf{d}_{\text{RR}} = \beta \, \mathbf{d}_{\text{SBP}} + \boldsymbol{a}\mathbf{1}_{\mathbf{N}} + \boldsymbol{\epsilon}$, where $\boldsymbol{a}$ is an unknown constant and $\boldsymbol{\epsilon}$ is a noise vector.

## 2.4. Cutoff to define short/long BEs

To perform BRS analysis from short and long BEs, a cutoff length $c$ to define short/long must be estimated. Then, two distinct BRS estimates can be obtained: one estimated from BEs shorter than $c$ ($\hat{\mathcal{B}}^{\text{E},\leq c}$) and another estimated from BEs longer than $c$ ($\hat{\mathcal{B}}^{\text{E},> c}$).

The $c$ value is expected to change for different subjects and conditions as sympathetic/parasympathetic modulations are known to change for different subjects and conditions [7]. Therefore, a cutoff length adjusted to each subject was considered. Intuitively, the cutoff could be BSs mean length, with BEs longer than that being long and vice-versa. However, the BSs length is directly related with the duration of inspiration and expiration phases in the respiratory cycle, with typical duration of 3 to 6 cardiac beats [12]. Therefore, the duration of a breathing cycle can be used as a majorant for BSs length. In this work, the breathing cycle duration was estimated as $1/f_r$, where $f_r$ is the respiratory frequency of the subject. As illustrated in Fig. 3(d) for one dataset subject, $f_r$ was taken as the central frequency of the spectral component with highest variance from the RESP parametric spectrum.

## 2.5. Measures extracted from MSNA

The MSNA power in B $= \{$LF,HF$\}$ bands were computed from the nonparametric MSNA spectrum as

$$\mathcal{P}^{\text{B}} = \frac{\mathcal{P}^{\text{B}}}{\mathcal{P}^{\text{TF}} - \mathcal{P}^{\text{VLF}}} \times 100 \;\text{ and }\; \mathcal{P}^{\text{B}} = \int_{f \in \text{B}} \hat{\mathcal{S}}_{\text{MSNA}}(f) df,$$

where VLF is defined in the [0,0.04]$Hz$ range and TF in [0,Nyquist]$Hz$ (see Fig. 3(c)). This normalization emphasizes the balance between the two ANS branches, with LF being more associated to sympathetic activity and HF being more associated with parasympathetic activity [13, 9]. Also, this normalization reduces the limitation that the acquired MSNA signal is not calibrated.

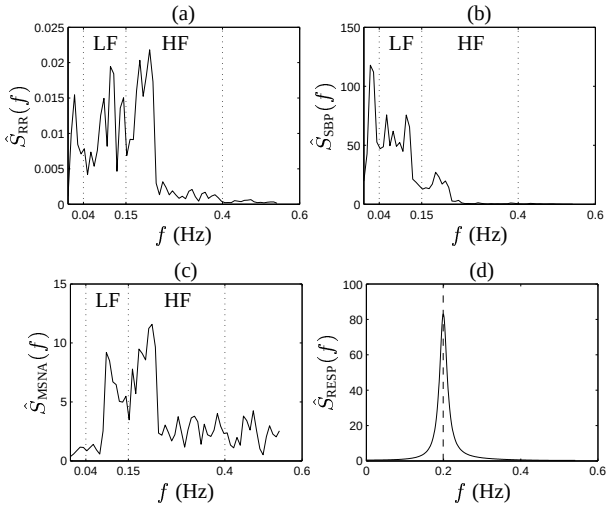


Figure 3. Series spectra for one dataset subject: (a–c) computed from Welch method (Hanning window, 62,5% overlap, 128 FFT points, 5 segments) and (d) computed from AR modelling (Yule-Yalker equations and model order 4). Frequency axis normalized by RR mean.

## 3. Results

Figure 4 shows the distribution of the segments number for the 15 dataset subjects, distinguishing the segments shorter and longer than a respiratory cycle. Because BEs are identified without being restricted to be monotone SBP and RR ramps over time, they can be either shorter or longer than a respiratory cycle (Fig. 4(a)). On the other hand, BSs are shorter than one respiratory cycle (Fig. 4(b)).

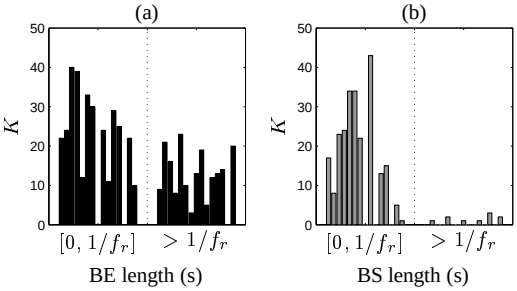


Figure 4. Barplot of segments number ($K$) per segment length (shorter and longer than $1/f_r$). Each bar represents one subject and are sorted by increasing RR mean value.

Figure 5 shows the dispersion diagrams between MSNA powers and BRS estimates from short and from long BEs. By one hand, BRS estimates from short BEs are not significantly correlated with $\mathcal{P}^{\text{LF}}_{\text{MSNA}}$ (Fig. 5(a)) and are significantly correlated with $\mathcal{P}^{\text{HF}}_{\text{MSNA}}$ (Fig. 5(c)). On the other hand, BRS estimates from long BEs are significantly correlated with $\mathcal{P}^{\text{LF}}_{\text{MSNA}}$ (Fig. 5(b)) and not significantly correlated with $\mathcal{P}^{\text{HF}}_{\text{MSNA}}$ (Fig. 5(d)).

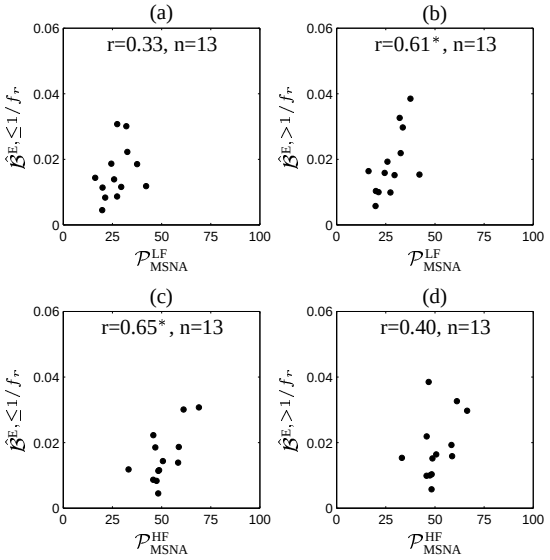


Figure 5. Dispersion diagrams between MSNA powers (evaluated in LF and HF bands) and BRS estimates from short ($\hat{\mathcal{B}}^{\mathrm{E},\leq 1/f_r}$) and from long BEs ($\hat{\mathcal{B}}^{\mathrm{E},>1/f_r}$). The symbol * denotes $p < 0.05$ for the hypothesis of no correlation.

The use of $f_r$ in the cutoff value demands acquiring a respiratory signal. Therefore, an alternative cutoff was estimated by maximizing of the product of the correlations ($\hat{\mathcal{B}}^{\mathrm{E},>c}$,$\mathcal{P}^{\mathrm{LF}}_{\mathrm{MSNA}}$) and ($\hat{\mathcal{B}}^{\mathrm{E},\leq c}$,$\mathcal{P}^{\mathrm{HF}}_{\mathrm{MSNA}}$), varying $2 \leq c \leq 15$ s. The optimal dataset cutoff of 3.5 s did not change considerably the results displayed in Fig. 5, what can be explained by the fact that 3.5 s is a value comparable to the typical length of a breathing cycle (12 cycles per minute), considering a normal and spontaneous breathing condition.

## 4. Conclusions

The results indicate that BRS from short(long) BEs are correlated with HF(LF), while not significantly correlated with LF(HF) powers. Therefore, this study brings evidence that short and long BEs carry different information on ANS modulations in baroreflex regulation. In this work, short and long BEs were defined as $1/f_r$, with $f_r$ being the respiratory frequency of the subject. Further studies are now needed to validate the indicative cutoffs, considering different experimental protocols.

## Acknowledgements

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