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# Relationship between heart rate variability, blood pressure and arterial wall properties during air and oxygen breathing in healthy subjects ☆

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ABSTRACT

Previous studies reported that normobaric hyperoxia influences heart rate, arterial pressure, cardiac output and systemic vascular resistance, but the mechanisms underlying these changes are still not fully understood. Several factors are considered including degeneration of endothelium-derived nitric oxide by reactive oxygen species, the impact of oxygen-free radicals on tissues and alterations of autonomic nervous system function. Recently, new devices for the detailed non-invasive assessment of large and small arteries have been developed. Therefore, the aim of our study was to assess heart rate variability (HRV) as a potential indicator of autonomic balance and its relation to blood pressure and vascular properties during medical air (MAB) and 100% oxygen breathing (OXB) in healthy volunteers.

In 12 healthy subjects we assessed heart rate and blood pressure variability, baroreflex sensitivity, respiratory frequency, common carotid artery diameter and its wall distensibility, as well as changes in the digital artery pulse waveform, stroke index and systemic vascular resistance during MAB and OXB. Mean and systolic blood pressure have increased significantly while digital pulse amplitude and carotid artery diameter were significantly lower during hyperoxia. Heart rate variability measures did not differ during MAB and OXB. However, the correlations between spectral HRV components and those hemodynamic parameters which have changed due to hyperoxia varied substantially during MAB (correlated significantly) and OXB (no significant correlations were noted).

Our findings suggest that autonomic nervous system might not be the main mediator of the cardiovascular changes during 100% oxygen breathing in healthy subjects. It seems that the direct vascular responses are initial consequences of hyperoxia and other cardiovascular parameter alterations are secondary to them.



## 1. Introduction

Peripheral chemoreceptors respond mainly to hypoxia and central chemoreceptors are mostly sensitive to hypercapnia; chemoreceptor reflex operates in a similar way as baroreflex (Kara et al., 2003; Nattie, 2006). Previous studies reported that normobaric hyperoxia deactivating peripheral chemoreceptors might impact heart rate, arterial pressure, cardiac output and systemic vascular resistance, but the mechanism of changes is still not fully understood. Alterations of autonomic nervous system function initiated by chemo- or baroreceptors as well as decreased synthesis and bioavailability of endothelium-derived nitric oxide by reactive oxygen species are considered as possible mechanisms underlying these hemodynamic changes.

Several cardiovascular alterations due to hyperoxia were noted in healthy subjects including the decrease of heart rate and cardiac output (Daly and Bondurant, 1962; Waring et al., 2003; Bak et al., 2007; Gole et al., 2011) and the increase in systemic vascular resistance and/or blood pressure (Waring et al., 2003; Bak et al., 2007; Anderson et al., 2010; Gole et al., 2011). Reactive hyperemic blood flow was reported to be reduced in forearm and digital arteries during oxygen breathing (Crawford et al., 1997; Nohria et al., 2006). Some studies described also the change in baroreflex sensitivity and in the power of high-frequency component of heart rate variability (Lund et al., 1999; Waring et al., 2003; Gole et al., 2011).

In patients with hypertension or sleep apnea, administration of 100% oxygen results in the reduction in heart rate, blood pressure and MSNA due to the underlying enhanced chemoreceptor activity (Narkiewicz et al., 1998). In some cases, supplemental oxygen might not be beneficial. In patients with heart failure hyperoxia

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reduces cardiac output and stroke volume and increases systemic vascular resistance (Haque et al., 1996) similarly to changes in healthy subjects. Better understanding of mechanisms underlying cardiovascular and neural changes during hyperoxia might help to identify groups of patients in which breathing with oxygen should be avoided because of the potential harm (Rawles and Kenmure, 1976; Wijesinghe et al., 2009; Moradkhan and Sinoway, 2010; Park et al., 2010).

The present study was designed to assess heart rate variability (HRV) as a potential indicator of autonomic balance and its relation to blood pressure and vascular properties during medical air (MAB) and 100% oxygen breathing (OXB) in healthy volunteers. All tested parameters (common carotid artery diameter and wall distensibility, changes in the digital artery pulse waveform, reactive hyperemia index, stroke index and systemic vascular resistance) were available noninvasively, and enabled us to assess the whole spectrum of hyperoxia-induced changes. We hypothesized that by having the more complete picture of cardiac, vascular and neural alterations during oxygen breathing we will be able to understand better the mechanisms mediating responses to hyperoxia.

## 2. Methods

### 2.1. Participants

Twelve healthy young volunteers (5 men; age 33.8 ± 7.4 years) participated in the study. None of the participants was a smoker, neither had any medical condition needing chronic drug treatment. None of the female participants was pregnant. Baseline characteristics of study participants are presented in Table 1.

All patients were informed about the aim of the study, its protocol and possible risks, before giving an informed written consent. The study was approved by the local Ethics Committee.

### 2.2. Study protocol

After signing the informed consent all patients were invited to the examination session which usually lasted 2–2.5 h. During the session in a room dedicated to the autonomic system and hemodynamic measurements, in a comfortable room temperature, patients stayed in supine position for the whole time of the experiment. All patients were breathing medical air and oxygen through a non-rebreathing face mask while recording the changes in hemodynamics and autonomic system. On the day of measurement the participants were asked to eat a light meal 4 h before the examination and abstain from drinking strong tea or coffee. All measurements took place two times: during medical air (MAB) and oxygen breathing (OXB) during one examination visit. Measurements were done after at least 10 min of exposure to medical air or oxygen. Blood pressure, HRV and hemodynamic parameters were assessed during HOTMAN parts of the study. Small differences between MAB and OXB parts (e.g. time sequence of ArtLab and HOTMAN) were due to technical limitations, but the difference of time exposure to gases did not exceed 5–10 min. The only exception was EndoPAT part, which we decided to perform at the beginning of the study (followed then with 10-minutes rest period with no-mask room air breathing) and at the end of the protocol. The detailed study protocol is presented in Fig. 1.

**Table 1**
Baseline characteristics of study participants.

| | |
|---|---|
| Number (male) | 12 (5) |
| Age (years) | 33.8 ± 7.4 |
| Height (m) | 1.74 ± 0.08 |
| Weight (kg) | 74.5 ± 8.6 |
| Body mass index (kg/m$^2$) | 24.6 ± 2.6 |
| Systolic blood pressure (mm Hg) | 118.7 ± 11.1 |
| Diastolic blood pressure (mm Hg) | 77 ± 5.6 |
| Resting heart rate (beats/min) | 63 ± 10 |

#### 2.2.1. Basic measurements, heart rate variability (HRV) and baroreflex sensitivity (BRS) assessment

All patients underwent short-term ECG recording using PowerLab system with Lab Chart software (ADInstruments, Australia). The sampling rate was 1000 Hz.

Fragments of 512 RR intervals were used for further HRV analyses with the use of Kubios HRV Pro Version software (University of Kuopio, Kuopio, Finland). Linear parameters of heart rate variability including time-domain analysis indices: mean RR interval, standard deviation of all normal-to-normal RR intervals (STD RR), root-mean-square of differences of adjacent normal-to-normal RR intervals (RMSSD), and the number and percentage of interval differences of successive normal RR intervals greater than 50 ms (NN50 and pNN50) were obtained. Frequency-domain HRV analysis was performed by fast Fourier transform-based Welch periodogram method in which the HRV sample is divided into overlapping segments and the spectrum is obtained by averaging the spectra of these segments (window with 256s and window overlap of 50% were used). The frequency bands of interest included the very low frequency (VLF, 0–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.4 Hz). The frequency-domain measures extracted from the power spectrum density (PSD) estimate for each frequency band include absolute and relative powers of VLF, LF, and HF bands, LF and HF band powers in normalized units, the LF/HF power ratio, and peak frequencies for each band (Task Force for HRV, 1996).

Blood pressure was measured using oscillometric device at baseline, during MAB and OXB. Systolic and diastolic values of blood pressure as well as mean arterial blood pressure (SBP DBP and MAP) were obtained.

Non-invasive beat-to-beat blood pressure recording was also done by the use of FINOMETER device (Finapres Medical Systems). Systolic BP variability was calculated as SD of systolic BP.

The respiratory belt, based on piezoelectric device, connected to PowerLab was used to derive respiratory rate.

Baroreflex sensitivity was assessed using the spectral method also known as the α-coefficient method. RR ECG intervals and blood pressure were obtained under spontaneous breathing, therefore BRS was calculated at the breathing frequency in a window width of 0.06 Hz according to previously described method (Parati et al., 2000). The breathing frequency was assessed individually for each patient. The mean value was 0.243 Hz (14.6 resp/min) while breathing oxygen and 0.248 Hz (14.9 resp/min) while breathing air with a standard deviation of 0.08 Hz in both cases. No statistically significant difference was observed. Data was linearly resampled to a sample frequency of 1 kHz. Due to numerical features data for the BRS analysis had a length of about 262s (the number of recorded data points was a power of 2) which resulted with analysis of over 256 beats. Artifacts generated by calibration of Finapres were eliminated by linear interpolation. The number of those artifacts did not exceed 3 in each recording and each artifact did not last for more than 3 beats. The calculations of the BRS were executed using ScopeWin software.

Baroreflex sensitivity assessment was then confirmed using the sequence method (La Rovere et al., 2008). The minimum length of sequences was 3 beats and the changes had to be equal or greater than 1 mm Hg and 5 ms for blood pressure and RR intervals respectively. The sequences were put on a plot RRi (SBP) and the slope of the regression line — the regression coefficient, was calculated.

#### 2.2.2. Carotid artery examination

Carotid artery ultrasonography examination was performed after at least 30 minute rest on the right side on a patient in a recumbent position. The examination was performed by two doctors skilled and certified in vascular ultrasonography (AS, BG). The linear probe