Non-Invasive Baroreflex Sensitivity Assessment in Heart Failure Patients with Frequent Episodes of Non-Sinus Rhythm

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Abstract

Baroreflex sensitivity (BRS) has strong independent prognostic value in chronic heart failure (CHF). Reliable noninvasive BRS assessment requires the presence of uninterrupted sinus rhythm during several minutes; however, this condition is often not met in CHF patients due to the frequent occurrence of arrhythmias.

Here, we present a novel method for the determination of a reliable BRS, by composing it from the multiple segments of sinus rhythm that occur throughout a BRS measurement session. This composite BRS is calculated from the multiple segment-based BRS values and their confidence intervals (CI) by using the best linear unbiased estimator (BLUE) method.

For validation we used a set of recordings made in CHF patients who had >7 minutes of uninterrupted sinus rhythm, sufficient for the straightforward computation of a session BRS. These long recordings were then split into multiple short segments from which a multiple-segment-based BRS estimate was computed. As errors were small (1-5%) our proposed method appears to be feasible.

1. Introduction

The arterial baroreflex dynamically buffers blood pressure and heart rate. Baroreflex vigor is characterized by an index termed baroreflex sensitivity (BRS): the reflex-induced change in interbeat interval in ms per mm Hg blood pressure change. BRS has prognostic value in chronic heart failure (CHF); and a rehabilitation-induced BRS increase improves prognosis.[1]

BRS assessment is done by analyzing a sequence of interbeat intervals (IBI) and the corresponding systolic blood pressure (SBP) values. For noninvasive BRS assessment, the SBP values are often measured in the blood pressure signal obtained by the Finapres technology.[2],[3] Although IBIs can be derived from the blood pressure signal, an ECG is preferable because (a) sinus node firing times cannot reliably be estimated from blood pressure[4] and (b) BRS assessment requires that IBI and SBP data be obtained under sinus rhythm, a condition that cannot be verified in the blood pressure.

Introducing a confidence interval (CI) for BRS, and investigating the effect of recording duration on CI, Pinna and Maestri computed that a minimal observation time of 7 minutes is desirable for a sufficiently reliable BRS.[5] The abundant presence of supraventricular and ventricular arrhythmias makes it difficult to obtain 7 minutes of uninterrupted sinus rhythm in CHF patients. Often, the 'harvest' of a BRS measurement session in a CHF patient consists of multiple shorter episodes of uninterrupted sinus rhythm, none of which have the desired minimal duration. As a result, BRS, computed from the longest data segment, will be unreliable.

Here, we present and validate a new method to compute a reliable composite BRS value from the multiple unreliable BRS values that can be computed from all arrhythmia-free segments in the full recording.

2. Methods

2.1. Data set

In the course of a currently ongoing study we measured BRS at four distinct times, several weeks apart, in 70 CHF patients with systolic heart failure and an ejection fraction <45%. BRS measurements consisted of simultaneous 10-minute long recording of a 12-lead ECG and the Finapres blood pressure signal, under 0.25 Hz metronome respiration.[6] Recordings were done supine, with a slight tilt of the upper part of the bed at the patient's choice. Purpose of this was to attain a comfortable position resembling the patient's sleeping position, thus preventing respiratory problems that often occur when CHF patients are lying completely horizontally. Preceding the measurements, the patients rested for 30 minutes in the same position, while the ECG and blood pressure measurement device were connected and tested and the metronome respiration procedure was explained.

All recordings were processed off-line, in order to obtain the SBP-IBI sequence needed for BRS computation. During this stage we checked all recordings on the presence of uninterrupted sinus rhythm for at least 7 minutes. This occurred in 27/70 patients (see Table 1).

Table 1. Group characteristics; N=27, values: mean±SD.

Male / Female	20/7
Age [years]	58±12
NYHA class	2.3±0.6
VO_{2peak} [$mlO_2 \cdot min^{-1} \cdot kg^{-1}$]	17±5

Only one recording with an arrhythmia-free episode of at least 7 minutes was present in 16/27 patients, two in 7/27 patients, three in 4/27 patients and four in none of the patients. In the 11/27 patients with >1 available recordings we selected the most stationary looking data. The thus selected 27 SBP-IBI sequences constituted the data set on which we validated our new method for composite BRS computation.

2.2. Purpose of the experiments

Two experiments were done with the 27 SBP-IBI data sequences: 1) data splitting in multiple segments of equal duration and 2) data splitting in two segments of unequal duration. Purpose of both experiments was to investigate how well the BRS of a patient as computed from the complete and uninterrupted >7 minute lasting data sequence can be reconstructed by computing a composite BRS value based on multiple BRS values computed from the same data after having been split into multiple data segments. Successful reconstruction would mean that a valid and reliable BRS value can be computed in recordings containing arrhythmias: 1) by splitting these recordings into the multiple segments with uninterrupted sinus rhythm that can be found in between the arrhythmias; 2) by subsequent computation of the multiple BRS values associated with all data segments, and 3) by final computation of a composite BRS value from the multiple segment-based BRS values.

2.3. Weighted BRS averaging

We computed BRS as the modulus of the SBP to IBI transfer function averaged over the 0.05-0.15 Hz band.[7] A negative phase angle of the transfer function was required for the complete recording, but not in segments in these recordings.

The BRS confidence interval (CI) depends on the SBP-to-IBI coherence and on data length: lower coherences and less data yield larger CI values.[5] Hence, when the data of a patient are split into various segments, the CI's of the segment-based BRS values differ because of segment-to-segment differences in coherence and data-length. This implies that attempts to compute, for a patient, a composite BRS on the basis of a number of segment-related BRS values, weighted BRS averaging is needed to prevent the disproportionate influence of segments with relatively unreliable data.

The weighting factors to compute a composite BRS from the segment-associated BRS_i were chosen as $(1/CI_i^2)/\Sigma(1/CI_i^2)$, because these weighting factors yield the best linear unbiased estimator (BLUE, a statistical procedure to combine multiple uncorrelated measurements that have the same unknown mean, but possibly different standard deviations[8]).

2.4. Multiple segments, equal duration

In the first experiment we split the recording of each patient into 2, 4 and 8 equal-length data segments. For each of these splitting states all segment-related BRS and CI values were computed. Finally, a composite BRS was computed with the BLUE method described above. See Figures 1 and 2 for an illustration of this process.

Figure 1. Experiment 1 (multiple equal-length segments). Panels A-D show the SBP-IBI data series of CHF patient E05, as a whole, and split into 2, 4 and 8 segments, respectively. The 'LO' and 'HI' segments contain the lowest/highest segment-related BRS values, respectively.

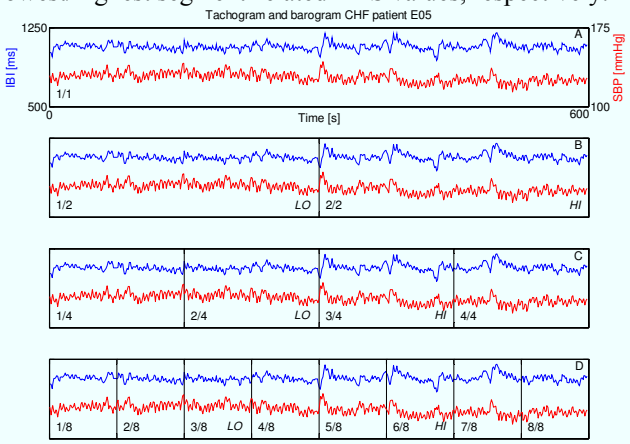
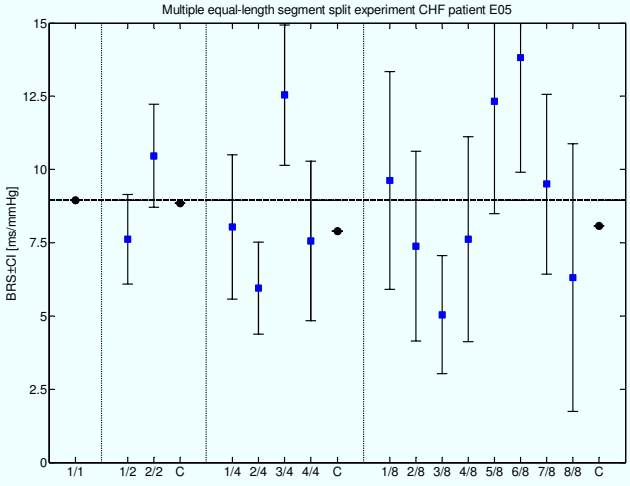


Figure 2. Squares: corresponding segment-related BRS and CI values. Circles: original & composite BRS values.



To characterize the performance of this BRS reconstruction experiment we compared the original and the composite BRS values by a paired t-test. Also, we computed the worst case under- and overestimation by selectively averaging the lowest and the highest segment-related BRS values in every individual, respectively.

2.5. Two segments, unequal duration

In the second experiment we split the recording of each patient into 2 complementary parts of unequal length, at 10, 20, ..., 90 percent of the recording. For each splitting percentage, the left-hand and right-hand BRS and CI values were computed. Finally, a composite BRS was computed with the BLUE method described above. See Figures 3 and 4 for an illustration of this process.

Figure 3. Experiment 2 (two unequal-length segments) in the same patient. Panels A-D show examples of a 10/90%, 30/70%, 70/30% and a 90/10% segmentation. The 'LO' and 'HI' segments contain the lowest/highest segment-related BRS values, respectively (not indicated in panel C because of almost equal values).

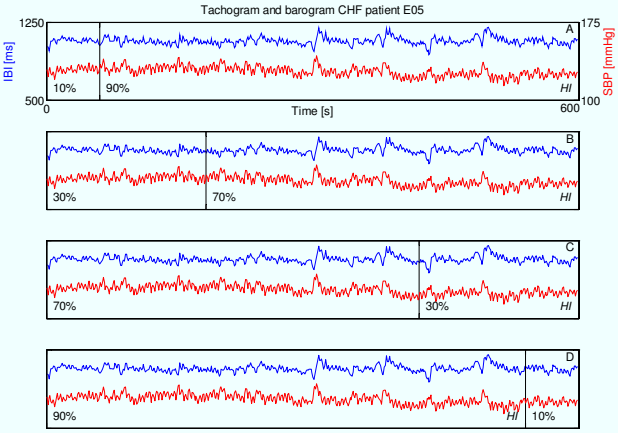
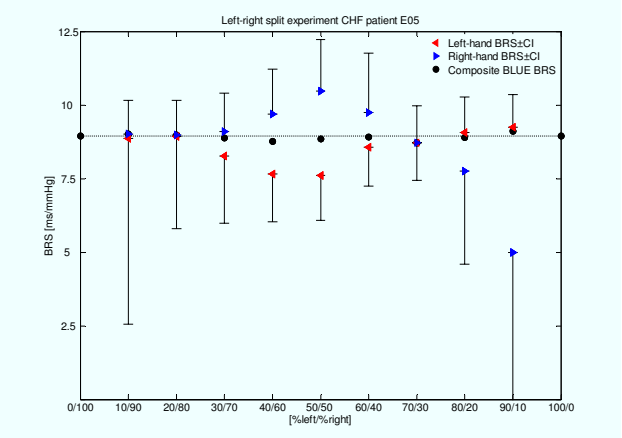


Figure 4. Arrows: corresponding segment-related BRS and CI values. Circles: original & composite BRS values.



The performance of this BRS reconstruction experiment was characterized in a similar way as described above for the multiple equal-duration segment experiment. Segments with a size <50% of the complete recording were excluded from the worst case analysis (in practice, one would not select the shortest segment for analysis).

3. Results

The 27 recordings on which we validated our BRS reconstruction method had an average ± SD duration of 589 ± 35 s [429 – 609 s]. BRS values computed from the complete recordings were 5.01 ± 3.96 [0.69 – 15.19] ms.mmHg^{-1}. The phase angles as computed from the complete recordings were -93 ± 28 [-166 – -50] °.

Table 2 shows the results of the first experiment (splitting of the recording in multiple segments of equal length). For all splitting states the average composite BRS is slightly under the average BRS as computed from the complete recordings. The order-of-magnitude of this error is 1 % and no statistical significantly difference is found between the composite and the original BRS values. Worst case analysis shows that BRS would be severely underestimated or overestimated when only the single segment results are used that have the lowest or the highest BRS, respectively. This error increases with an increasing amount of segments.

Table 3 shows the results of the second experiment (splitting of the recording into two complementary segments of different duration). For all splitting states the composite BRS slightly underestimates the original BRS; the error being somewhat larger than in the first experiment (maximum error is -5.7% in the 40/60 split state). Worst case analysis tends to yield somewhat less dramatic errors than in experiment 1.

Table 2. Results of the first experiment (multiple segments, equal length). P: probability (paired t-test of composite vs. original BRS values); %co: percent difference of averaged composite and averaged original BRS values; %lo (%hi): percent difference of the averaged lowest (highest) segment-related BRS values and the averaged original BRS values.

# Segments	Mean ± SD composite BRS [ms.mmHg^{-1}]	*P*	%co	%lo	%hi
2	4.96±3.88	.86	-0.9	-15	24
4	4.93±3.77	.83	-1.5	-27	56
8	4.95±3.68	.87	-1.1	-41	93

Table 3. Results of the second experiment (two segments, different length). Explanation: see legend of Table 2.

% Segments	Mean ± SD composite BRS [ms.mmHg^{-1}]	*P*	%co	%lo	%hi
10/90	4.89±3.84	.56	-2.2	-10	66
20/80	4.98±3.96	.91	-0.4	-6	39
30/70	4.79±3.71	.20	-4.2	-14	33
40/60	4.72±3.51	.30	-5.7	-18	23
50/50	4.96±3.88	.86	-0.9	-15	24
60/40	4.88±3.91	.67	-2.5	-14	19
70/30	4.74±3.66	.43	-5.2	-22	16
80/20	4.83±3.97	.58	-3.5	-15	21
90/10	4.92±3.95	.75	-1.7	-14	16

4. Discussion and conclusions

In a patient with frequent arrhythmias, a BRS measurement session yields multiple short (instead of one long) data segments of uninterrupted sinus rhythm. This hampers conventional BRS computation. Here, we proposed a method that first computes BRS and the corresponding CI in each of these segments, and finally computes a composite BRS value for the complete recording by weighted averaging of the segment-related BRS values according to the best linear unbiased estimator (BLUE) method. We validated this method by segmentation of long arrhythmia-free recordings, which permitted us to compare the composite BRS with the true original BRS.

Both the multiple equal-length segment and two unequal-length segment experiments showed good results, with a small systematic underestimation of the group average. This may be caused by a slight violation of the BLUE-method related assumption that segment BRS values are uncorrelated, a condition that in general will not be fully met because of the influence of previous SBP and IBI values on successive SBP and IBI values. Another reason for this difference could be that the confidence intervals tend to be somewhat smaller than nominal at high coherence values.[5] Nevertheless, the composite 'BLUE' BRS is preferable above the selection of one (e.g., the longest) segment, that in the worst case might yield dramatically bad results.

Obviously, a sufficient total amount of data should be present, and we have in our experiments maintained the criterion put forward by Pinna and Maestri that the minimum amount of data has to be 7 minutes.[5] The essential step forward in our new method is that it is not necessary to have these data available in one uninterrupted data stream: multiple shorter data segments are also acceptable (as long as the patient is stable).

In conclusion, BRS computation in patients which fragmented episodes of sinus rhythm can reliably been done by composing a session BRS from multiple segment BRS values by weighted averaging. This solution contributes to a better feasibility of noninvasive BRS measurement in the clinic.

Acknowledgements

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