Beat-To-Beat Autonomic Cardiovascular Response to Short-Term 100%O_2 Breathing: a Time-Frequency Analysis Approach

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Abstract

In sixteen healthy volunteers, we assessed the effects produced by short-term 100%O_2 breathing on the instantaneous time courses of R-R intervals (RR), arterial pressure (AP), arterial oxygen saturation (SaO_2), respiratory volume (Res), and, estimated by a time frequency distribution, the high frequency powers of RR (HF_{RR}) and Res (HF_{Res}), the low frequency powers of RR (LF_{RR}) and systolic pressure (LF_{SP}), the LF_{RR}/HF_{RR} ratio, baroreflex sensitivity (BRS) by alpha index and respiratory sinus arrhythmia sensitivity (RSAS). Short-time hyperoxemia provoked various effects with different latencies: a) RR lengthening, with 15-s latency; b) AP increase, with 75-s latency, c) BRS and RSAS increases with 120-s latency, d) HF_{RR} increase and LF_{SP} and LF_{RR}/HF_{RR} decreases, with 135-s latency, and d) no significant changes on Res. During hyperoxemia, the instantaneous time courses of these variables are fluctuating, with subtle yet significant changes at different latencies. Initially, hyperoxemia lengthens RR by direct inhibition of the sinoatrial node, and later on, it elicits a direct vasoconstriction-dependent increment of AP, which, via baroreflex with augmented sensitivity, increases vagal outflow and reduces sympathetic activity, changes strengthened by the augmented RSAS, but hyperoxemia does not modify the respiratory variables.

1. Introduction

Despite the extensive therapeutic use of supplemental oxygen in normoxemic and hypoxemic patients [1], which is not risk-free, the reported autonomic-cardiovascular effects of 100%O_2 breathing in healthy subjects are not consistent. On the one hand, there is consensus that hyperoxia directly causes vasoconstriction [1], vagal activity increase with heart rate (HR) reduction [2,3] and sympathetic activity decrease [2,4]; but on the other hand, contradictory effects of hyperoxia on pulmonary ventilation (PV) [5], arterial pressure (AP) [3,6] and baroreflex sensitivity (BRS) [2,3,7] have been reported. Apparently, hyperoxia produces various effects on different organs in a parallel manner, directly, and separately [1]. Moreover, the participation of either the baroreflex or the respiratory sinus arrhythmia (RSA) mechanisms in these effects remains unclear. Additionally, spectral analysis of cardiovascular variability under hyperoxemic conditions has only been performed using steady-state techniques [2,3,7,8], so the transient changes of the autonomic-cardiovascular variables in the first minutes of hyperoxemia are still unknown. To clarify these issues, by using a time-frequency spectral analysis approach, we assessed the instantaneous time course of the effects produced by short-term 100%O_2 breathing on the spectral measures of heart rate variability (HRV) and systolic pressure variability, BRS, RSA sensitivity (RSAS), R-R intervals (RR), AP and respiratory variables.

2. Methods

2.1. Subjects

Sixteen healthy, normotensive and sedentary subjects, 8 men and 8 women, were studied. Their mean age, height and weight were 22.3±1.7 years, 163.2±6.4 cm and 61.6±9.6 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 was carried out. It consisted of 1-min control (air breathing), 2-min maneuver during which the subjects, with occluded nose, breathed 100%O_2 gas stored in a Douglas bag through a non-rebreathing valve (Hans Rudolph), followed by 1.5-min recovery breathing air.

ECG, AP, arterial oxygen saturation (SaO_2), expired CO_2 concentration, and respiration (Res) were recorded throughout the entire study.

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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). 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). ECG, AP, Res, SaO_2 and CO_2 signals were digitized at a sampling rate of 1 kHz via an acquisition system (Biopac Systems).

2.4. Data processing

From ECG, AP, Res, SaO_2 and CO_2 signals, R-wave peaks, systolic pressure (SP), diastolic pressure (DP), respiratory peaks and end-tidal maximum values of CO_2 ($ETCO_2$) were detected to generate RR, SP, DP, their difference, pulse pressure (PP), tidal volume (TV), respiratory frequency (RF), their product, PV, and $ETCO_2$ time series. All series were cubic-spline interpolated, resampled at 4Hz and separated into trends and oscillations by the smoothness priors method with a cut-off frequency of 0.03Hz. Time-frequency spectra of the oscillations of the series of RR, SP and Res were estimated with the smoothed pseudo-Wigner-Ville distribution and integrated in the standard low frequency (LF) and high frequency (HF) bands of HRV to compute LF power of SP (LF_{SP}), LF of RR (LF_{RR}), HF power of RR (HF_{RR}), HF of Res (HF_{Res}), and the low-to-high frequency ratio of RR (LF_{RR}/HF_{RR}). Instantaneous values of LF_{RR} and LF_{SP} were used to compute BRS by alpha index and their time-frequency coherence. Instantaneous RSAS was estimated as the square root of the HF_{RR}/HF_{Res} ratio and their time-frequency coherence. Coherence values greater than 0.5 were considered significant. The dynamics of all the variables were ensemble-averaged for visualization after subtracting their mean baseline value, and segmented into 15-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 epochs were pooled and expressed as mean±SD. Differences of the mean values were tested by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test. Time elapsed from the significant increase of SaO_2 to the first significant sustained change of each variable in relation to its mean baseline value was considered the latency of the respective response. Statistical significance was accepted at $p<0.05$.

3. Results

Time-frequency spectra of RR and SP series showed that the increase of HF_{RR} and decrease of LF_{RR} powers (Fig. 1A) as well as the reduction of LF_{SP} power (Fig. 1B) began around 120s after the onset of hyperoxemia. In the typical example presented, important fluctuations of the instantaneous power are noticeable in both frequency bands of the two variables.

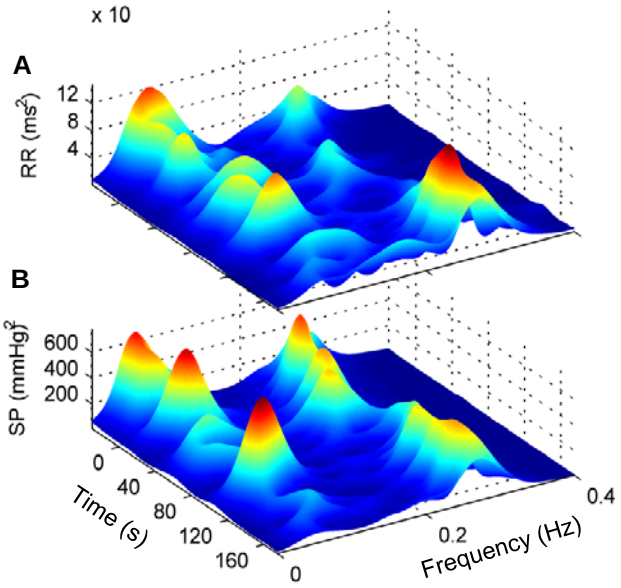

Fig. 1. Representative time-frequency distributions of A) RR and B) SP series during hyperoxemia, spanning from 0 to 170 s.

About 30s after the beginning of 100%O_2 breathing, SaO_2 increased progressively from a baseline of 94.7±1.9% to a plateau with a mean value of 99.5±0.6% ($p<0.001$), which lasted for at least 170s (Fig. 2A).

Hyperoxemia increased RR, AP, BRS and RSAS. RR lengthening began around 15s after the onset of hyperoxemia, reaching, 30s later, a plateau ($p<0.008$) that lasted until the end of the maneuver (Fig. 2B). Means of instantaneous values of SP, DP and PP behaved in a similar manner, subtly increasing ($p<0.04$) 75s after hyperoxemia settled (Fig. 2C-E). Mean values of BRS (mean LF_{RR}-LF_{SP} coherence=0.89±0.06) and RSAS (mean HF_{RR}-HF_{Res} coherence=0.95±0.01) dynamics began to increase progressively ($p<0.01$) 120s from the onset of hyperoxemia (Fig. 2F and K).

Mean values of the dynamics of $lnHF_{RR}$, LF_{RR}, LF_{RR}/HF_{RR}, and LF_{SP} powers presented significant changes with respect to their baseline values 135s after the beginning of hyperoxemia. While $lnHF_{RR}$ power (Fig. 2G) increased ($p<0.04$), mean values of LF_{RR} (in normalized units, Fig. 2H), LF_{RR}/HF_{RR} (Fig. 2I) and LF_{SP} powers (Fig. 2J) decreased ($p<0.04$).

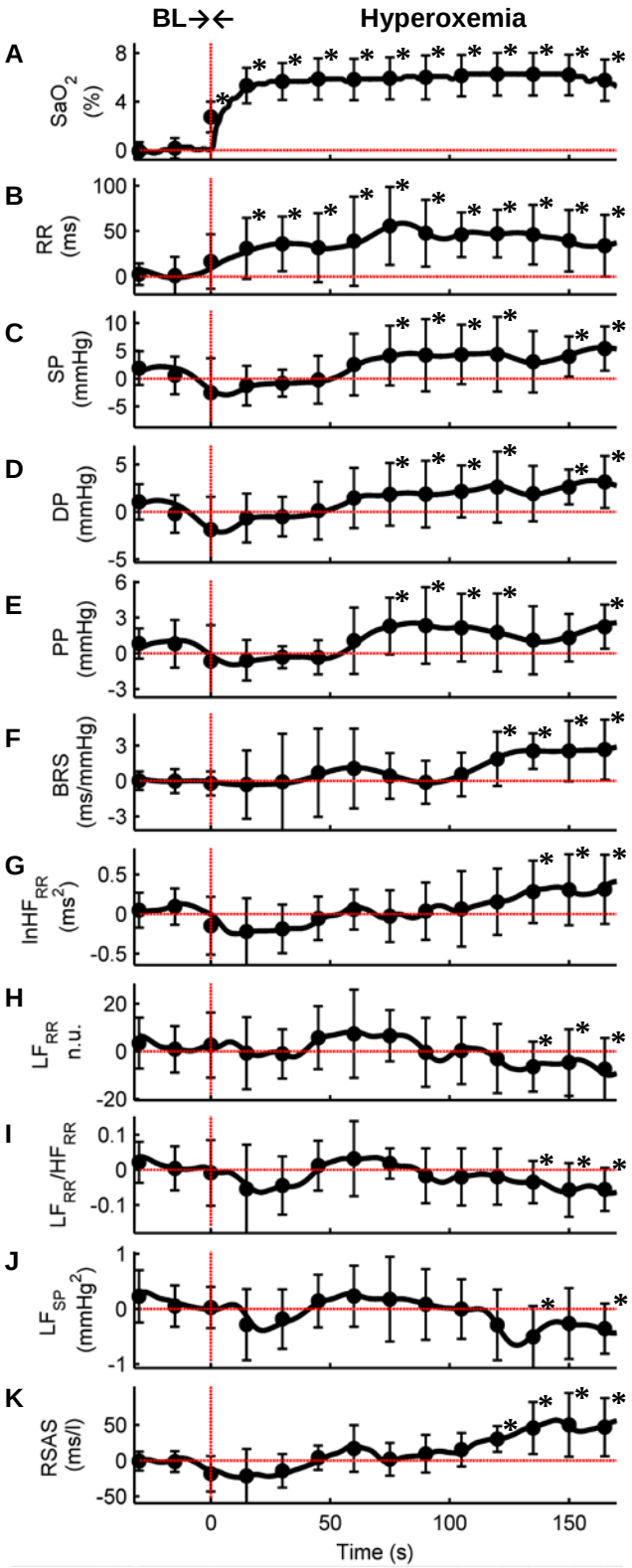

Fig. 2. Ensemble averages of A) SaO_2, B) RR, C) SP, D) DP, E) PP, F) BRS, G) $lnHF_{RR}$, H) LF_{RR}, I) LF_{RR}/HF_{RR}, J) LF_{SP}, K) RSAS dynamics, with their respective 15-s pooled means±SD. *p<0.01 hyperoxemia vs. baseline (BL).

Pooled means of HF_{Res}, TV (0.65±0.25 l), RF (17.4±7.5 breaths/min), PV and $ETCO_2$ dynamics were not different from control (Fig. 3).

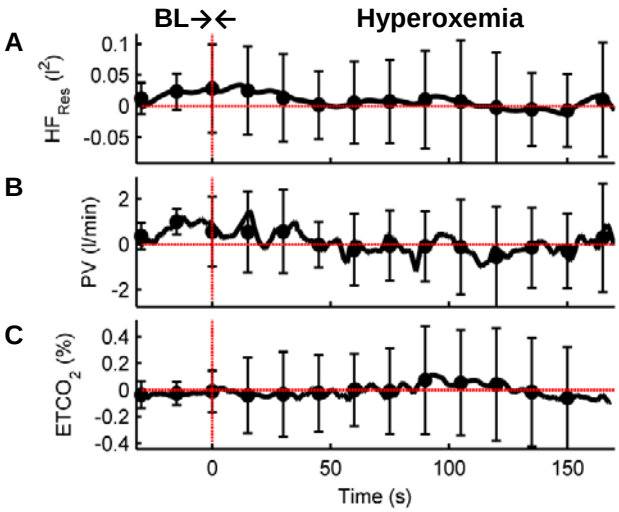

Fig. 3. Ensemble averages of the instantaneous values of A) HF_{Res}, B) PV and C) $ETCO_2$, with their respective pooled means ±SD each 15s. *p<0.01 hyperoxemia vs. baseline (BL).

4. Discussion

In healthy subjects, short-term hyperoxemia provokes subtle effects with different latencies on the instantaneous time courses of autonomic-cardiovascular variables, as supported by our main findings: a) lengthening of RR intervals, with a 15-s latency; b) increase of SP, DP and PP, with a 75-s latency, c) increase of BRS and RSAS with a 120-s latency, d) increase of $lnHF_{RR}$ power and decrease of LF_{SP}, LF_{RR}, and LF_{RR}/HF_{RR} ratio, effects with a 135-s latency, and d) no significant effects on HF_{Res} power, PV and $ETCO_2$.

To the best of our knowledge, this is the first study to establish, in a beat-to-beat format, that hyperoxemia causes two types of autonomic-cardiovascular effects: the early ones, RR and AP increments, and the late ones, decrease of sympathetic activity and increase of vagal outflow, produced with the participation of both the baroreflex and RSA mechanisms, whose sensitivities are augmented.

There is substantial consensus on the effects that long-term hyperoxia causes in healthy subjects: sympathetic activity decrease, as evaluated by muscular sympathetic nerve activity [4], by LF_{SP} power [2] and by the LF_{RR}/HF_{RR} ratio [8]; augmented vagal activity as indicated by the increase of HF_{RR} power [2,3,8], associated with HR reduction [2,3,4,8,9]; decreased stroke volume [2,9]; vasoconstriction due to a local effect [7,9], which has recently been considered the primary effect of hyperoxemia [1], eliciting an increase in

peripheral resistance [2,3] and decreased blood flow to the limbs [4]. However, contradictory effects of hyperoxia have also been reported: reduction [6], no change [4] or increase [3] of AP; no change of BRS evaluated by alpha technique [7], and, when estimated by sequence analysis, increase [3] or reduction [2]; and either no change, decrease or increase of PV [5].

No studies on the effects of hyperoxia have used a time-frequency distribution for the instantaneous spectral analysis of cardiovascular variability. Our findings of reductions in LF_{SP}, LF_{RR} and LF_{RR}/HF_{RR}, as well as the increases of RR, BRS and $lnHF_{RR}$ are similar to the reported ones upon which there is general consensus [3,8]. Nevertheless, obtaining the instantaneous dynamics of the autonomic-cardiovascular variables allowed us to establish that they present brief, apparently isolated and not persistent fluctuations such as those of $lnHF_{RR}$ and LF_{SP} between 15 and 30s after the onset of hyperoxemia, or sustained increases like those of RR and AP (Fig. 2). Moreover, the different latencies of the significant changes of the variables suggest that the effects of hyperoxemia on autonomic-cardiovascular function are produced by two consecutive mechanisms, first by direct action on the sinoatrial (SA) node and vascular smooth muscle and later on by indirect influence mediated by the baroreflex and RSA mechanisms. Thus, in the first 15s after hyperoxemia settles, it causes a direct inhibition of the SA node, reducing HR, as suggested by its lack of temporal association with a significant rise in $lnHF_{RR}$ power (Fig. 2B and G). This notion contrasts with the accepted view that HR reduction is mediated by increasing vagal outflow [3]. Shortly after, vasoconstriction occurs with 75-s latency, manifested by the increments of SP, DP and PP (Fig. 2C-E). These AP changes trigger the baroreflex mechanism, whose sensitivity is augmented with 120s latency, and which progressively increases vagal activity and reduces the sympathetic outflow, as indicated by the changes with 135-s latencies of $lnHF_{RR}$, LF_{SP}, LF_{RR} powers and LF_{RR}/HF_{RR} ratio (Fig. 2G-J). In addition, the increase of vagal activity is influenced by the increase of RSAS with 120s latency (Fig. 2K), similar to that of BRS. The slight increment of PP suggests a rise of stroke volume (Fig. 2E). This finding is contrary to the reported effect [2,9].

We cannot rule out the possibility that the deactivation of peripheral chemoreceptors provoked by hyperoxia contribute to the sympathetic activity decrease, as has been reported [4,6]. In our subjects hyperoxemia was associated with isocapnic condition because it did not affect PV or $ETCO_2$, which implies that the autonomic-cardiovascular effects are not influenced by changes in CO_2 arterial pressure. Our above-mentioned explanation, based on the analysis of the instantaneous values of the variables, differs from the reported ones [1,3] because pointing out the time and order of appearance of the significant changes in the different autonomic-cardiovascular variables allows establishing causal relationships among them, interactions that are integrated by the baroreflex and RSA mechanisms.

Because the effects of hyperoxemia are potentially harmful to the heart and vessels [1,3,9] and the risk of organic damage is proportional to the exposure time, in this study we limited $100\%O_2$ breathing to a few minutes.

In conclusion, during isocapnic hyperoxemia, the instantaneous time courses of autonomic-cardiovascular variables are fluctuating, with subtle yet significant changes at different latencies. Initially hyperoxemia lengthens RR by direct inhibition of the SA node, and later on, elicits a direct vasoconstriction-dependent increment of AP, which, via baroreflex mechanism with augmented sensitivity, intensifies the vagal outflow and reduces the sympathetic one, effects that, in addition, are influenced by the increase of RSAS, without modifying the respiratory variables.

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