Time-courses of the Central Frequencies of Low-Frequency Components of RR Intervals, Systolic and Diastolic Pressure Variabilities in Response to Active Orthostatic Test

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Abstract

In 25 healthy subjects we assessed the effects provoked by 1-min of active orthostatic test (AOT) on time-courses of central frequencies and powers of low frequency components ($_{CF}LF$, $_{P}LF$) of RR ($_{CF}LF_{RR}$, $_{P}LF_{RR}$), systolic ($_{CF}LF_{SP}$, $_{P}LF_{SP}$) and diastolic ($_{CF}LF_{DP}$, $_{P}LF_{DP}$) pressures, estimated by a time-frequency distribution. Ensemble averages of the three $_{P}LF$-$_{CF}LF$ pairs dynamics depicted an initial sudden change (ISC), followed by a recovery change (RC) and a final sudden change (FSC). The rapid changes were upwards for $_{P}LF$ and downwards for $_{CF}LF$. Means of the maximal $_{P}LF$ surges and of minimal $_{CF}LF$ falls were greater and smaller ($p<0.01$) than their respective control means. Mean correlations of the three $_{P}LF$-$_{CF}LF$ relations ranged from -0.95±0.05 to -0.97±0.04 in ISC, -0.86±0.13 to -0.87±0.15 in RC and -0.30±0.59 to -0.41±0.63 in FSC. In all stages, means of $_{CF}LF_{RR}$ were greater ($p<0.04$) than those of $_{CF}LF_{DP}$. That the patterned responses of the three $_{P}LF$-$_{CF}LF$ pairs time-courses present rapid initial and final changes, upstrokes for $_{P}LF$ and falls for $_{CF}LF$, significantly inversely correlated, and the greater level of $_{CF}LF_{RR}$ than $_{CF}LF_{DP}$, refine the time-course of cardiovascular sympathetic activation in AOT, possibly non-uniform, and suggest that $_{CF}LF$ are trustable quantitative sympathetic measures, with some specificity, $_{CF}LF_{RR}$ for the cardiac and $_{CF}LF_{DP}$ for the vasomotor one.

1. Introduction

In the Task Force report on HRV standards [1] it was mentioned that the central frequency of the low-frequency component ($_{CF}LF$) of RR intervals ($_{CF}LF_{RR}$) is mobile, that it has been documented that it shifts to the left in diabetic neuropathy and head-up tilt, and that further studies were required to clarify its functional correlate, suggestion that has not been followed so far.

In previous studies, using a time-frequency distribution (TFD), we provided evidence that static exercise provokes, in the post-metaboreflex activation phase, the downward shift of $_{CF}LF_{RR}$, $_{CF}LF$ of systolic pressure ($_{CF}LF_{SP}$) and of diastolic pressure ($_{CF}LF_{DP}$) that also present strong negative correlations with their respective low frequency powers ($_{P}LF$). Additionally, it was documented that $_{CF}LF_{RR}$ level is greater than that of $_{CF}LF_{DP}$ [2]. These findings, which had not been reported before, suggested that $_{CF}LF_{RR}$, $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ show the potential capability to quantitatively indicate and differentiate between cardiac and vasomotor sympathetic modulations in a beat-to-beat format.

During the first minute of active orthostatic test (AOT), large and sudden increments of heart rate and arterial pressure (AP) have been reported in a beat-to-beat format [3], effects that indicate the great increment of sympathetic activity provoked by this maneuver, as has been documented by muscle sympathetic nerve activity (MSNA) recordings [4]. However, the time-course of HRV-based spectral indexes of sympathetic activity has not been reported.

In the current study we sought for the inverse correlation of the time-courses of $_{P}LF$ of RR ($_{P}LF_{RR}$), systolic pressure ($_{P}LF_{SP}$) and diastolic pressure ($_{P}LF_{DP}$) with their respective $_{CF}LF$ during AOT, as well as greater $_{CF}LF_{RR}$ values than $_{CF}LF_{DP}$, so that, in case that they are documented, additional evidence supporting the potential capability of $_{CF}LF$ as quantitative indicators of cardiac and vasomotor sympathetic modulation is provided. Thus, in healthy subjects we assessed the effects provoked by 1-min stages of supine position, AOT and return to supine on the instantaneous time-courses of $_{CF}LF_{RR}$, $_{CF}LF_{SP}$, $_{CF}LF_{DP}$ and their respective $_{P}LF_{RR}$, $_{P}LF_{SP}$ and $_{P}LF_{DP}$, all estimated by a TFD.

2. Methods

2.1. Subjects

Twenty five healthy, nonsmoking and sedentary subjects, 14 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. This study was approved by the ethics committee of our university.

2.2. Protocol

In the first visit to the laboratory, the subjects' health status and anthropometric variables were evaluated, and in the second visit the experimental stage was carried out. Volunteers underwent 1-min control, 1-min AOT and 2-min recovery stages. To perform AOT, the subjects rapidly stood up from the supine position, returning to this position at the end of the maneuver stage. ECG, noninvasive arterial pressure (AP), and respiratory signals were recorded throughout the entire session.

2.3. Signal recording and acquisition

ECG was detected at the thoracic bipolar lead CM5 using a bioelectric amplifier (Biopac Systems). Non-invasive AP was measured by Finapres (Ohmeda). Respiratory signal was obtained by an inductance transducer (Respitrace). All signals were digitized at a sampling rate of 1 kHz via an acquisition and display system (Biopac Systems).

2.4. Data processing

Fiducial points of ECG and AP recordings were detected to construct the RR, systolic pressure (SP) and diastolic pressure (DP) time series, which were cubic-spline interpolated, resampled at 4 Hz and detrended. Time-frequency spectra of the series were estimated with the smoothed pseudo-Wigner-Ville distribution and their first two-order moments were computed in the standard low frequency (LF) band to obtain the instantaneous time courses of ${}_{P}LF_{RR}$, ${}_{P}LF_{SP}$, ${}_{P}LF_{DP}$, ${}_{CF}LF_{RR}$, ${}_{CF}LF_{SP}$ and ${}_{CF}LF_{DP}$. Once their baseline level was subtracted, the ensemble averages of the individual ${}_{P}LF$ and ${}_{CF}LF$ dynamics were obtained, which clearly showed a response pattern of two fast changes at the beginning and the end of AOT. The maximal and minimal points of the patterned response of each subject were detected to limit the stages, form the ${}_{CF}LF$–${}_{P}LF$ relationships and perform statistical comparisons.

2.5. Statistical analysis

Data were expressed as mean±SD. Inter- and intra-indexes dynamics mean values comparisons were performed by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test.

Individual dynamics were used to compute the correlations and regressions between each ${}_{P}LF$ and its respective ${}_{CF}LF$ in each stage of the response to AOT. Statistical significance was accepted at $p<0.05$.

3. Results

The time-courses of the patterned responses of the ${}_{P}LF_{RR}$-${}_{CF}LF_{RR}$, ${}_{P}LF_{SP}$-${}_{CF}LF_{SP}$, ${}_{P}LF_{DP}$-${}_{CF}LF_{DP}$ pairs depicted an initial sudden change (ISC), followed by a recovery change (RC) and a final sudden change (FSC) (Fig. 1). The rapid changes of ${}_{P}LF$ were upwards and those of ${}_{CF}LF$ were downwards (Fig. 1). Mean values of the maximal points of the three ${}_{P}LF$ surges were greater ($p<0.01$) than their respective control mean (Fig. 1 A, C, E). Mean values of the minimal points of the three ${}_{CF}LF$ falls were smaller ($p<0.04$) than their mean control value (Fig. 1 B, D, F). The means of RC and of the post-maneuver recovery period of ${}_{P}LF$ and ${}_{CF}LF$ were not different from their mean control value.

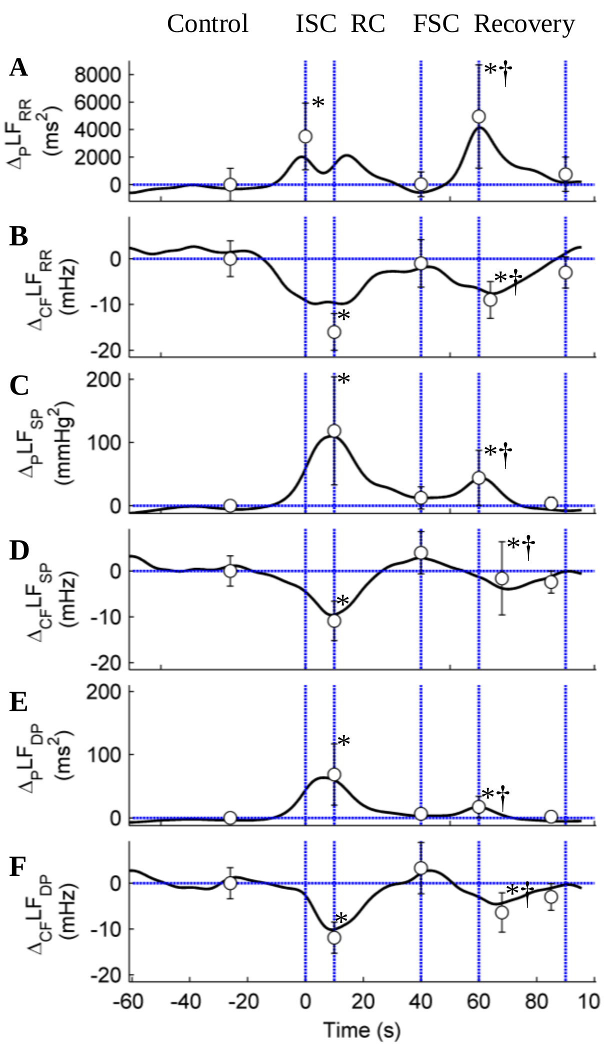

Fig.1. Ensemble averages and mean±SD values of the fiducial points of the time-courses of: A) ${}_{P}LF_{RR}$, B) ${}_{CF}LF_{RR}$, C) ${}_{P}LF_{SP}$, D) ${}_{CF}LF_{SP}$, E) ${}_{P}LF_{DP}$ and F) ${}_{CF}LF_{DP}$ during control, ISC, RC, FSC and recovery. *p<0.04 vs. baseline. † p<0.01 ISC vs. FSC.

In ISC, the beginning of the increment of $_{P}LF_{RR}$ and the reduction of $_{CF}LF_{RR}$ started 6±10s before the beginning of AOT, and was of smaller amplitude ($p<0.03$) than the FSC ones (Fig. 2A, B). The time-courses of the response patterns of the $_{P}LF_{SP}$-$_{CF}LF_{SP}$ and $_{P}LF_{DP}$-$_{CF}LF_{DP}$ pairs were similar: in both $_{P}LF_{SP}$ and $_{P}LF_{DP}$ the peak of ISC was larger ($p<0.001$) than the FSC one and their RC was first fast and later slow.

The comparison among the time courses of $_{CF}LF_{RR}$, $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ showed that the levels of $_{CF}LF_{RR}$ were greater ($p<0.01$) than those of $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ in all the stages, except in FSC, where it was similar to $_{CF}LF_{SP}$. The ranges of variation of the three $_{CF}LF$ were similar (Fig. 2, Table 2).

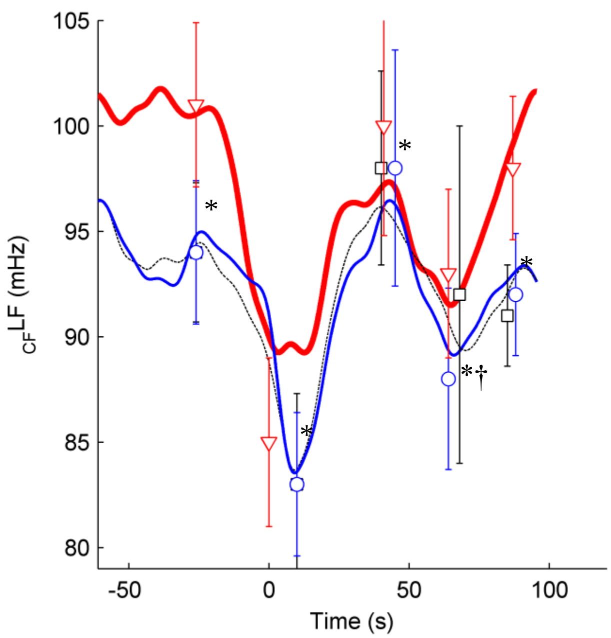

Fig. 2. Ensemble averages and mean±SD of the time-courses of $_{CF}LF_{SP}$ (black thin dotted line), $_{CF}LF_{DP}$ (blue thin solid line), $_{CF}LF_{RR}$ (red thick solid line) during control, ISC, RC, FSC and recovery. *$p<0.04$ $_{CF}LF_{RR}$ vs. $_{CF}LF_{SP}$. †$p<0.01$ $_{CF}LF_{DP}$ vs. $_{CF}LF_{SP}$.

Mean correlations of the $_{CF}LF_{RR}$–$_{P}LF_{RR}$, $_{CF}LF_{SP}$–$_{P}LF_{SP}$ and $_{CF}LF_{DP}$–$_{P}LF_{DP}$ relations during the three phases of AOT are shown in Table 1. All correlations were significant ($p<0.04$).

Table 1. Means ± SD of the $_{CF}LF$–$_{P}LF$ correlations in ISC, RC and FSC. N=25.

	ISC	RC	FSC
$_{CF}LF_{RR}$–$_{P}LF_{RR}$	-0.95±0.05	-0.86±0.13	-0.37±0.45
$_{CF}LF_{SP}$–$_{P}LF_{SP}$	-0.95±0.07	-0.87±0.10	-0.41±0.63
$_{CF}LF_{DP}$–$_{P}LF_{DP}$	-0.97±0.04	-0.87±0.15	-0.30±0.59

Table 2. Means ± SD of $_{CF}LF_{RR}$, $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ in control, ISC, RC, FSC and recovery. N=25.

	Control	ISC	RC	FSC	Recovery
$_{CF}LF_{RR}$ (mHz)	101±4	85±4	100±5	92±4	98±3
$_{CF}LF_{SP}$ (mHz)	94±3	83±4	98±5	92±8	91±2
$_{CF}LF_{DP}$ (mHz)	94±3*	83±3*	98±6*	88±4*	92±3*

*$p<0.01$ $_{CF}LF_{RR}$ vs. $_{CF}LF_{DP}$

3. Discussion

Performing spectral analysis of time series using a TFD allows assessing the time-course of the changes of the power and central frequency of their spectral components during a specific condition, properties that can extend the knowledge of HRV. Specifically, in the present study the application of these TFD capacities to the time series of RR intervals, SP and DP during the execution of AOT show the patterned responses of the $_{P}LF_{RR}$-$_{CF}LF_{RR}$, $_{P}LF_{SP}$-$_{CF}LF_{SP}$, $_{P}LF_{DP}$-$_{CF}LF_{DP}$ pairs, characterized by opposite $_{P}LF$-$_{CF}LF$ changes strongly and negatively correlated to each other (Table 1): while at the beginning and the end of AOT $_{P}LF$ present two sudden increments that recover, $_{CF}LF$ show two abrupt decrements that recover (Fig. 1). Additionally, we document that instantaneous $_{CF}LF_{RR}$ values are greater than those of $_{CF}LF_{DP}$ (Fig. 2, Table 2).

The relevance of AOT lies in the fact that it is a common behavior in daily life that is also extensively used for the evaluation of the baroreflex (BR) mediated cardiovascular response. A search of the keywords “standing” and “active orthostatic test” in PubMed returned 178,496 studies published from 1816 to 2021, supporting its great importance. Although it has been reported that during the first 15 seconds of head-up tilting significant increases of $_{P}LF_{RR}$ and $_{P}LF_{SP}$ occur [5], we were unable to find available reports that assessed the time-course of the spectral components of cardiovascular variability during the performance of AOT.

While the studies that reported the leftward shift of only $_{CF}LF_{RR}$ during AOT [6] and dynamic exercise [7] employed spectral analysis methods for stationary signals and attributed its mobility to the reduction of vagal activity associated to sympathoexcitatory maneuvers, in the present study we were able to document the similar patterned response (two downward shifts followed by recoveries) of the time-courses of $_{CF}LF_{RR}$, $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ to AOT (Fig. 2) that we consider indicate the cardiac and vasomotor sympathetic activity behavior, because of their strong inverse correlation with their respective $_{P}LF$ (Table 1) and the fact that parasympathetic activity is not involved in the genesis of $_{P}LF_{SP}$ and $_{P}LF_{DP}$.

In addition, the finely depicted time-courses of $_{CF}LF$ and $_{P}LF$ contrast with the gross dynamic of sympathetic activity indicated by MSNA during 30 s of AOT [4].

Based on the finding that sympathetic nerve activity presents a rhythmic modulation in a frequency band similar to that of the LF components [8], we hypothesized that the mobility of $_{CF}LF$ is a consequence of the central frequencies of the sympathetic nervous activity spectrum. The increases in sympathetic modulation would be caused by the greater recruitment of intrinsic oscillatory neuronal discharges, modulated at a lower frequency and with greater synchrony. The decrease in sympathetic activity would be due to the opposite mechanism. The inverse variation between the power and the central frequency of the spectral components can be an intrinsic property of the frequency response of the participating structures, characterized as a low-pass filter, or both parameters can change independently, a situation that requires further studies to be clarified. Furthermore, the frequency of cardiac sympathetic modulation would present a higher central frequency than that of vasomotor sympathetic modulation in a wide range of sympathetic excitatory activities. The previous effect would imply that the cardiovascular sympathetic activity does not present uniformity, that is, that the sympathetic nuclei of the brainstem handle the cardiac and vasomotor function in a distinctive way. This suggestion is also supported by the differences in innervation of the heart and vessels and in the patterned responses of $_{P}LF_{RR}$ in relation to $_{P}LF_{SP}$ and $_{P}LF_{DP}$ dynamics that we obtained: while the peaks of $_{P}LF_{SP}$ and $_{P}LF_{DP}$ at the onset of AOT are greater than those at the end, the amplitude of the initial peak of $_{P}LF_{RR}$ is smaller than the final peak (Fig. 1).

A possible explanation for the time-courses of sympathetic activity indexes in response to AOT that we found is that the network of complex interaction between cortical and subcortical motor areas of the brain, the central command, produces an anticipatory response that facilitates the cardiac sympathetic pathway and later activates the spinal motoneurones for the execution of the voluntary postural change. This provokes the fall of AP that, via the BR, decreases the inhibition of sympathetic nuclei, increasing their outflow, which in turn augments cardiac output and peripheral vascular resistance, effects that cause the elevation of AP that, again via the BR, induce the inhibition-recovery of sympathetic activity, resulting in the damping and stabilization of AP changes. To return to the supine position, the central command increases both the cardiac and vasomotor sympathetic activity, which result in the increase of AP that, via the BR, inhibit-recover sympathetic activation with the consequent fall of AP.

To the best of our knowledge this is the first study that reports the time-courses of the strongly inversely correlated changes of $_{P}LF_{RR}$, $_{P}LF_{SP}$ and $_{P}LF_{DP}$ (two upstrokes) with those of $_{CF}LF_{RR}$, $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ (two downward shifts) during the first minute of AOT, as well as the greater instantaneous level of $_{CF}LF_{RR}$ than $_{CF}LF_{DP}$.

In conclusion, our findings that the patterned responses of $_{CF}LF_{RR}$, $_{CF}LF_{SP}$ and $_{CF}LF_{DP}$ dynamics to AOT show, at the beginning and the termination of the maneuver, two downward shifts that recover, that were strongly and inversely correlated with $_{P}LF_{RR}$, $_{P}LF_{SP}$ and $_{P}LF_{DP}$ dynamics that present distinctive peaks at the beginning and the end of AOT, and that $_{CF}LF_{RR}$ is greater than $_{CF}LF_{DP}$, refine the time-course of sympathetic activity during AOT and support that it provokes similar cardiac and vasomotor sympathetic activations, although not uniform: the vasomotor one presents smaller central frequency and is of greater amplitude at the onset and smaller at the ending than the cardiac one. Thus, $_{CF}LF$ are possibly trustable quantitative measures of sympathetic activity that complement $_{P}LF$, with some branch-specificity: $_{CF}LF_{RR}$ indicates the cardiac sympathetic activity and $_{CF}LF_{DP}$ the vasomotor one.

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