Instantaneous Time Course of Autonomic Cardiovascular Response to Short-Term Hypoxemia in Healthy Subjects: a Time-Frequency Analysis Approach

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Abstract

In ten healthy volunteers, we assessed the effects produced by 2-min 12% O_2 breathing on the instantaneous time course of: arterial oxygen saturation (SaO_2), respiratory frequency (RF), end-tidal CO_2 ($ETCO_2$), R-R intervals (RR), systolic pressure (SP), diastolic pressure (DP), pulse pressure (PP), maximal amplitude of arterial pressure derivative (dmAP), and, estimated by a time frequency distribution, their low frequency powers (LF_{RR}, LF_{PP} and LF_{dmAP}) and high frequency powers of RR (HF_{RR}) and respiration (HF_{Res}) as well as baroreflex sensitivity (BRS) and respiratory sinus arrhythmia sensitivity (RSAS) by alpha index. Mean SaO_2 of 82±2% provoked consistent response patterns in all variables: with 9-s latency, progressive decrease ($p<0.002$) until the end of LF_{dmAP}, LF_{PP}, RR, HF_{RR}, RSAS, dmAP, $ETCO_2$ and BRS (36-s latency), and gradual increase ($p<0.004$) of RF; with 108-s latency, a sustained decrease ($p<0.004$) of SP and DP. Hypocapnic hypoxemia provokes: an immediate functional depression shown by gradual reductions of sympathetic and vagal activities that contribute to the progressive fall of RR, RSAS and BRS with unchanged arterial pressure, and, through chemoreflex activation, a progressive increase of RF; and later, via direct vasodilation, a reduction of arterial pressure.

1. Introduction

Hypoxemia is a dangerous condition because it renders insufficient one of the crucial life-supporting mechanisms, the cellular production of energy. Unfortunately, it results from various, frequent and disabling diseases associated with respiratory and heart failure syndromes [1]. Acute hypoxemia triggers compensatory mechanisms, of which chemoreflex activation is considered the most relevant, because it rises pulmonary ventilation and cardiovascular sympathetic activity, which preserves cardiac output [2, 3].

Measures computed from spectral analysis of cardiovascular variability have been used in several studies to assess the effects of hypoxia on the autonomic cardiovascular function. These studies have in common that: they used spectral analysis techniques only suitable for stationary signals [4, 5, 6, 7]; they have been performed on subjects exposed to altitude [4, 5], or to hypoxic gas mixtures with 10% to 17% O_2 and exposure times of 12 to 20 min [6, 7]; and they have reported equivocal findings for almost all the autonomic estimators. Thus, it has been reported that, during hypoxemia, sympathetic activity indexes increase [2, 4, 6] or decrease [5]; vagal estimators decrease [5] or do not change [6, 7]; and that arterial pressure (AP) raises [2], drops [2] or remains unchanged [6, 7]. Therefore, there is still some uncertainty concerning the effect of hypoxemia on the autonomic cardiovascular function. Even more, a possible contributing factor to that uncertainty is the lack of timing of the occurrence of its diverse effects, which make it difficult to establish cause-effect relationships between variables. To provide insight on this issue, we applied time-frequency analysis to assess the beat-to-beat effects of moderate short-term hypoxemia on the spectral measures derived from heart rate and AP variabilities, baroreflex sensitivity (BRS), respiratory sinus arrhythmia sensitivity (RSAS) and respiration (Res); and thus, search for their latencies.

2. Methods

2.1. Subjects

Ten healthy, normotensive and sedentary subjects, 6 men and 4 women, were studied. Their mean age, height and weight were 22.1±1.8 years, 163±6 cm and 64±11 kg respectively. Their written informed consent was requested to participate. The present study was approved by the ethics committee of our university.

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

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was carried out. In sitting position, volunteers breathed room air for 1 min (control), then a 12% O_2 in N_2 gas mixture stored in a Douglas bag through a non-rebreathing valve (Hans Rudolph) for 2 min (maneuver), and then room air for 1 min (recovery).

2.3. Signal recording and acquisition

ECG was detected at the CM5 bipolar lead using a bioelectric amplifier (Biopac Systems). Noninvasive AP was measured by Finapres (Ohmeda). Arterial oxygen saturation (SaO_2) was measured with a pulse oxymeter (Criticare). Respirogram was computed by a set of pneumotachometer (Hans Rudolph), pressure transducer (Validyne), carrier demodulator (Validyne) and integrator (Validyne). CO_2 concentration was measured with an infrared analyzer (Biopac Systems). All recorded signals were digitized at a sampling rate of 1 kHz via an acquisition system (Biopac Systems).

2.4. Data processing

From ECG, AP and its first derivative (dAP), Res, SaO_2 and CO_2 signals, maxima and minima were detected to generate time series of R-R intervals (RR), systolic pressure (SP), diastolic pressure (DP), their difference, pulse pressure (PP), maximal amplitude of dAP (dmAP), tidal volume (TV), respiratory frequency (RF) and end-tidal CO_2 ($ETCO_2$). All series were cubic-spline interpolated, detrended and resampled at 4 Hz. Time-frequency spectra of the series of RR, SP, PP, dmAP and Res were estimated with the smoothed pseudo-Wigner-Ville distribution and integrated in the standard frequency bands of heart rate variability to compute low frequency powers of SP (LF_{SP}), RR (LF_{RR}), PP (LF_{PP}) and dmAP (LF_{dmAP}), and high frequency powers of RR (HF_{RR}) and Res (HF_{Res}). Instantaneous values of LF_{RR}, LF_{SP}, HF_{RR} and HF_{Res} were used, respectively, to compute BRS and RSAS by alpha index, and their required time-frequency coherences were considered significant when greater than 0.5. After subtracting their mean baseline value, the individual dynamics of all the variables were ensemble-averaged for visualization, and segmented into 9-s epochs for statistical analysis.

2.5. Statistical analysis

Due to its skewed distribution, a logarithmic transformation was applied to HF_{RR} ($lnHF_{RR}$). Data of the variables 9-s epochs were pooled and expressed as mean±SD. Differences between baseline and epochs mean values were tested by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test. For each variable, the first mean value significantly different from baseline was taken as the onset of the effect, and the time elapsed from the onset of SaO_2 decrease to the onset of each variable effect was considered as the latency. Statistical significance was accepted at $p<0.05$.

3. Results

Time-frequency spectra of RR, dmAP and Res series during hypoxemia presented decreases of both LF_{RR} and HF_{RR} power (Fig. 1A), reduction of LF_{dmAP} (Fig. 1B), and gradual increase of the frequency of HF_{Res} (Fig. 1C).

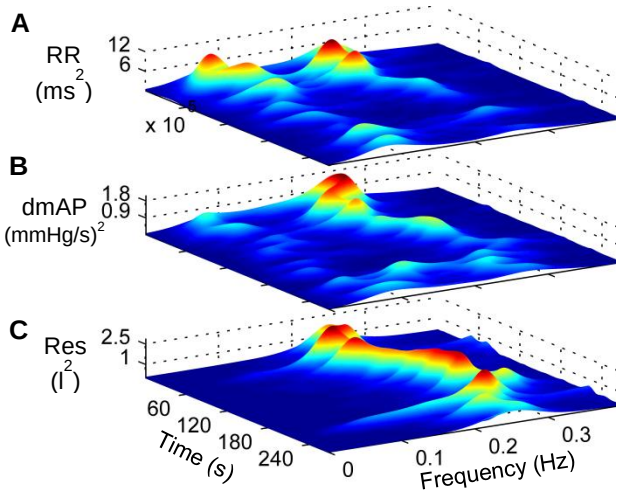

Fig. 1. Representative time-frequency distributions of A) RR, B) dmAP and C) Res series during hypoxemia, spanning from 60 to 180 s.

Associated to the effects of 12% O_2 breathing, the ensemble averages of the individual dynamics of the studied variables showed consistent response patterns with different latencies. SaO_2 progressively fell from 96±2 to 82±2% ($p<0.001$) over 115 s (Fig. 2A). The variables that showed latencies shorter than 9 s and progressively decreasing sequence of means until the end of hypoxemia were: $lnHF_{RR}$ ($p<0.002$; Fig. 2B), RR ($p<0.006$; Fig. 2C), LF_{dmAP} ($p<0.001$; Fig. 2D), LF_{PP} ($p<0.003$; Fig. 2E), dmAP ($p<0.01$; Fig. 2F), RSAS ($p<0.02$; Fig. 2G), $ETCO_2$ ($p<0.01$; Fig. 2I); and progressive increase, RF ($p<0.04$; Fig. 2H). After a latency greater than 36 s, means of BRS decreased progressively ($p<0.02$; Fig. 2J) and some means of LF_{SP} showed a transitory decrease ($p<0.03$; Fig. 3A). After 72 s, some means of LF_{RR} ($p<0.04$; Fig. 3B) underwent transitory increments. And with latencies greater than 108 s, means of SP ($p<0.03$; Fig. 3C) and DP ($p<0.04$; Fig. 3D) presented sustained decreases until the end of the recording. TV showed non-significant fluctuations with respect to its control value. Mean values of LF_{RR}-LF_{SP} time-frequency coherence decreased ($p<0.04$) from 0.90±0.04 to 0.88±0.04.

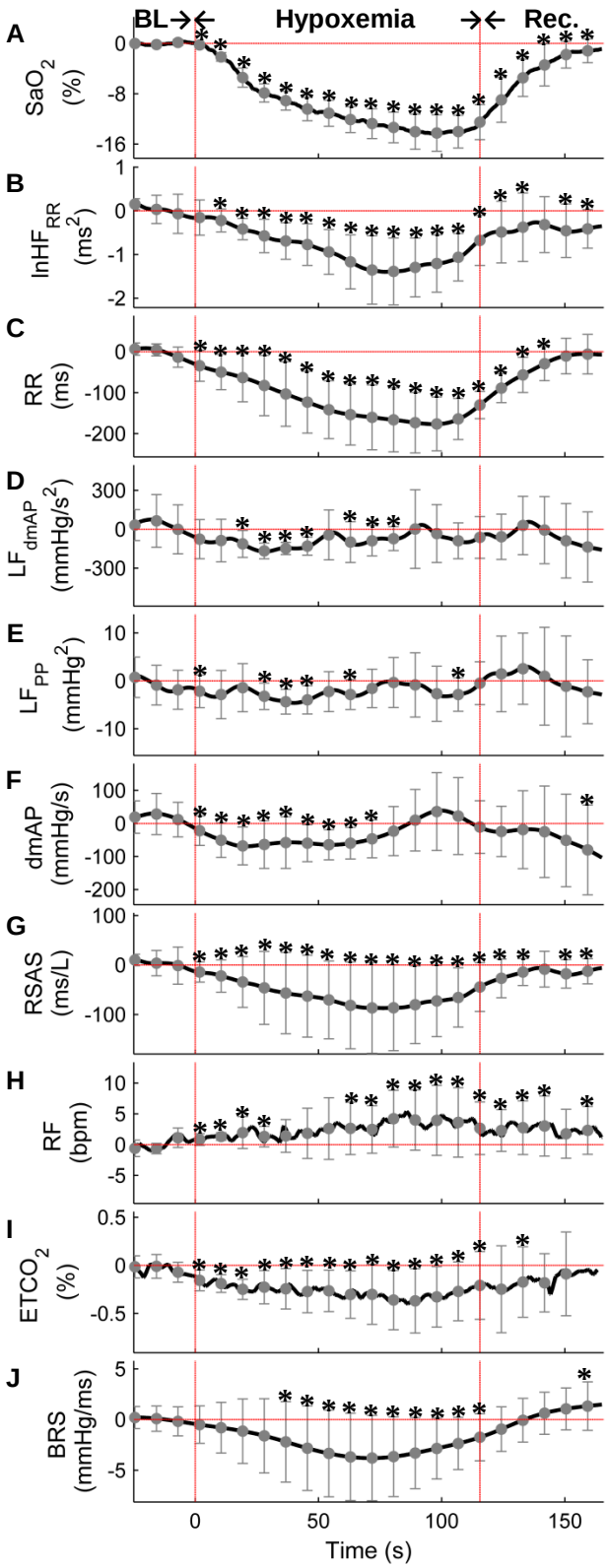

Fig. 2. Ensemble averages with their respective 9-s pooled means±SD of: A) SaO_2, B) $lnHF_{RR}$, C) RR, D) LF_{dmAP}, E) LF_{PP}, F) dmAP, G) RSAS, H) RF, I) $ETCO_2$, J) BRS dynamics. *p<0.04 hypoxemia vs. baseline (BL).

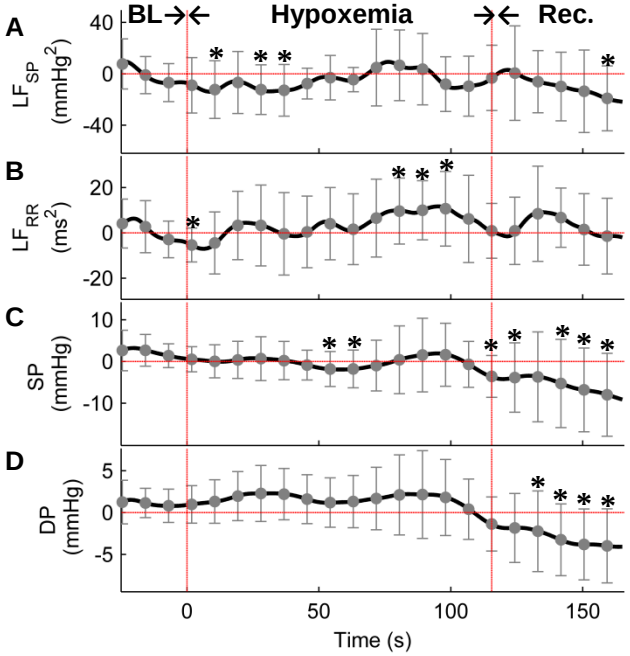

Fig. 3. Ensemble averages with their respective pooled means ±SD each 9s of the instantaneous values of A) LF_{SP}, B) LF_{RR} C) SP and D) DP. *p<0.04 hypoxemia vs. baseline (BL).

4. Discussion

In healthy subjects, short-term moderate hypocapnic hypoxemia provokes depressive response patterns in the instantaneous time courses of most of autonomic-cardiovascular-respiratory variables, with different latencies: not after 9 s, $lnHF_{RR}$, RR, RSAS, dmAP, LF_{PP}, LF_{dmAP} and $ETCO_2$ display patterns of progressive decrease, and RF of gradual increase; 36 s into hypoxemia, BRS is progressively reduced and LF_{SP} shows a transient decrease; after a 72-s latency, transitory elevation of LF_{RR} occurs; and, after a 108-s latency, SP and DP decrease. Additionally, BRS coherence decrease.

To the best of our knowledge, this is the first study to report, in a beat-to-beat format, that short-term hypoxemia causes immediate decreases in sympathetic and vagal activities that are associated to RR, BRS, RSAS and cardiac contractility reductions, and the increase of RF. Later on, AP is reduced by local vasodilation.

The use of time series and their time-frequency distributions allows to: 1) track the instantaneous time-course of the variables; 2) determine the latencies of the effects; and 3) obtain consistent response patterns through the ensemble averaging of individual dynamics. These features of our methodological approach differ from those of the majority of the published studies on the effects of hypoxia, where a single mean value of each variable is considered representative of the whole effect and their

temporal course is not tracked, making it difficult to determine cause-effect relationships between variables. Additionally, as part of our battery of measures, we assessed the performance of two promising sympathetic indexes derived from the AP signal, LF_{dmAP} and LF_{PP}, that we have previously reported [8].

Extant reports of the autonomic, cardiovascular and respiratory effects produced by hypoxia, albeit contradictory [7], suggest a mechanism triggered by the activation of chemoreflex, which increases pulmonary ventilation [2, 3] and sympathetic activity [2, 4, 6], although decreases of the latter have been found [5]. The sympathetic activation is responsible for increasing the heart rate [2, 4, 5, 6, 7] and AP [2], even though no change in AP [7] or even AP decrease by direct vasodilation [2] have been documented. The AP rise, via the baroreflex with either reduced [2, 5] or unchanged [6] BRS, buffers the sympathetic activation and AP climb without affecting the vagal activity [6, 7]; however, there are also reports of vagal decrease [5]. The unchanged vagal outflow does not affect respiratory sinus arrhythmia [7]. The heart rate increase is the most consistent effect of hypoxia because there is no equivocal data reported.

Based on our findings we propose that moderate hypoxemia directly causes, with a 9-s latency, progressive reductions of both sympathetic (Fig. 2 D-E) and vagal outflows (Fig. 2B). The gradual decrease of cardiac sympathetic activity, indicated by our cardiac sympathetic markers LF_{dmAP} and LF_{PP} (Fig. 2D-E) [8], contributes to the gradual depression of cardiac contractility (indicated by dmAP; Fig. 2F), with no changes in the vasomotor sympathetic tone (marked by LF_{SP}; Fig. 3A); but all these factors do not change AP (Fig. 3C-D). 72 s into hypoxemia, LF_{RR} undergoes a subtle transient increase (Fig. 3B) with no effect on cardiovascular function. The progressive withdrawal of vagal activity determines the gradual decreases of RR (despite the depressed sympathetic activity; Fig. 2C), BRS (Fig. 2J), and RSAS (Fig. 2G), the latter effect reinforced by the increase of RF (Fig. 2H). The lack of appreciable changes in AP indicates that baroreflex does not participate in the observed autonomic effects. With a latency 108 s long, hypoxemia elicits reductions of SP (Fig. 3C) and DP (Fig. 3D) that are not associated with significant reductions of sympathetic activity, thus suggesting a direct vasomotor depression without baroreflex involvement. The reduction of the LF_{RR}-LF_{SP} coherence suggests a certain decoupling between the input and output of the baroreflex mechanism that contributes to blunting its responsiveness, thus providing an additional index of BRS. Additionally, an immediate chemoreflex activation occurs, indicated by the gradual increase of RF (Fig. 2H) without TV changes, determining the progressive decrease of $ETCO_2$ (Fig. 2I) but not provoking sympathetic activation.

Some of the equivocal findings reported may be explained by their possible different time of occurrence, as shown by our findings of initial lack of change that turns into reductions of BRS (Fig. 2J) and AP (Fig. 3C-D).

The reduced tissue O_2 delivery and the consequent decrease in the energy production determined by short-term hypoxemia, is somewhat compensated by the increases of RF and heart rate, which increase, to some extent, the respiratory O_2 exchange and blood O_2 transport, respectively. Nevertheless, hypoxemia possibly causes a generalized function depression.

In conclusion, the study of the instantaneous time course of autonomic cardiovascular variables provides a novel and highly dynamic picture of their depressive responses to short-term moderate hypocapnic hypoxemia, which provokes direct immediate and progressive decrease of both sympathetic and vagal activities that contribute to the reduction of RR, BRS, RSAS and contractility, without changes in AP or baroreflex involvement. Chemoreflex activation that increases RF does not elicit a sympathetic cardiovascular increase. Later, AP decreases, probably due to direct vasodilation.

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