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Estimation of arterial baroreflex sensitivity in relation to carotid artery stiffness

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Abstract— **Arterial baroreflex has a significant role in regulating blood pressure. It is known that increased stiffness of the carotid sinus affects mecanotransduction of baroreceptors and therefore limits baroreceptors capability to detect changes in blood pressure. By using high resolution ultrasound video signal and continuous measurement of electrocardiogram (ECG) and blood pressure, it is possible to define elastic properties of artery simultaneously with baroreflex sensitivity parameters. In this paper dataset which consist 38 subjects, 11 diabetics and 27 healthy controls was analyzed. Use of diabetic and healthy test subjects gives wide scale of arteries with different elasticity properties, which provide opportunity to validate baroreflex and artery stiffness estimation methods.**

I. Introduction

Characterization of elastic behavior of arteries is important, because increased stiffness reflects atherosclerotic changes in vascular wall [1] and, thus, is potential risk marker for cardiovascular diseases [2]. Arterial compliance has also been reported to be related to baroreflex function [3].

Arterial baroreflex has a significant role in regulating blood pressure homeostasis and its impairment may result in exaggerated blood pressure fluctuations. Estimate of the gain of baroreflex is usually referred as baroreflex sensitivity (BRS). In modern methods, BRS can be estimated from spontaneous fluctuations of blood pressure and heart rate [4].

It is known that increased stiffness of the carotid artery affects mecanotransduction of baroreceptors and therefore limits baroreceptors capability to detect changes in blood pressure [5], [6]. For this reason two different types of BRS estimates have been used, which are; overall BRS ($\mathrm{BRS_o}$) and neural BRS ($\mathrm{BRS_n}$). $\mathrm{BRS_o}$ is estimated using relation between systolic blood pressure time series (SBP) and RR interval time series (RR) [7]. Estimation of $\mathrm{BRS_n}$ parameter systolic artery diameter time series ($\mathrm{d_s}$) is used instead of SBP timeseries. $\mathrm{BRS_n}$ calculated from the $\mathrm{d_s}$ variations is thought to describe better neural component of BRS, because elasticity changes are eliminated by using a signal which baroreseptors detect directly i.e stretch of artery. Figure 1 shows how cardiovascular variability signals are linked to each other.

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By using high resolution ultrasound video signal and continuous measurement of blood pressure, it is possible to define elastic properties of artery from beat-to-beat stress and strain values. When these measurement are done synchronously with ECG recording also $\mathrm{BRS_o}$ and $\mathrm{BRS_n}$ can be estimated simultaneously (see Fig. 1).

The overall and neural component of BRS have been studied in healthy subjects [8]. Also there are few studies where artery elasticity is compared to BRS [5]. However all these studies have been done on healthy subjects. In this paper, we analyzed data set consisting of 38 subjects, 11 diabetics and 27 healthy controls. Use of diabetic and healthy test subjects gives wider scale of artery elasticities, which provide better opportunity to study relation between artery stiffness and baroreflex sensitivity. The aim of this study was to validate $\mathrm{BRS_o}$ and $\mathrm{BRS_n}$ estimation methods by comparing healthy subjects and diabetic patients whose elastic properties of an artery and/or functioning of neural pathways is reduced.

II. Materials and methods

A. Subjects and measurement

Total of 38 volunteers, 11 diabetics and 27 healthy controls participated in this study. Characteristics of both groups are shown in Table I.

TABLE I
The number of subjects (N), age (years, Mean±SD) and gender (female/male) of test subjects in the two groups.

	Healthy	Diabetic
N	27	11
Age	20 ± 1	37±9
Sex f/m	23/4	9/3

ECG, blood pressure and carotid artery ultrasound images were recorded in Kuopio University Hospital. During the measurement subjects were in supine position. The ultrasound scanner used was a Acuson Sequoia 512 (Siemens, USA). The carotid artery was visualized with B-mode ultrasound using linear 14 MHz transducer. The measurements were made approximately 10 mm proximal to the bifurcation. Continuous blood pressure was measured from finger level using volume clamp method and Finapres device (Ohmeda Englewood, CO).

ECG and blood pressure signals were recorded to a PC computer using standard A/D-converter card and ultrasound

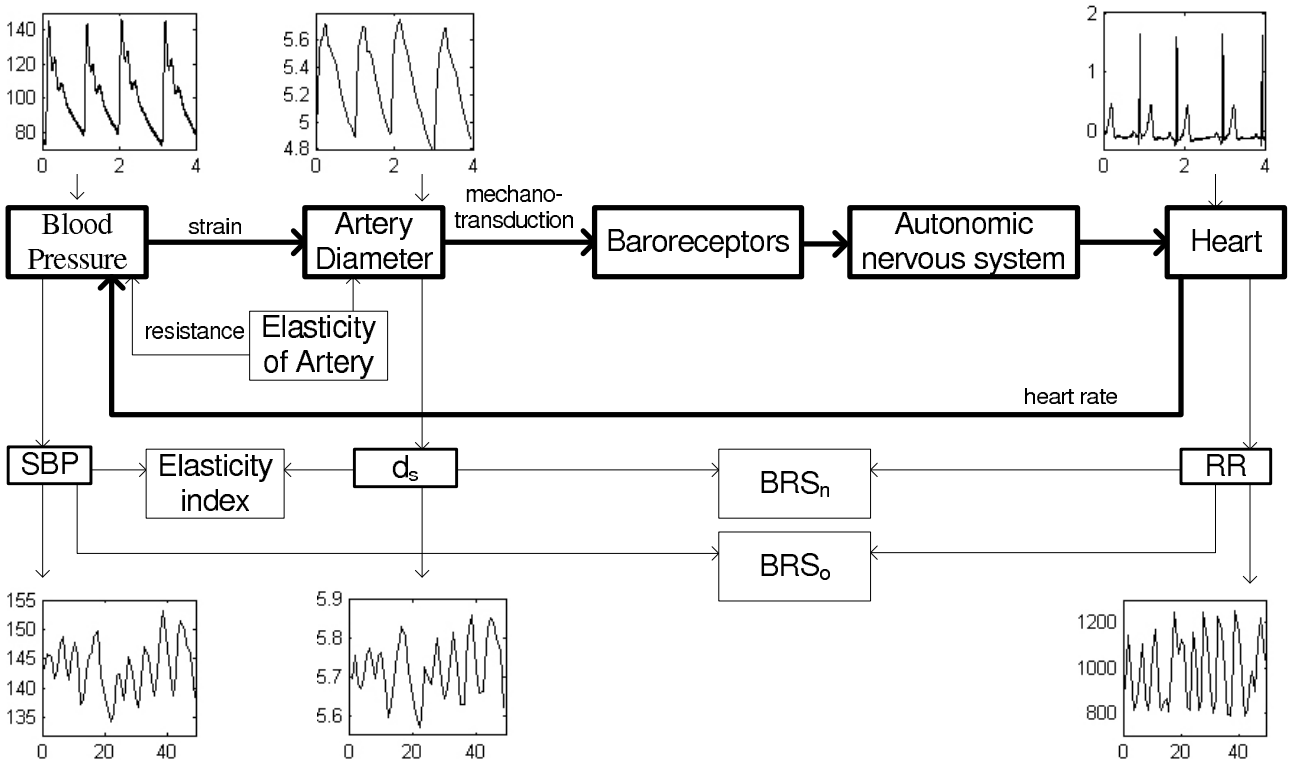

Fig. 1. Schematic representation of cardiovascular variability signals and parameters. The bolded arrows indicates a closed loop which regulates blood pressure. $\mathrm{BRS_o}$ indices have been evaluated by using systolic blood pressure (SBP) and heart rate. Elasticity of artery affects these indices. $\mathrm{BRS_o}$ indices evaluated by using diameter variability instead of SBP estimates better the activity of neural pathways, because elasticity of artery does not affect the estimate.

images as a video signal using video card. Sampling frequency of ECG and blood pressure signals was 1000 Hz and video signal frame rate 25 fps. The duration of recorded signals and videos were 2 minutes.

B. Arterial stiffness and baroreflex sensitivity analysis

The analysis begins by detecting R-wave time points from the ECG signal and by constructing a RR interval time series and subsequently systolic and diastolic blood pressure (SBP and DBP, respectively) time series. Carotid artery diameter is detected frame-by-frame from ultrasound images by using a neural network edge detection algorithm [9].

RR, SBP and d_s time series were resampled by using cubic spline interpolation with sampling rate of 4Hz. Before spectrum estimation each time series was detrended by using a smoothness priors based detrending method [10]. The smoothness priors method corresponds to a time varying high-pass filter, the cut-off frequency of which can be changed by smoothing parameter λ. A smoothing parameter $\lambda = 500$ which corresponds a cut-off frequency of 0.039 Hz was used.

Frequency contents of the time series were calculated by using Welch's periodogram method with Hanning window. Time series were divided into three smaller segments which overlapped 50%. Coherence where then estimated by using autospectrum and crosspectrum estimates which were averaged over the three smaller segments of the time series.

For BRS estimation spectral method was used. BRS_o index is estimated on frequency domain as follows [11]

$$\mathrm{BRS}_o = \sqrt{\frac{P_{\mathrm{RR}}}{P_{\mathrm{SBP}}}}. \tag{1}$$

where P_{RR} and P_{SBP} are the low frequency LF (LF: 0.04-0.15 Hz) band powers of RR interval and SBP segments were coherence of these time series is more than (> 0.5). BRS_o index can be considered to be a transfer function gain of a linear system where SBP values are system input and RR interval values are system output. Therefore BRS_o index is meaningful only if it is estimated for those frequency values were coherence is high enough [12].

$\mathrm{BRS_n}$ which describes functioning of neural BRS is estimated similarly:

$$\mathrm{BRS}_n = \sqrt{\frac{P_{\mathrm{RR}}}{P_{d_s}}}. \tag{2}$$

Where P_{d_s} is the LF-band power of the d_s time series.

Mechanical properties of an artery were estimated using artery compliance C_a which is defined as a ratio of strain (defined from carotid artery ultrasound images) and stress (pulse pressure) as follows

$$C_a = \frac{d_s - d_d}{\mathrm{SBP} - \mathrm{DBP}} \tag{3}$$

where SBP and DBP are systolic and diastolic blood pressures, $\mathrm{d_s}$ is end systole artery diameter and $\mathrm{d_d}$ is end diastole

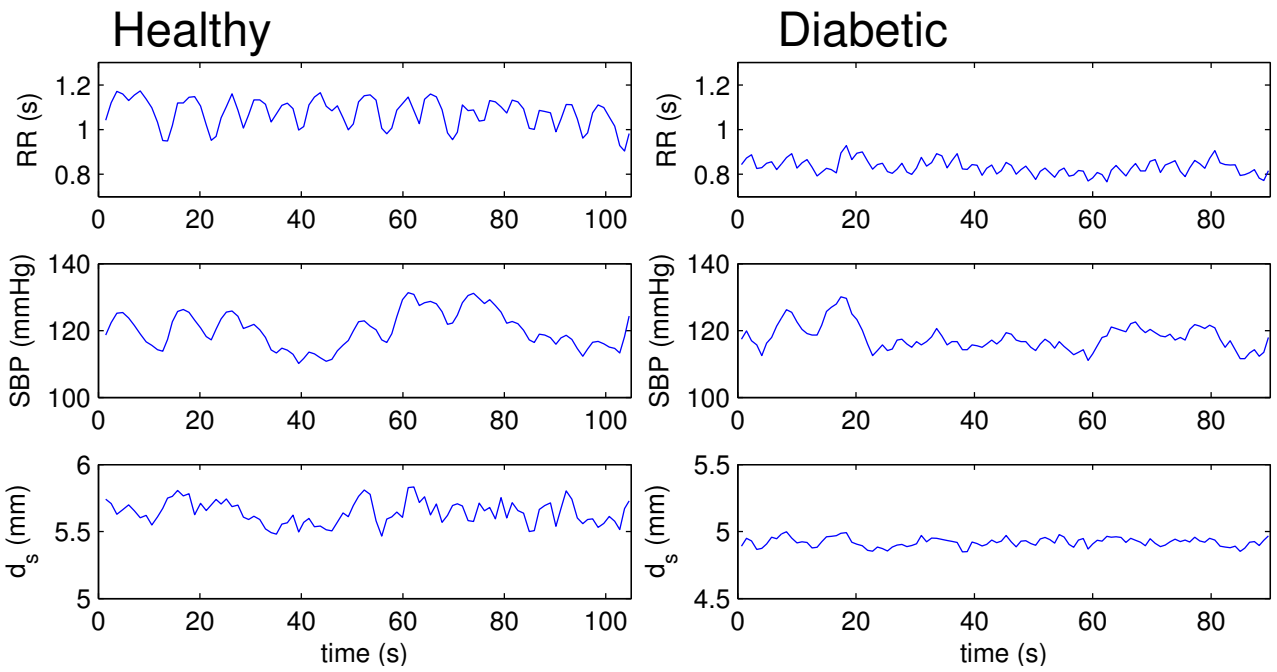

Fig. 2. Two representative examples of measured timeseries, Healthy (left) and Diabetic (right). The upper plot illustrates RR timeseries, in middle plot there is SBP timeseries and in lowest plot diameter timeseries is shown.

artery diameter.

III. Results

Figure 2 shows time series of one representative subject from both groups. Presented time series are RR-interval (top row), systolic blood pressure (middle row) and end systole diameter (bottom row). Estimated parameters for healthy subject were $\mathrm{BRS_o}$ = 16.4 ms/mmHg, $\mathrm{BRS_n}$ = 811 ms/mm, $\mathrm{C_a}$ = 0.0149 mm/mmHg and for diabetic subject $\mathrm{BRS_o}$ = 7.2 ms/mmHg, $\mathrm{BRS_n}$ = 747 ms/mm and $\mathrm{C_a}$ = 0.0092 mm/mmHg. Mean SBP and SBP variation are similar for both subjects, however $\mathrm{d_s}$ variation is lower and thus compliance is lower in diabetic subject which indicates reduction of artery elasticity. RR-interval variation is smaller and overall $\mathrm{BRS_o}$ is smaller for diabetic subject, however $\mathrm{BRS_n}$ is not reduced which indicates that reduction of $\mathrm{BRS_o}$ is caused by lower artery elasticity.

In figure 3, $\mathrm{BRS_o}$ (left) and $\mathrm{BRS_n}$ (right) estimates are presented as a function of artery compliance. Diabetic group results are presented as red color and healthy group results as blue color. Correlation line is presented using black line.

IV. Discussion

Stiffening of carotid arteries and aortic arch, where baroreceptors are located, affects mechanotransduction of baroreceptors and limit capability of baroreceptors to detect blood pressure fluctuations [5], [6]. As seen in figure 2, even remarkable changes of blood pressure, in diabetic subject, are not capable to stretch artery normally when elasticity is reduced. Only way to study, whether the reduced BRS is associated with reduction of elasticity and/or reduction of neural pathways, is to measure the carotid artery diameter variation where baroreceptors are located and BRS at the same time.

From figure 3 can be noticed that due to the reduced artery compliance $\mathrm{BRS_o}$ is also reduced in diabetic subjects. Group mean value is clearly lower than in control subject group. Although it was surprising that such low as < 5 ms/mmHg $\mathrm{BRS_o}$ values were found from control group also. $\mathrm{BRS_n}$ on the other hand is reduced only on few diabetics. Larger $\mathrm{BRS_n}$ values indicates that neural pathways are still working but baroreceptors are not capable to detect blood pressure fluctuations because of reduced artery compliance.

In earlier studies artery elasticity has been found to correlate well (r=0.78) with baroreflex sensitivity in healthy young subjects [5]. Even though our dataset contains diabetics whose artery elasticity is reduced and young healthy subjects with high arterial elasticity such strong correlation could not be found. Correlation was only r = 0.268 for whole dataset and it was even lower for healthy subjects' group. Nevertheless low elasticity affects clearly overall BRS of few diabetics whose elasticity is lowest and neural $\mathrm{BRS_n}$ estimate on the other hand is in normal range when comparing to healthy group.

There are few situations when BRS estimation methods are not working reliably. Very low BRS values are troubled because in spectral method, frequency bins where coherence is higher than 0.5 may not be found. This means that there is no clear feedback between SBP and RR. In this study BRS could not be determined from five diabetic subjects and thus they were excluded from final analysis. Secondly low respiratory frequency (below 0.15 Hz) affects greatly on BRS estimates, because variation caused by respiratory sinus

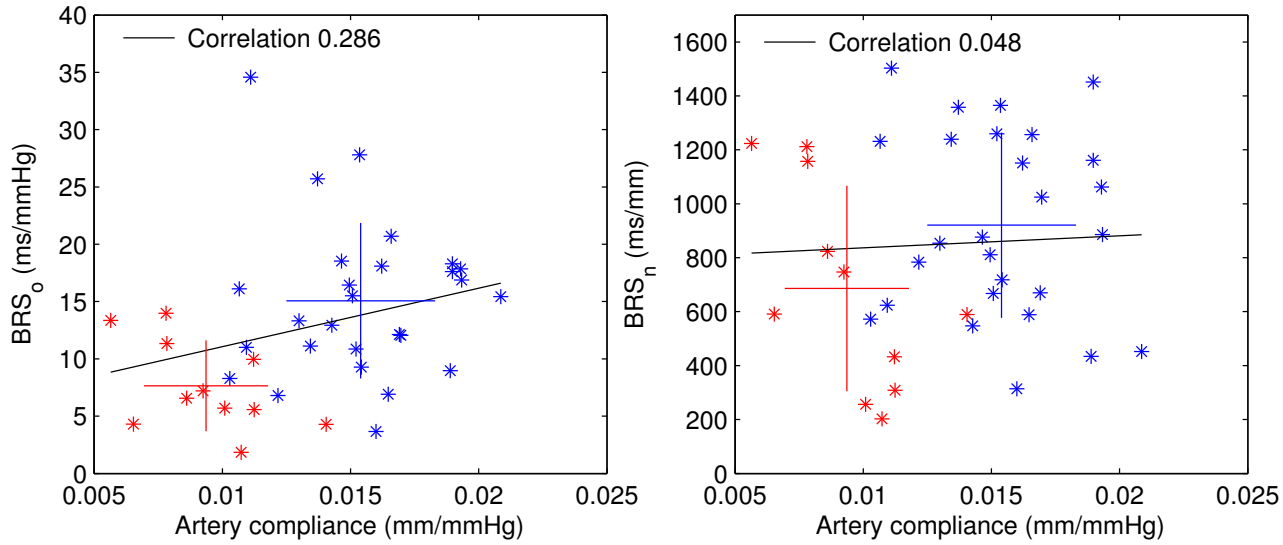

Fig. 3. $\mathrm{BRS_o}$ (left) and $\mathrm{BRS_n}$ (right) as a function of artery compliance. Results of diabetic subjects are marked as a red stars and group mean $\pm$ standard deviation is marked as a red lines. Results of healthy subjects are marked using blue color.

arrhythmia and baroreflex can not be separated. Two healthy subjects were excluded because of low respiratory rate.

We have presented method for analyzing the connection between artery stiffness and baroreflex sensitivity. Methods were tested using 11 diabetics and 27 healthy subjects. Overall BRS was reduced with all diabetics because of reduced elasticity but $\mathrm{BRS_n}$ parameter revealed that neural pathways are still functioning in some diabetics. The results of this study suggest that the methods can be usefull in analyzing the relationship between BRS and carotid artery stiffening and in evaluating the degree of cardiovascular autonomic neuropathy for example diabetic patients.

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