Instantaneous Time-Courses of Baroreflex Sensitivity, Sympathetic and Vagal Activities in Response to Valsalva Maneuver

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Abstract

We assessed, in 59 recordings of healthy volunteers, the effects induced by Valsalva maneuver (VM) on the 140-s time-courses of the low frequency components of RR (LF_{RR}), systolic blood pressure (LF_{SBP}), diastolic blood pressure (LF_{DBP}), high frequency component of RR (HF_{RR}), estimated by a time frequency distribution, and BRS computed by alpha index. Ensemble averages of BRS, LF_{RR}, LF_{SBP}, LF_{DBP}, and HF_{RR} dynamics showed similar response patterns in each phase of VM: decreased in early phase II (II_E), LF_{SBP} and LF_{DBP} after an initial increment; raised progressively in late phase II (II_L), except HF_{RR} which remained reduced; peaked in phase IV, LF_{RR} and LF_{SBP} in the early part, and BRS and HF_{RR} in the late part. Mean phase-IV-to-phase-II_L ratios (IV/II_L) of all indexes ranged from 1.1±0.2 to 7.0±2.1. In phases II_L and IV, BRS and HF_{RR} were significantly correlated. The moderate effects of SBP, sympathetic activity increments, and RR and vagal activity reductions in phase II_L are associated to a BRS decrement, in phase IV the BRS increment is associated with large peaks of sympathetic activity, SBP, vagal activity and RR, indicated by the IV/II_L ratios of indexes >1, suggesting that BRS changes possibly drive the autonomic cardiovascular response to VM.

1. Introduction

The time-courses of systolic blood pressure (SBP) and RR intervals responses to Valsalva maneuver (VM), extensively studied, have been used to: characterize the response into four phases; compute the Valsalva ratio, index used for the clinical evaluation of the patients' response to VM, and to make assumptions about the normality or alteration of the autonomic cardiovascular function, including the baroreflex control [1]. In contrast, only few studies [2, 3, 4] have dealt with the behavior of the spectral sympathetic and vagal indexes in response to VM, despite them being the immediate functional variables determining the cardiovascular response.

In clinical settings, baroreflex sensitivity (BRS) is a relevant indicator of the alteration of autonomic cardiovascular short-term control, with prognostic value in cardiology [4, 5]. The transfer function method for computing BRS has been most frequently used to obtain a single BRS value from stationary signals than a BRS time-series from non-stationary recordings [6]. A variety of methods that distinguish between vagal and sympathetic BRS have been applied to assess BRS in VM, among which the SBP-RR regression and pressure recovery time (PRT) analysis stand out [1]. Only two reports using modern computer-based methods for obtaining BRS in VM were found [3, 4].

If it is considered that the fluctuations of BRS are associated with the fluctuations of autonomic activity, as exemplified by the BRS reduction associated with the increase in sympathetic outflow and vagal activity reduction that occur during dynamic and static exercise and in cardiovascular diseases [5], we hypothesize that during the VM strain there will be an association between BRS reduction and the diminution of the range of variation of sympathetic activity increase and vagal reduction, and that in the post-strain the opposite effects will occur. To test this hypothesis we assessed, in healthy volunteers, the effects provoked by VM on the instantaneous time-courses of the low frequency components of RR (LF_{RR}), SBP (LF_{SBP}), diastolic blood pressure (DBP, LF_{DBP}), high frequency component of RR (HF_{RR}), the LF_{RR}/HF_{RR} ratio, all estimated by a time frequency distribution (TFD), BRS computed by alpha index and its coherence (BRS_{CO}).

2. Methods

2.1. Subjects

Thirty (18 male and 12 female), healthy, non-smoking, non-addicted and sedentary subjects participated. Age, weight and height were 23.2±2.4 years, 64.4±10.3 kg and 165±10 cm respectively. Their written informed consent was requested to participate.

2.2. Protocol

Volunteers visited the laboratory twice. In the first

visit, their health status was evaluated and they were trained to perform VM correctly. In the second visit, the experimental condition was carried out, which comprised three successive stages: control, 1 min long, maneuver, 20 s long, and recovery, 2 min long. Subjects performed VM twice, in sitting position and aided by visual feedback that displayed the mouth pressure (MP) level. 10 s before the maneuver execution, subjects were notified. VM strain was achieved by performing an expiratory effort into a closed tube to sustain a MP of 40 mmHg, with a 5-min rest period between tests. During the control and recovery stages, subjects breathed spontaneously.

2.3. Signal recording and acquisition

ECG was detected at CM5 lead using a bioelectric amplifier (Biopac Systems). Noninvasive arterial pressure was recorded by Finapres (Ohmeda). Respiratory movements were measured by a pneumograph (Biopac Systems). MP was recorded by a pressure transducer (Validyne) connected to the distal end of a closed tube which had a mouthpiece attached to the proximal end. All signals were digitized at a sampling rate of 1 kHz via an acquisition and display system (Biopac Systems).

2.4. Data processing

From 59 valid recordings, R-wave peaks and fiducial points of ECG and arterial pressure signals were beat-to-beat detected to generate RR, SBP and DBP time series. These were cubic-spline interpolated, resampled at 4 Hz and detrended by the smoothness priors method. Auto and cross time-frequency spectra of RR, SBP and DBP were estimated with the smoothed pseudo-Wigner-Villé TFD. We extracted the instantaneous HF_{RR}, LF_{RR}, LF_{SBP}, LF_{DBP} from the first moment of their TFD in the standard HRV low- and high-frequency bands, from which we computed: the LF_{RR}/HF_{RR} ratio, BRS by alpha index (square root of LF_{RR}/LF_{SBP} ratio), and the respective BRS_{CO} by cross-time-frequency analysis.

The limiting points (LP), maxima and minima that mark the four phases into which VM response has been divided, were detected semi-automatically on each recording of SBP and RR response patterns dynamics. From the respective LP, the IV/II_L ratio of each index was obtained. Due to the different maximal overshoot times of the spectral indexes, phase IV was divided into early (IV_E) and late (IV_L). To highlight any patterned responses to VM, individual indexes dynamics were ensemble-averaged once their mean baseline level was subtracted.

2.5. Statistical analysis

Data were expressed as mean ± SD. Differences among the LP of each index dynamics, including mean baseline, were tested by ANOVA for repeated measures, with post-hoc pairwise comparisons by the Tukey test. Pairs of linear regressions and correlations of BRS with LF_{RR}/HF_{RR}, RR and HF_{RR} were computed using the data segments of phases II_L and IV. Statistical significance was set at $p<0.05$.

3. Results

The changes shown by the ensemble averages of the studied indexes dynamics were expressed in relation to their mean control value. The means of LP of all indexes were different ($p<0.001$) from their baseline and between phases II_L and IV ($p<0.01$).

10-s prior to the onset of VM, the indexes dynamics presented a significant increment ($p<0.01$), except BRS and RR, which decreased ($p<0.01$). In general, these changes were accentuated by the onset of VM strain (phase I) (Fig. 1, Fig. 2).

With the beginning of VM strain, ensemble averages of SBP (Fig. 1A) and DBP (Fig. 1B) dynamics continued rising (phase I) to later decrease (phase II_E) and then increase up to the end of the VM strain, where they fell (phase III) to then rapidly increase until reaching a peak (phase IV_E). The amplitude of the peak of DBP was smaller than that of SBP ($p<0.01$). SBP and DBP mean IV/II_L ratios were 1.42±0.16 and 1.08±0.11 respectively. RR dynamics presented a reduction (phase II_E) sustained until the end of the strain, then recovered progressively and peaked (phase IV). Its mean IV/II_L ratio was 2.11±0.30.

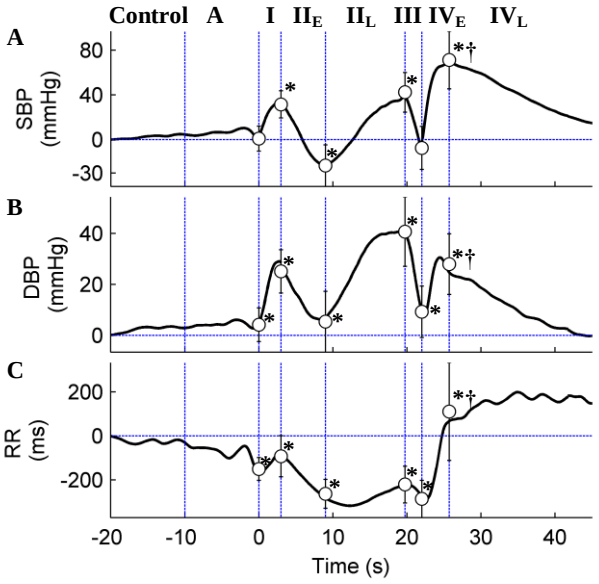

Fig. 1. Ensemble averages and LP means±SD of the time courses of: A) SBP, B) DBP, and C) RR. *$p<0.001$ vs. mean baseline. † $p<0.01$ vs. phase II_L.

The most relevant changes of the spectral measures dynamics were: LF_{RR} decreased in phase II_E, increased largely in phase II_L and peaked in phase IV_E (Fig. 2A), its mean IV/II_L ratio was 4.30±1.84; LF_{SBP} increased initially until reaching a peak in phase II_E, then recovered partially, increasing again in phase II_L and peaked in phase IV_E (Fig. 2B). LF_{DBP} response was similar but of smaller amplitude ($p<0.01$, Fig. 2C). Their mean IV/II_L ratios were 1.50±0.59 and 1.09±0.43 respectively.

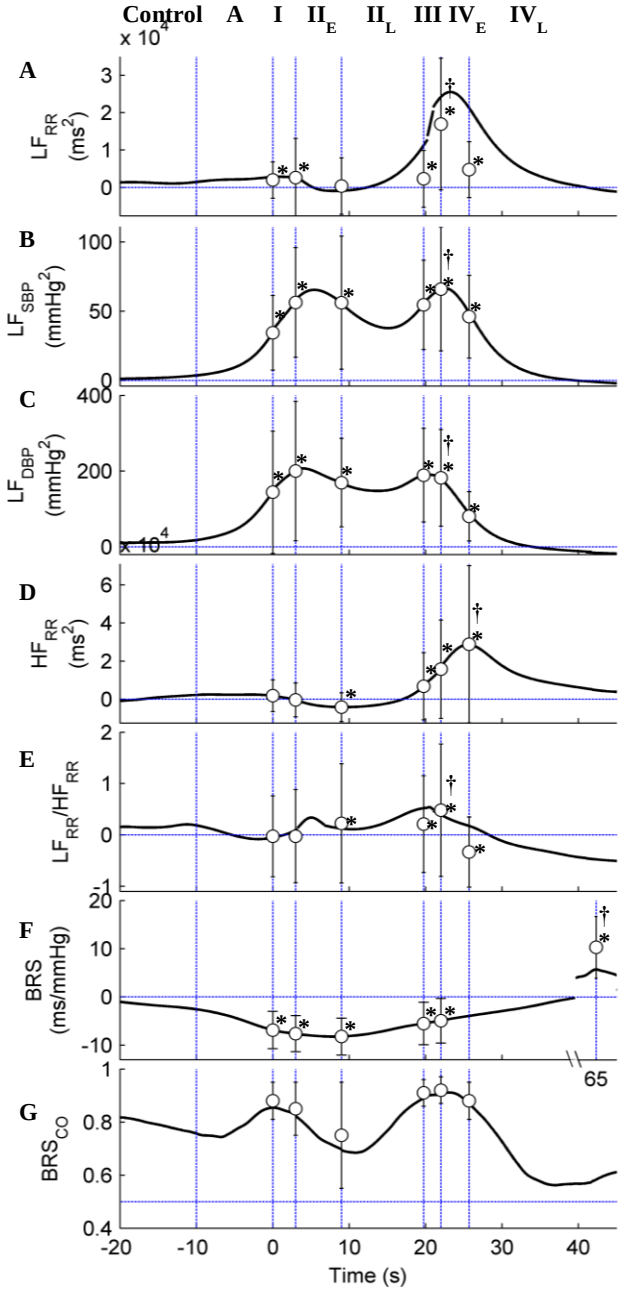

Fig. 2. Ensemble averages and LP means±SD of the time courses of: A) LF_{RR}, B) LF_{SBP}, C) LF_{DBP}, D) HF_{RR}, E) LF_{RR}/HF_{RR}, F) BRS, G) BRS_{CO} spectral measures. *$p<0.001$ vs. mean baseline. † $p<0.01$ vs. phase II_L.

HF_{RR} decreased in phase II_E and remained reduced through phase II_L until the termination of the strain, after which it increased progressively and peaked in phase IV_L (Fig. 2D). Its mean IV/II_L ratio was 7.01±2.10; BRS presented an initial diminution that persisted until phase II_E, then, in phase II_L, started a slow and progressive increment that reached a peak in phase IV_L (Fig. 2F). Its mean IV/II_L ratio was 5.89±2.27. Pooled means of BRS_{CO} were 0.79±0.16 in phase II and 0.69±0.10 in phase IV_L (Fig. 2G). LF_{RR}/HF_{RR} ratio dynamics showed progressive increase in phase II up to phase IV_E and progressive decrease in phase IV (Fig. 2E).

In phase II_L and phase IV, BRS showed significant correlations ($p<0.04$) with: LF_{RR}/HF_{RR} (r_{II}=0.86±0.22, r_{IV}=-0.36±0.33), RR (r_{II}=0.63±0.27, r_{IV}=0.74±0.22), and HF_{RR} (r_{II}=0.97±0.04, r_{IV}=0.87±0.17) (Fig. 3).

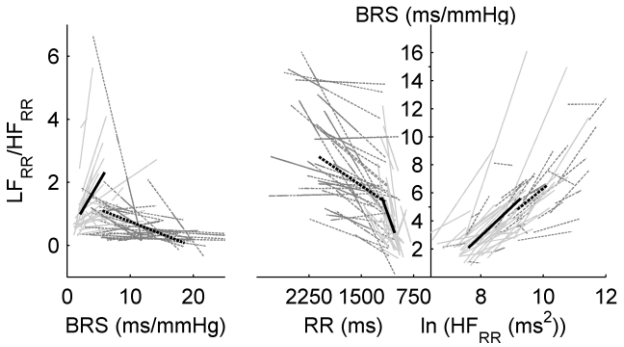

Fig. 3. Individual (grey) and mean (black) linear regressions in phase II (solid) and phase IV (dashed) of BRS relationships with: LF_{RR}/HF_{RR}, RR and HF_{RR}.

4. Discussion

Computing and analyzing the time-courses of BRS, by alpha index, its BRS_{CO}, and of sympathetic and vagal spectral measures, allows building an integrative dynamic functional picture that explains the autonomic cardiovascular response to VM, supported by our main findings: BRS and HF_{RR}, significantly correlated, decrease in phase II and increase to an overshoot in phase IV_L, LF_{SBP} and LF_{DBP} increase in phase II, with a partial intermediate recovery, to overshoot in phase IV_E; LF_{RR} decreases in phase II_E, increases in phase II_L and peaks in phase IV_E. The IV/II_L ratios of the spectral indexes and cardiovascular variables responses ranged from 1.1±0.2 to 7.0±2.1.

In clinical settings, changes of SBP and RR time series in phases II, IV, the Valsalva ratio and PRT are used to infer the state of normality or alteration of the cardiac vagal and sympathetic control, and even the BRS [1, 7]. The current functional explanation of the patterned response of SBP time series to VM is based on the pharmacological blockage of alpha and beta receptors, which abolishes the SBP elevation in phase II_L and the

overshoot of phase IV (by restricting the cardioacceleration), respectively [1, 7].

Our findings refine and extend the usual explanation by making explicit, through the computation and analysis of the reliable autonomic spectral measures [2], the time-courses of the characteristic changes, phase by phase, of BRS, vagal and cardiac and vasomotor sympathetic activities, all according to the current physiological background [1, 7], that are the inducing factors of the characteristic response of SBP and RR to VM. Thus, LF_{SBP} and LF_{RR} correctly indicate the increase of sympathetic activity, the vasomotor one in phase II_L (Fig. 2B), and the cardioaccelerating one in phase IV_E (Fig. 2A), respectively. The LF_{RR}/HF_{RR} ratio indicates the predominance of sympathetic activity during the VM strain and in phase IV_E, and of vagal activity in phase IV_L (Fig. 2E). By the findings of this study, notifying the subject in advance of the onset of the maneuver elicits a reduction of BRS and increase of cardiac and vasomotor sympathetic activities (Fig. 2) associated to increased SBP and DBP and reduced RR (Fig. 1), an anticipatory response that in other experimental conditions has been attributed to the central command [8]. In phase II_E, the reductions of SBP and DBP (Fig. 1) trigger the baroreflex which, with reduced gain (Fig. 2F), restricts the degree of vagal activity reduction (HF_{RR}, Fig. 2C), of cardioaccelerating (LF_{RR}, Fig. 2A and RR, Fig. 1C), and of vasomotor (LF_{SBP}, Fig. 2B; SBP, Fig. 1A; LF_{DBP}, Fig. 2C; DBP, Fig. 1B) sympathetic activity increase. The reduction of SBP and DBP (Fig. 1) due to the end of VM strain, activates the baroreflex which, now with increased gain (Fig. 2F), widens the degree of cardiac (Fig. 2A and 1C) and vasoconstrictor sympathetic activity response (Fig. 2B-C), that result in the raise of SBP and DBP (Fig. 1B-C), effect that elicits, via baroreflex, the overshoots of vagal activity (Fig. 2B) and RR (Fig. 1C) in phase IV_L. Therefore, it is possible that the reduction of BRS in the anticipatory stage and in phase II minimizes the range of change of the indexes, while the BRS increase in phase IV widens the range of change, thus determining that the IV/II_L ratios of the autonomic and cardiovascular indexes are all greater than one.

Our findings are in accordance with the changes of the mean values of LF_{RR} and LF_{SBP} increments [1, 3, 4] and HF_{RR} and BRS reductions [3, 4] reported in VM strain, spectral autonomic indexes that, despite being estimated by wavelets- [2] and trigonometric regressive - based methods [3, 4], do not report the characteristic changes of the time-courses of autonomic indexes in a phase-by-phase format. Moreover, in our study, the autonomic spectral indexes response: is detailed by the ensemble averages of the instantaneous time-courses; includes DBP; phase IV is divided by the different timing of the peaks into early and late; is assessed by the IV/II_L ratio and, relevantly, show that BRS is significantly correlated with LF_{RR}/HF_{RR} ratio, RR and HF_{RR} in phases II_L and IV (Fig. 3). To the best of our knowledge, this is the first study to report the aforementioned findings.

In conclusion, while the moderate effects of SBP and sympathetic activity increment, and RR and vagal activity reduction in phase II_L are associated with BRS decrement, in phase IV the BRS increment is associated with large peaks of sympathetic activity, SBP, vagal activity and RR, effects that, together with the strong correlations, in phases II_L and IV, of BRS with the LF_{RR}/HF_{RR} ratio, RR and HF_{RR}, suggest that BRS changes possibly drive the autonomic cardiovascular patterned response to VM.

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