Beat-to-beat Response Patterns of Spectral Sympathetic Estimators to the Cold Face Test and their Comparison to those of the Active Orthostatic Test

Salvador Carrasco-Sosa[1], Alejandra Guillén-Mandujano[1], Aldo R Mejía-Rodríguez[2]

[1]División de Ciencias Biológicas y de la Salud, Universidad Autónoma Metropolitana-I, DF, México
[2]Universidad Autónoma de San Luis Potosí, San Luis Potosí, México

Abstract

We assessed the effects of cold face test (CFT) and active orthostatic test (AOT) on the RR intervals (RR), systolic pressure (SP) and maximal amplitude of arterial pressure first derivative (dmAP) time series of 25 healthy volunteers, and the instantaneous dynamics of their low-frequency powers (LF_{RR}, LF_{SP} and LF_{dmAP}), to characterize their time course, and compare their performance as sympathetic markers as well as the magnitude of the sympathetic response evoked by each maneuver. All the variables studied displayed distinct instantaneous response patterns to each maneuver: while in CFT they increased to a plateau, in AOT they presented overshoots at the beginning and end of the test. In both tests, LF_{dmAP} and LF_{SP} dynamics were similar and strongly correlated, and presented a weak correlation with LF_{RR}. Means of LF_{dmAP} and LF_{SP} in CFT were 7 times smaller than in AOT. Our findings support that LF_{SP} and LF_{dmAP} powers exhibit similar performance as noninvasive sympathetic markers and that all variables studied show distinctive beat-to-beat response patterns to each maneuver. Using the sympathetic response produced by AOT as reference, the one evoked by CFT is smaller.

1. Introduction

We recently proposed that the low-frequency (LF) power of the maximal amplitude of arterial pressure first derivative (LF_{dmAP}) is a suitable noninvasive sympathetic activity marker with the distinguishing characteristic of showing some specificity to cardiac contractility [1], given the association of this function with the maximal amplitude of the arterial pressure first derivative (dmAP) [2]. Similarly, increasingly available evidence supports that the LF power of systolic pressure (LF_{SP}) is a satisfactory sympathetic activity index [1,3].

Because they are simple, easy to apply, safe and noninvasive, both cold face test (CFT) and active orthostatic test (AOT) are provocative maneuvers used in research and clinical settings for assessing the functional integrity of the cardiovascular autonomic control, each with an important distinctive physiological attribute: CFT produces a baroreflex-independent sympatho-vagal coactivation [4] and AOT a baroreflex-dependent sympathetic response [5]. There are no studies available that have used the instantaneous LF_{SP} power to characterize the time course of the sympathetic responses to CFT and AOT.

Our novel methodological approach utilizes the time series of several cardiovascular variables (CV) and their time-frequency spectral powers as instantaneous dynamics to: assess the temporal course and continuity of the physiological phenomena, the complexity of the responses to the maneuvers, and to test, by means of ensemble averaging, if the individual responses exhibit a pattern. Also, it employs at least two provocative maneuvers for obtaining, by comparison, a notion of the magnitude of the autonomic response elicited by each one. Thus, to further support the estimation capability of LF_{dmAP} and to establish the instantaneous time course of sympathetic activity spectral indexes during CFT and AOT we assessed the effects of the two tests on the instantaneous dynamics of LF_{dmAP} and LF_{SP}, and compared their performance as sympathetic markers as well as the magnitude of the sympathetic response evoked by each maneuver.

2. Methods

2.1. Subjects

Twenty-five healthy, normotensive and sedentary subjects, 14 men and 11 women, were studied. 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.

2.2. Protocol

Volunteers visited the laboratory twice. The first time, their 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 maneuver and 2-min recovery stages for both CFT and AOT, applied in random order. To perform AOT, the subjects rapidly stood up from the supine position, returning to this position at the end of the maneuver stage. CFT consisted of applying a bag filled with iced-water at 0°C on the face, excluding the eyes, with the subject in supine position. ECG, noninvasive arterial pressure (AP), and respiration (Res) signals were recorded during each test.

2.3. Signal recording and acquisition

ECG was detected at the CM5 bipolar lead using a bioelectric amplifier (Biopac Systems). AP was measured by Finapres (Ohmeda). Respirogram was obtained by Inductotrace (Ambulatory Monitoring).

All signals were digitized at a sampling rate of 1 kHz via an acquisition system (Biopac Systems).

2.4. Data processing

The dmAP was beat-to-beat computed as the amplitude from the zero crossing to the peak value of the first derivative of AP waveform. R-wave peaks, systolic pressure (SP), and diastolic pressure (DP) were beat-to-beat detected to generate R-R intervals (RR), its inverse, heart rate (HR), SP and DP time series. The resulting series and Res were cubic-spline interpolated, resampled at 4 Hz and detrended by the smoothness priors method. Time-frequency spectra of the oscillations of the series were estimated with the smoothed pseudo-Wigner-Ville distribution and integrated in the standard LF and high-frequency (HF) bands to compute the instantaneous dynamics of LF_{SP}, LF_{dmAP}, LF of RR (LF_{RR}) powers, and HF powers of dmAP (HF_{dmAP}), RR (HF_{RR}), and Res (HF_{Res}). To highlight any patterned responses, individual indexes dynamics were ensemble-averaged once their baseline level was subtracted. Additionally, for statistical purposes indexes dynamics were segmented into 6-s epochs.

2.5. Statistical analysis

Data are expressed as mean±SD. Inter-stage differences were tested by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test. Inter-maneuver differences were tested by paired t-test.

Mean values of the 6-s segments of the indexes dynamics during the two tests were used to compute linear regressions and correlations for each subject. Statistical significance was accepted at $p<0.05$.

3. Results

Instantaneous dynamics of HR, SP, DP and dmAP were similar to each other during both maneuvers. In CFT, while the last three CV increased to a plateau that persisted until the end of the maneuver period, followed by a slow recovery, HR decreased below its control value (Fig. 1).

In AOT, while the pattern of SP, DP and dmAP consisted in an initial sudden fall, a rebound followed by an overshoot, then an intermediate partial recovery, and a second overshoot at the end of the maneuver, followed by a gradual recovery, that of HR starts with an overshoot (Fig. 1).

CV pooled means during the maneuver stage were different ($p<0.001$) from their control levels in both AOT and CFT. In AOT, pooled means of HR and DP were greater ($p<0.001$) and dmAP was smaller ($p<0.03$) than in CFT, and SP means were similar (Fig. 1).

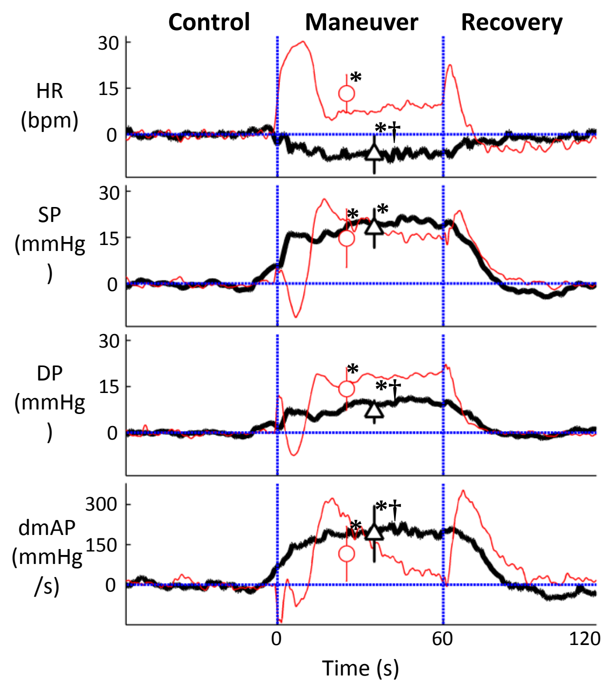

Fig. 1. Ensemble averages of the dynamics of CV time series in CFT (thick line) and AOT (thin line) and their respective pooled means±SD. * $p<0.001$ maneuver stage vs. control, † $p<0.03$ CFT vs. AOT.

In both dmAP and SP time-frequency spectra, power in the LF band depicted the patterned response of each maneuvers: two peaks at the beginning and end of AOT and a smooth increment that tended to recover in CFT, with greater power in the former. Additionally, in both tests the LF powers were greater than HF powers (Fig. 2).

Important fluctuations of the instantaneous power are noticeable in both frequency bands in each maneuver.

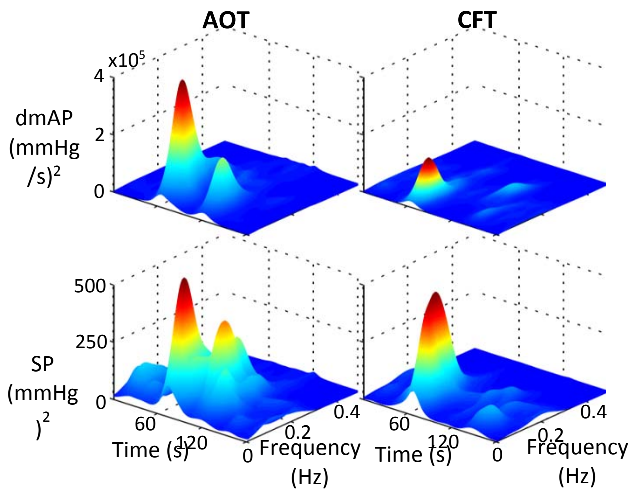

Fig. 2. Representative time-frequency distributions of dmAP and SP series during AOT (left column) and CFT (right column). Maneuver stage spans from 60 to 120 s.

The time course of three LF powers were also similar during both maneuvers: in CFT, they presented a discrete initial elevation with a tendency towards recovery, and in AOT, two overshoots with an intermediate recovery (Fig. 3). Pooled means of LF_{SP}, LF_{dmAP} and LF_{RR} powers dynamics in the maneuver stage were different ($p<0.03$) from their baseline level in both AOT and CFT. While pooled means of LF_{dmAP} and LF_{SP} were greater for AOT than for CFT ($p<0.001$), LF_{RR} were similar between tests (Fig. 3).

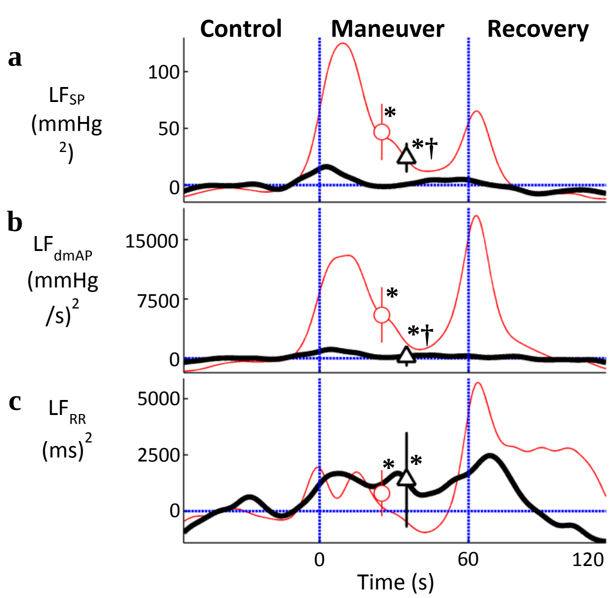

Fig. 3. Ensemble averages of the dynamics of a) LF_{SP}, b) LF_{dmAP} and c) LF_{RR} in CFT (thick line) and AOT (thin line) and their respective pooled means±SD. * $p<0.03$ maneuver stage vs. baseline, †$p<0.001$ CFT vs. AOT.

Mean correlations of LF_{dmAP} with LF_{SP} was 0.87±0.10 (Fig.4), with LF_{RR} was 0.52±0.45 ($p>0.05$). Mean LF_{SP}-LF_{RR} correlation was 0.38±0.42 ($p>0.05$).

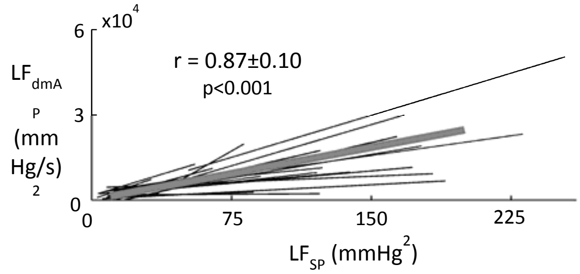

Fig. 4. Individual (thin black lines) and mean (thick grey lines) linear regressions of LF_{dmAP} vs. LF_{SP}.

Mean $lnHF_{RR}$ in CFT (9.1±0.8 ms^2) was greater ($p<0.001$) than in AOT (7.7±0.5 ms^2, below baseline level).

4. Discussion

The present study establishes that, in healthy subjects, LF_{SP} and LF_{dmAP} powers exhibit similar performance as sympathetic activity markers and the instantaneous autonomic cardiovascular variables (ACV) dynamics present distinctive patterns in response to AOT and CFT, as supported by the following findings: 1) LF_{dmAP}, LF_{SP}, LF_{RR}, HR, SP, DP and dmAP displayed distinct instantaneous response patterns to each maneuver: while during CFT they increased to a plateau, (excepting HR, which decreased), during AOT they presented overshoots at the beginning and end of the maneuver. 2) In response to both maneuvers, LF_{dmAP} and LF_{SP} displayed similar dynamics and were very strongly correlated, while presenting weak correlations with LF_{RR}. 3) Mean values of LF_{dmAP}, LF_{SP} and HR in CFT were seven times smaller than in AOT, while means of LF_{RR} and SP were similar.

Reported evidence [1,6] supports the satisfactory performance of LF_{SP} as a noninvasive sympathetic activity marker, including its strong correlation with the invasive measure muscular sympathetic nerve activity (MSNA) [3]. Recently, we reported that LF_{dmAP} adequately indicates the sympathetic activity level provoked by different maneuvers [1].

There is agreement that the autonomic cardiovascular response to CFT consists in a functionally unusual sympatho-vagal coactivation expressed as hypertension and non-baroreflex bradycardia [4]. One of the few available studies that performed the spectral analysis of SP variability to characterize the sympathetic response to CFT reported that LF_{SP} power does not change during the maneuver stage [7]. However, a marked elevation of MSNA has been found during early and late CFT [8]. In contrast, our results indicate a slight increase of instantaneous LF_{SP} and LF_{dmAP} power at the beginning of the maneuver, followed by a sympathetic withdrawal.

To the best of our knowledge, this is the first study to establish that the instantaneous dynamics of SP, dmAP, HR and their respective LF powers show consistent response patterns to both maneuvers, characterized by an increase of the ACV in CFT and by two overshoots with an intermediate partial recovery in AOT.

Based on the similar instantaneous dynamics of LF_{SP} and LF_{dmAP} in both AOT and CFT (Fig. 3) and the strong correlation between them (Fig. 4), similar to the one we previously obtained in other experimental conditions [1], our results further support that LF_{dmAP} power is a suitable marker of sympathetic activity, more specific to the cardiac modulation than to the vasomotor one, given the association observed between dmAP and cardiac contractility [2]. The unchanging values of LF_{RR} in the two tests and its nonsignificant correlations with both LF_{SP} and LF_{dmAP}, are additional evidence supporting the reported ambiguity of LF_{RR}, which reflects both sympathetic and parasympathetic modulations [6].

In the present study, all of the ACV employed fit a consistent patterned response of minimal complexity to CFT, consisting of an increase that is sustained until the termination of the maneuver with the exception of HR, which decreases, while the sympathetic indexes tend to recover. The observed increases of HF_{RR}, LF_{SP} and LF_{dmAP} powers (Fig. 3) agree with the notion that CFT initially provokes a sympatho-vagal coactivation [4] responsible of the abrupt increase of SP and DP as well as the bradycardia (Fig. 1), but our finding that afterwards LF_{SP} and LF_{dmAP} tend to recover suggests a baroreflex-mediated sympathetic withdrawal.

Only the responses of AP and HR during the first 30s of AOT have been reported in a beat-to-beat format: HR rises promptly and then decreases, and AP decreases sharply followed by a rapid rebound and overshoot [9], without considering the time course of the variables at the termination of the maneuver, when the subject returns to the supine position. In our study, all of the ACV instantaneous dynamics show a highly consistent and complex patterned response during the first minute of AOT, which consists of a first abrupt overshoot at the beginning (Fig. 1 and 3), followed by a partial recovery and a second rapid overshoot at the end of the maneuver with a gradual recovery. These findings can be explained by the interaction, at autonomic nuclei level, of the afferences of both the central command, a complex system that drives voluntary movement, and the baroreceptors. Central command participates at the beginning and the end of the maneuver, contributing to the generation of the two sympathetic activity overshoots, and the baroreflex intervenes at the start of the maneuver and to buffer the two AP overshoots, generating the subsequent AP recoveries.

How big is the sympathetic activation evoked by CFT? By comparison with the LF_{SP} and LF_{dmAP} powers evoked by AOT, it is about seven times smaller, quite small and contrasting with the enormous vagal outflow it produces, as compared with the minuscule HF_{RR} power elicited by AOT. Due to its physiological relevance and popularity, ACV responses to AOT could be considered as references for normalizing those evoked by other maneuvers.

In conclusion, supported by their similar instantaneous response patterns, their ability to adequately indicate the sympathetic increases evoked by CFT and AOT, and their very strong correlation, LF_{SP} and LF_{dmAP} powers exhibit similar performance as noninvasive sympathetic markers. Furthermore, our results show that ACV, in a beat-to-beat format, exhibit distinctive patterns in response to both maneuvers, simple for CFT and complex for AOT. Considering the autonomic activity levels produced by AOT as reference values, the vagal activation evoked by CFT is enormous and the sympathetic one is minuscule.

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Address for correspondence.

Salvador Carrasco-Sosa
Depto. Ciencias de la Salud, S-353
Universidad Autónoma Metropolitana–Iztapalapa.
Av. San Rafael Atlixco # 186, C.P. 09340 D.F., México.
scas@xanum.uam.mx