The Beat-to-Beat Responses of the Reflection Index and Stiffness Index Are Linked to the Increases in Arterial Pressure and Heart Rate in Active Standing

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Abstract

The present study aimed to assess the beat-to-beat association between the increases in blood pressure (ABP) and heart rate (HR) induced by active standing (AS) with changes in the reflection index (RI) and stiffness index (SI), respectively. The similar and strongly correlated time courses of responses to AS of RI, Systolic pressure (SBP), and dicrotic wave pressure (DWP) were used to divide it into phases: fast fall (FF), fast increment (FI), slow change (SCH), and recovery (R). The RI time course changes were associated with the inequality between the DWP and SBP changes. The decrease in RI in FF and its rapid increase in FI were associated with a greater change in DWP than in SBP. The slow rise in SCH and return to baseline were due to a greater change in SBP than in DWP. The time course response of SI, slight diminution in FF, quick increment in FI, slow increment in SCH, and return to baseline was similar and strongly correlated with the time course response of the systolic time (ST). Therefore, the increases in SBP and HR induced by the increase in sympathetic activity in AS provoke the characteristic responses of RI associated with inequality between DWP and SBP changes and SI associated with ST shortening.

1. Introduction

The scarce clinical use, due to the difficulty of measurement presented by the so-called gold standard measures of reflection waves and arterial stiffness, contrasts with the growing clinical use of photoplethysmography (PPG)-derived reflection index (RI) and stiffness index (SI), due to the ease of non-invasive registration of PPG and its extraction [1]. The normal ranges of RI and SI depend on the individual's age, heart rate (HR), and arterial blood pressure (ABP) [1].

The RI has shown its clinical utility in the assessment of arterial stiffness and vasomotor tone. Arterial stiffness is recognized as an independent and significant predictor of cardiovascular morbidity and mortality [1].

The SI is considered to be a reliable measure of arterial stiffness [1]. This measure, in hypertensive patients, showed significant correlations with ABP levels and cardiovascular risk scores [2]. It has also demonstrated clinical utility for cardiovascular disease prevention.

It has been widely documented that active standing (AS) elicits increments in heart rate (HR), systolic (SBP), and diastolic blood pressure (DBP) [3] due to increased sympathetic activity mediated by the baroreflex. This attribute makes AS a valuable test for the evaluation of baroreflex alteration in variants of orthostatic hypotension or hypertension and autonomic dysfunction [3].

Using a beat-to-beat approach for tracking the time courses of the variables from ABP – SBP, DBP, dicrotic wave pressure (DWP) – and from HR – interbeat period (IP) and their subperiods, diastolic time (DT) and systolic time (ST) –, we assume that AS causes characteristic changes in RI (DWP/SBP ratio) and SBP to DWP time (SDWT, inverse of SI), which can be associated with the well-known effects induced by AS of increases in ABP and decrease in IP. In particular, we focus on the search for the functional relationship between the impact on the amplitude and the intervals of SBP and DWP, which are the variables in common that define IR and SI. Therefore, we assessed the effects of AS on the beat-to-beat time courses of SBP, DWP, RI, SDWT, SI, IP, ST, and DT series, all features extracted from the ABP.

2. Methods

2.1. Subjects

Twenty-three healthy, nonsmoking, and sedentary volunteers, 12 men and 11 women, participated. Their mean age, height, and weight were 22.2±2.2 years, 167±8 cm, and 69.1±10.4 kg, respectively. Their written informed consent was requested to participate. The ethics committee of our university approved this study.

2.2. Protocol

During the first visit to the laboratory, the subjects' health status and anthropometric variables were assessed. During the second visit, the experimental stage was carried out. Subjects underwent 1-min control, 1-min AS, and 2-min recovery stages. To perform AS, the subjects rapidly stood up from the supine position, remained standing for a minute, and returned to the supine position to end the

maneuver. Throughout the entire session, ECG and noninvasive ABP were recorded.

2.3. Signal recording and acquisition

ECG was detected at the thoracic bipolar lead CM5 using a bioelectric amplifier (Biopac Systems). Noninvasive ABP was measured by Finapres (Ohmeda). All signals were digitized at a sampling rate of 1 kHz via an acquisition and display system (Biopac Systems).

2.4. Data processing

From the ABP wave, the first derivative signal was computed to perform the beat-to-beat extraction of the ABP features and construct the time series of SBP, DBP, DWP, IP, its subintervals ST, DT, and SDWT (SBP to DWP time), features used to compute RI (DWP/SBP) and SI as the individual's height/SDWT. The time series were cubic-spline interpolated and resampled at 4 Hz.

To highlight any patterned responses and characterize the time course response of the variables to AS, their assembled averages were obtained. The time course responses of ABP and HR showed characteristic changes that were used to divide the response into sequential phases of fast fall (FF), fast increase (FI), slow change (SCH) and return to baseline (R), phases that were used to characterize, in each of them, the changes in the response patterns of RI, SI and their integrative index RIxSI to AS. The phase-by-phase functional association between the changes in SBP and DWP with those in RI and, by correlation, the functional association of the SDWT period with ST and DT were also assessed.

2.4. Statistical analysis

Data are expressed as mean±SD. Differences between the control and mean value of each variable in each AS phase were tested by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test. Indexes dynamics were used to compute correlations between them. Statistical significance was set at $p<0.05$.

3. Results

The mean values of each phase of all the variables were different ($p<0.01$) compared to their baseline means, except for RI and DT in SCH.

AS induced, in relation to the baseline, a response pattern characteristic of the RI time course that was adjusted to the phases of ABP (Fig. 1B), consisting of: an initial deep decline, followed by an increase toward baseline, which was rapid at first and then slow (Fig. 1B, Table 1), which is continued with a sustained slow light increase until the end of AS. During the FF phase, DWP decreased at a faster rate than SBP; in the FI phase, DWP increased at a quicker rate than SBP, and during the SCH phase, DWP sustained its increase and SBP reduced its rate of increase (Fig. 1A). In the R phase, DWP first decreases slightly while SBP increases, and later on, the degree of decrease in DWP is less than that of SBP, so RI decreases, followed by an increase above the baseline (Fig. 1). DWP showed the deepest drop in FF, and SBP the largest rise in FI. The variation in DBP was intermediate in the DWP-SBP range. The mean correlation of DWP was higher ($p<0.01$) with DBP ($r=0.96\pm0.02$) than with SBP ($r=0.88\pm0.06$), and that of RI was higher ($p<0.01$) with DWP ($r=0.78\pm0.08$) than with SBP ($r=0.46\pm0.17$).

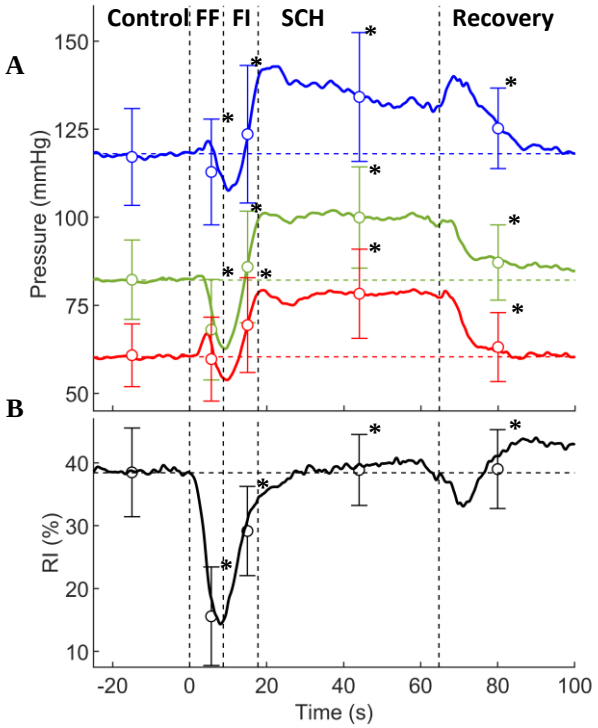

Fig. 1. Ensemble average and mean ± SD in the AS phases of the time courses of: A) SBP (blue), DBP (red), DWP (green), and B) RI. *$p<0.01$ vs. control

Table 1. Mean values of RI, SBP, DWP, and DBP time courses in control and the AS phases. (N=23)

Feature	Control	AS		
		Fast Fall	Fast Increase	Slow change
RI (%)	38±7	13±7*	36±7*	42±6*
SBP (mmHg)	117±14	113±15*	124±20*	134±18*
DWP (mmHg)	82±11	68±14*	86±16*	100±14*
DBP (mmHg)	61±9	60±12	69±13*	78±13*

*$p<0.02$ vs. control

The response pattern of IP and DT time courses showed changes consistent with the response pattern of ABP to AS: initial shortening, rapid increment, and plateau, where IP

remained shortened but DT reached its baseline value. The ST changes were a slight initial increase in the FF phase, followed by rapid shortening in the FI, whose level is sustained in the SCH phase (Fig. 2A). AS provoked, in relation to baseline, a SI time course response pattern consisting of a slight decrease in the FF phase, a rapid increase in the FI phase, and a slow growth, which was maintained in the SCH phase (Fig. 2C). SDWT was similar to the ST response (Fig. 2), with a higher correlation ($p<0.01$) with ST ($r=0.88\pm0.09$) than DT ($r=-0.55\pm0.17$).

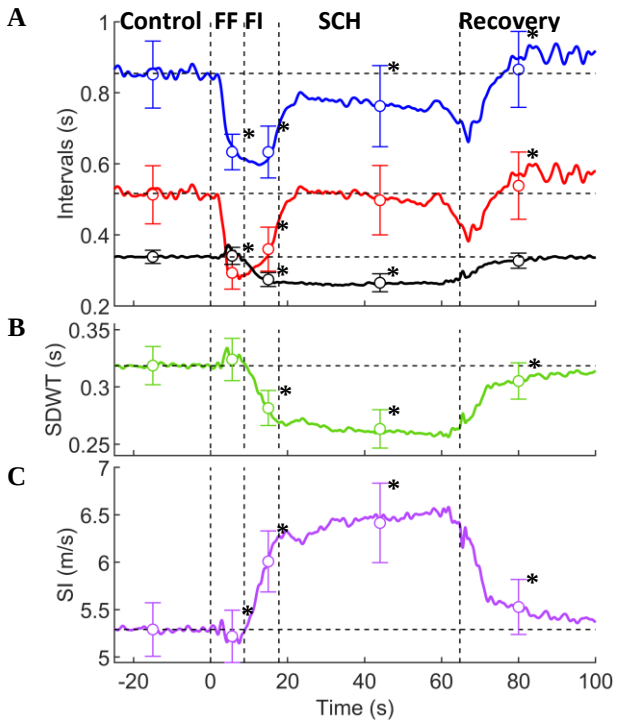

Fig. 2. Ensemble average and mean ± SD in the AS phases of the time courses of: A) IP (blue), DT (red), ST (black), B) SDWT, and C) SI. *p<0.01 vs. control

Table 2. Mean values of SI, IP, ST, DT, and SDWT time courses in control and AS phases (N=23)

Feature	Control	AS		
		Fast Fall	Fast change	Slow change
SI (m/s)	5.29±0.28	5.22±0.28*	6.01±0.32*	6.41±0.42*
IP (s)	0.85±0.09	0.63±0.05*	0.63±0.07*	0.76±0.11*
ST (s)	0.34±0.02	0.34±0.02	0.27±0.02*	0.27±0.03*
DT (s)	0.51±0.08	0.29±0.05*	0.36±0.06*	0.50±0.10
SDWT (s)	0.32±0.02	0.32±0.02	0.28±0.02*	0.26±0.02*

*p<0.02 vs. control

The association of phase-by-phase SI changes with ST changes was inverse: the slight initial decrease in SI was associated with the slight initial increase in ST; its rapid increase with the shortening of ST; the sustained slow increase of SI associated with the sustained shortening of ST; and the return to baseline of SI is associated with the return of ST to its baseline (Fig. 2, Table 2). The mean correlation of the time courses of RI and SI was $r=0.7\pm0.1$.

The time course of the RIxSI index was in accordance with the phases of ABP and HR response patterns: an initial deep drop in the FF phase, associated with the deep fall of RI; a rapid increase in FI followed by a slow increase in the SCH phase, associated with the rapid and slow increases of both RI and SI; and then returning to its baseline in R, associated with RI and SI recoveries (Fig. 3).

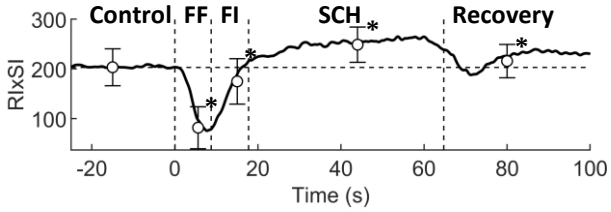

Fig 3. Ensemble average and mean±SD in the AS phases of the time course of the RIxSI index. *p<0.01 vs. control

4. Discussion

The main findings of the present study are that AS induces a characteristic response in the time courses of RI, SI, ABP variables, and HR subperiods; and that the changes in the time courses of: a) RI are provoked by the inequality of the changes of the SBP and DWP time courses, and b) SI depends on the changes in ST, by the strongly correlated similarity of their time courses. These findings provide relevant insights into the functional basis of RI and SI and the beat-to-beat AS physiology.

Part of our methodological strategy is the use of the time series of RI, SI, and the ABP and IP variables to characterize the non-stationary beat-to-beat response of each one of them to AS, to assess the similarities and differences of their respective time courses, and to obtain the correlations between them.

Beat-to-beat responses to AS of DWP, DT, and ST have not been reported. The beat-to-beat similar responses of SBP, DWP, DBP, and HR have not been classified into phases. However, the ABP features, maxima, and minima, documented in one of the few studies on the subject [3], agree with some of the phases we identified.

Supported by our findings, the time course responses of ABP and IP variables to AS have the following attributes:

- Great similarity, strongly correlated, of SBP, DWP, and DBP, characterized by a sequence of rapid fall, rapid increase, slow change, and rapid recovery (Fig. 1A). Phases used to characterize changes in RI and SI time course responses; pressure changes of different amplitude, the largest increase in SBP, and the deepest drop in DWP (Fig. 1A). Despite presenting a greater correlation with DBP than with SBP, DWP changes may depend in a similar proportion on the increases in peripheral vascular resistance and in left ventricular function, elicited by AS in a baroreflex manner. In contrast to extensive studies of the

physiology of SBP and DBP, that of DWP is not fully understood. DWP, the intermediate pressure between SBP and DBP, is influenced by arterial function, in a relevant way, by the elastic recoil and the reflected waves. The SBP-DWP difference has been used as an index to predict the outcome of a fluid challenge in surgical patients [4].

- Great similarity, strongly correlated, between IP and DT time courses, with a minor effect on ST. These time course responses fit the same phases as the ABP and HR response patterns (Fig. 2A).

Reported findings that support the RI function are that during non-REM sleep, the reduction in ABP resulting from a decrease in vasomotor tone is associated with a reduced RI [5]. The deep breathing maneuver reduces the RI [6]. In athletes, larger maximal oxygen uptakes are associated with smaller RI [7]. There are no available studies on the beat-to-beat response of RI to any intervention or disease.

The time course response of RI to AS adjusts to the phases of the ABP response pattern, similarity strongly correlated, consisting of a significant drop in FF, rapid recovery in FI, slow increase above the baseline in the SCH phase, which falls and then increases above the baseline in R. This answer can be explained by the inequality in the changes of ascent and descent of SBP and DWP, which occur in the same direction in the FF and FI phases but in the opposite direction in the SCH and R phases (Fig. 1). RI changes depend more on DWP changes than on SBP changes, supported by its greater correlation with DWP.

One of the few published studies about the SI physiology documents that, in healthy subjects, the increase in ABP provoked by an isometric exercise load is associated with increased SI [8]. There are no available studies on the effect of AS on SI or the beat-to-beat response of SI to any intervention or disease. The characteristic response of the time course of SI also adjusts to the phases of the ABP and IP responses: a slight decrease in FF, first a rapid increase in FI, then a slow increase maintained until the end in the SCH phase. The striking visual similarity of the time course response of SDWT to that of ST (Fig. 2), as well as the greater correlation of SDWT with ST than with DT, suggests the greater dependency of SDWT on the changes of ST (Fig. 2, Table 2), because ST partially contains SDWT. Analogously, the remarkable similarity of the time course response of IP with that of DT and the greater correlation of IP with DT than with ST, support that the IP shortening depends on the DT shortening in FF and FI phases, and only on the ST shortening in SCH phase (Fig. 2, Table 2).

Remarkably, AS makes the time courses of SBP, DBP, DWP, IP, ST, DT, RI, and SI respond similarly, supported by the moderate to strong correlations between them.

Since RI and SI are computed from variables in common, the ratio between DWP and SBP, and the period between SBP and DWP, it is possible to integrate the two indices in the RIxSI product. This index that we propose presents the ability to characterize the relevant changes both in RI and SI time courses: initial fall followed by increment, first rapid and then slow, which is sustained until the end of AS (Fig. 3). Further studies are required to validate its possible physiological and clinical utility.

In conclusion, AS induces similar and moderately correlated characteristic time course responses in RI and SI: an initial fall, deeper in RI and lighter in SI, a quick increase followed by a slow increase in both indexes, and recovery to baseline. While RI changes are associated with the unequal changes in SBP and DWP, those of SI depend on the strongly correlated shortening changes in ST. We propose the RIxSI index, which integrates the RI and SI responses induced by AS. Thus, the RI and SI time course responses are produced by the fluctuating increments of the left ventricular-arterial function and of HR, caused by sympathetic activation triggered by AS via the baroreflex.

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