Effects of alterations of inspiratory oxygen fractions on heart rate variability

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Editor’s key points

- Heart rate variability (HRV) can indicate perioperative stress and depth of anaesthesia.
- Effects of breathing oxygen on HRV were studies in awake and anaesthetized subjects.
- Breathing 100% oxygen significantly affected the HRV variables.
- The study shows how breathing oxygen can confound the interpretation of HRV to assess the depth of anaesthesia.

Background. Changes in heart rate variability (HRV) during anaesthesia depend on multiple influences such as hypnosis, analgesia, surgical stress, and interacting drugs. Several recent studies have aimed to establish HRV-based monitoring tools to measure perioperative stress or anaesthetic depth. Although hyperoxic ventilation (HV) is known to alter autonomic cardiovascular regulation, there have been no studies investigating its influence on time- and frequency-domain analysis during general anaesthesia. Therefore, we have examined the effects of HV on cardiovascular neuroregulation of anaesthetized patients and conscious volunteers by analysis of relevant HRV parameters.

Methods. Fourteen healthy volunteers and 14 anaesthetized, ventilated ASA I patients sequentially breathed room air ($F_{IO_2}$ 0.21), pure oxygen ($F_{IO_2}$ 1.0), and then room air. During each episode, standardized HRV parameters were calculated from 5 min ECG recordings.

Results. HV significantly reduced HR and increased the standard deviation of RR interval values, the root mean square of successive RR interval differences, and the high-frequency (HF) power of the spectral components, whereas the low-frequency (LF) power and the LF/HF ratio of HRV were reduced in both groups. All changes were reversible after $F_{IO_2}$ was reduced to normoxia.

Conclusions. In both healthy volunteers and anaesthetized patients, HV resulted in comparable and reversible changes of established HRV parameters. These changes might be relevant enough to bias HRV-based analgesia and anaesthesia monitoring and could result in a clinically relevant misinterpretation of HRV parameters as indicators of anaesthetic depth during HV.

Keywords: anaesthesia, depth; analgesia; echocardiography; measurement techniques, oxygen

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Measuring heart rate variability (HRV) is a well-known and non-invasive technique to assess autonomic function. As a steady reflection of sympathetic and parasympathetic activity, HRV is expected to reflect cardiovascular adaptability to changing circumstances and has proven to be effective as an early indicator of morbidity and mortality in cardiac disease. During the last 10 yr, varying approaches have been tested to integrate HRV analysis into monitoring of perioperative stress. In addition to several studies using HRV-based parameters to monitor anaesthesia depth, recent studies have resulted in an interesting differentiation of the balance between nociception and analgesia by HRV. These studies identified the high-frequency (HF) component of HRV (HFnu) as an early autonomic indicator of abating analgesia. However, investigators calculating HRV parameters have to consider multiple influencing factors such as awareness, different effects of hypnotics and analgesics, β-blocking agents or vagolytic medication, and changing autonomic or haemodynamic conditions.

Only a few of the studies investigating HRV-based analgesia monitoring have discussed levels of inspired oxygen fractions ($F_{IO_2}$) as a possible influencing factor. Even fewer have discussed the effects of oxygen on HRV, although most observation periods range at the induction and termination intervals of general anaesthesia, when $F_{IO_2}$ is usually considerably changing.

Although hyperoxic ventilation (HV, $F_{IO_2}$ 1.0) is known to alter autonomic cardiovascular regulation in volunteers, there have been no studies that have observed its influence on time- and frequency-domain analysis during general anaesthesia. Therefore, we have investigated the influence of O2 on HRV during general anaesthesia to identify a possible
confounding factor of HRV on intraoperative monitoring of analgesia and stress. As such, the aim of our study was to determine changes in relevant HRV parameters during alternating levels of $F_{IO2}$ in anaesthetized patients and in a control group of healthy volunteers.

**Methods**

Our study is a prospective analysis of ECG data collected for determination of the effects of different levels of $F_{IO2}$ (0.21–1.0–0.21) on HRV changes of anaesthetized patients and a control group of healthy volunteers. After governmental approval of the local Ethics Committee and written informed consent from all subjects, the experiments were performed in anaesthetized patients and in volunteers of both genders.

**Volunteers**

Fourteen healthy non-smoking volunteers (six women/eight men) participated in this study. Clinical history and physical examination were completed, and written informed consent was obtained according to the University of Frankfurt Ethics Committee. The exclusion criteria were neurological, cardiovascular, pulmonary, hepatic, renal, haematopoietic, gastrointestinal, metabolic, or psychiatric dysfunctions; receiving medication on a regular basis.

**Experimental protocol**

Measurements were made in the beach-chair position in a temperature-controlled room (21°C). Hyperoxic breathing was facilitated by the use of an intensive care respirator (Vela, Viasys Healthcare, Würzburg). After 30 min of acclimatization, the volunteers sequentially breathed room air ($F_{IO2}$ 0.21; time point NOX1), pure oxygen ($F_{IO2}$ 1.0; time point HOX), and room air ($F_{IO2}$ 0.21; time period NOX2) for 20 min each. After each change of $F_{IO2}$, there was an equilibration period of 8 min to achieve steady-state conditions. All volunteers were blinded to the $F_{IO2}$ used; however, the different $F_{IO2}$ were not applied in a randomized order. The gas mixture was administered through a non-rebreathing system including a tightly fitting facemask. The resistance of the breathing system was compensated automatically by pressure support (about +2 mm Hg) of the ventilator throughout the complete protocol. No continuous positive airway pressure was applied. Oxygen sensors in the circuit controlled the inspiratory oxygen fraction.

In addition to the 12-channel ECG (see below), brachial arterial pressure was recorded at 5 min intervals with a semi-automated non-invasive oscillometric sphygmomanometer (Datascope Passport, NJ, USA). Pulse oximeter saturation ($SpO2$) was monitored non-invasively by a standard anaesthesia monitor (Datascope Passport).

**Patients**

Fourteen healthy non-smoking patients (seven women/seven men; ASA I) undergoing minor orthopaedic, traumatic, gynaecologic, or visceral surgery participated in the study. Clinical history and physical examination were completed, and written informed consent was obtained according to the University of Frankfurt Ethics Committee. The exclusion criteria were the same as for volunteers (see above).

The patients were premedicated with 7.5 mg midazolam 30 min before the surgery. After preoxygenation with 50% $O2$, general anaesthesia was induced by i.v. injection of remifentanil (1.0 $\mu$g $kg^{-1}$) and propofol (2 mg $kg^{-1}$) and was maintained by continuous infusion of propofol (5 mg $kg^{-1}$ h$^{-1}$) and remifentanil (0.25 $\mu$g $kg^{-1}$ h$^{-1}$). Muscular relaxation was induced by injection of mivacurium (0.2 mg $kg^{-1}$) for intubation. After securing the airway with a tracheal tube, patients were mechanically ventilated with an inspiratory oxygen fraction of 0.21. The minute volume was adjusted individually to maintain normocapnia and then kept constant throughout the complete protocol. Body temperature was kept normal by use of a ‘Warm Touch’ whole-body warming system (Mallinckrodt Medical, Hazelwood, MO, USA). Measurements were started after complete recovery from muscular relaxation was achieved, in a time frame of within a maximum of 45 min after induction of anaesthesia and before the planned surgery was started.

The monitoring of the patients was identical to the monitoring of the volunteers. No further invasive measurements were established.

**Determination of HRV**

Twelve-channel ECG data were collected continuously at 500 Hz in volunteers and patients and recorded directly with a commercial hardware interface on a PC notebook (Cardiox© v.3.41.1 Mesa Medizintechnik GmbH, Germany). R-wave peaks were detected by an automated algorithm (Nevrokard© HRV v.9.2.1, Slovenia). RR intervals were calculated as the difference between successive R-wave peaks. All RR intervals and beat classifications were edited automatically in a first step, and thereafter, manual modifications were performed and artifacts or premature beats were removed if necessary. Linear and non-linear analysis was performed on three short-term recordings (5 min of consecutive, non-overlapping RR intervals each) at NOX1, HOX, and NOX2, according to the guidelines presented by the Task Force of The European Society of Cardiology and the North American Society of Pacing and Electrophysiology.

**Time- and frequency-domain analysis**

In time-domain analysis, the standard deviation ($SD$) of all ‘normal-to-normal’ RR intervals (SDNN) and the square root of the mean ($SD$) (RMSSD) were calculated according to standard formula (Nevrokard© HRV v.9.2.1, Slovenia). A fast Fourier transformation (FFT) was performed for calculation of frequency-domain parameters. In frequency-domain analysis, the total power (TP) of HRV and the power of spectral components in the low frequency (LF: 0.04–0.15 Hz) and HF (0.15–0.4 Hz) were calculated according to the standard formula (Nevrokard© HRV v.9.2.1, Slovenia). Values of these components were expressed as normalized units (nu),
which represent the relative value of each power component in proportion to the TP minus the very LF component.\cite{12}

**Statistical analysis**

Statistical analysis was performed using a standard software package (Statistica 5.1; StatSoft, Tulsa, OK, USA). All data were expressed as median and quartiles, since most, but not all analysed parameters were distributed normally. As a consequence, differences between time points NOX1, HOX, and NOX2 were tested with a Friedman repeated-measures ANOVA on ranks. Post hoc analysis was performed with a Student–Newman–Keuls test (Statistica 5.1; StatSoft). The overall level of significance was set at \( P<0.05 \) for all tests. Differences between the two groups (volunteers vs patients) were not tested due to major differences in several HRV parameters induced by general anaesthesia.

**Results**

**Volunteers**

The mean physical characteristics of the volunteers were as follows: age 29.3 yr (range: 24–37 yr); height 176 cm (range: 162–198 cm); and weight 74.5 kg (range: 53–105 kg).

The variables of time- and frequency-domain data analysis from the volunteers are summarized in Table 1. There was no statistical significant change of arterial pressure between the measurement time points. After the onset of HV at time point HOX, HR was reduced by \(-9\% (P<0.05)\) with the onset of HV at time point HOX. SDNN and RMSSD increased significantly by \(+57.6\% (P<0.05)\) and \(+124.6\% (P<0.05)\), respectively. The frequency-domain parameters TP, HF, and HFnu increased significantly at time point HOX (TP: \(+180.4\%\), HF: \(+39\%\), and HFnu \(+47.8\%\), \(P<0.05\)). LFnu decreased by \(-35.7\% (P<0.05)\), whereas the LF/HF ratio decreased markedly \((-55.7\%, P<0.05)\). After reduction in \( F_{IO2} \) to baseline values at time point NOX2, all parameters except HR returned to baseline levels. LF power did not change significantly throughout the experiment.

**Discussion**

The main findings of our study were that ventilation with pure oxygen reversibly changed HRV in conscious volunteers and anaesthetized, mechanically ventilated patients in a similar fashion (Figs 1 and 2). Comparable changes have been demonstrated in part by other groups in conscious volunteers, suggesting clinical implications for astronauts and divers.\cite{15, 16} Our data suggest that changes of \( F_{IO2} \) mimic pain induced changes of HRV and might therefore present a confounding factor of HRV-based monitoring of perioperative stress and analgesic depth (Tables 1 and 2).

While hypnosis depth is predominantly monitored by electroencephalography-based devices (e.g. bispectral index),\cite{17} monitoring of HRV was effective for indicating intraoperative stress\cite{5} and mismatches of nociception–analgesia balance.\cite{9, 18} While most studies have investigated only

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>NOX1</th>
<th>NOX2</th>
</tr>
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<tbody>
<tr>
<td>Heart rate (min(^{-1}))</td>
<td>67 (61/75)</td>
<td>64 (56/68)*</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>115 (107/119)</td>
<td>115 (110/122)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>69 (67/72)</td>
<td>70 (68/77)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>52.8 (39.4/77.8)</td>
<td>77.5 (56.5/91.5)*</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>45.7 (33.1/63.2)</td>
<td>58.2 (43.9/78.1)*</td>
</tr>
<tr>
<td>TP (ms(^2))</td>
<td>2497 (1547/6074)</td>
<td>3543 (2639/8217)*</td>
</tr>
<tr>
<td>HFnu</td>
<td>39.2 (26.7/67.7)</td>
<td>60.2 (41.5/70.5)*</td>
</tr>
<tr>
<td>HF (ms(^2))</td>
<td>824 (438/1869)</td>
<td>1614 (1068/5098)*</td>
</tr>
<tr>
<td>LFnu</td>
<td>50.9 (28.2/67.8)</td>
<td>35.8 (24.9/51.7)*</td>
</tr>
<tr>
<td>LF (ms(^2))</td>
<td>1182 (753/2102)</td>
<td>1604 (628/2206)</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.36 (1.02/1.61)</td>
<td>0.6 (0.38/0.9)*</td>
</tr>
</tbody>
</table>
Table 2  Patients. Time-domain analysis and spectral components at NOX1 ($F_{\text{IO2}}$ 0.21), HOX ($F_{\text{IO2}}$ 1.0), and NOX2 ($F_{\text{IO2}}$ 0.21). All values are given as median and quartiles. Systolic arterial pressure (SAP); diastolic arterial pressure (DAP); SD of normal to normal RR intervals (SDNN); square root of the mean (RMSSD); total power (TP); high-frequency power (HF, 0.15–0.4 Hz); high-frequency power expressed in nu; low-frequency power (LF, 0.04–0.15 Hz); low-frequency power expressed in nu; LF/HF ratio (LF/HF); NOX1 vs NOX2 was tested NS for all parameters; *P < 0.05 vs NOX1; †P < 0.05 vs HOX.

<table>
<thead>
<tr>
<th>Patients</th>
<th>NOX1</th>
<th>HOX</th>
<th>NOX2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (min$^{-1}$)</td>
<td>56 (52/60)</td>
<td>51 (47/54)$^*$</td>
<td>55 (50/58)$^†$</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>98 (92/106)</td>
<td>98 (92/105)</td>
<td>95 (90/102)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>56 (49/61)</td>
<td>57 (51/59)</td>
<td>54 (51/59)</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>18.1 (14.4/24.3)</td>
<td>28.4 (19.4/37.8)$^*$</td>
<td>20.6 (15.2/24.9)$^†$</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>13.9 (8.8/24.3)</td>
<td>31.3 (22.0/46.6)$^*$</td>
<td>21.3 (10.1/29.8)$^†$</td>
</tr>
<tr>
<td>TP (ms$^2$)</td>
<td>255 (138/574)</td>
<td>717 (421/1216)$^*$</td>
<td>344 (169/563)$^†$</td>
</tr>
<tr>
<td>HF (nu)</td>
<td>38.1 (33.8/45.0)</td>
<td>56.2 (48.6/68.9)$^*$</td>
<td>43.9 (33.1/52.9)$^†$</td>
</tr>
<tr>
<td>HF (ms$^2$)</td>
<td>58.9 (31.8/192.6)</td>
<td>291.3 (207.2/562.3)$^*$</td>
<td>129.4 (24.2/237.2)$^†$</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>50.3 (47.1/56.7)</td>
<td>35.9 (24.6/43.9)$^*$</td>
<td>45.8 (42.5/57.8)$^†$</td>
</tr>
<tr>
<td>LF (ms$^2$)</td>
<td>80.7 (61.2/181.6)</td>
<td>161.9 (95.6/280.1)</td>
<td>133 (81.3/206.7)</td>
</tr>
<tr>
<td>LF:HF ratio</td>
<td>1.36 (1.02/1.60)</td>
<td>0.60 (0.38/0.90)$^*$</td>
<td>1.05 (0.81/1.75)$^†$</td>
</tr>
</tbody>
</table>

Fig 1  Box plot graph of HR, SD of normal-to-normal RR intervals (SDNN), and root mean square of successive differences (RMSSD) at time points NOX1 ($F_{\text{IO2}}$ 0.21), HOX ($F_{\text{IO2}}$ 1.0), and NOX2 ($F_{\text{IO2}}$ 0.21). NOX1 vs NOX2 for all parameters were NS.
changes in HRV parameters, others have included an HRV analysis into multivariable approaches (e.g. surgical stress index; Clinical Signs-Stimulus-Antinociception). Parameters identified to reflect sympathovagal imbalance during stress/pain in a clinical setting (i.e. HR, SDNN, TP, HFnu, LFnu, and the HF/LF ratio) are the same as those monitored in our study during normoxic ventilation and HV.

However, up to now, influences of different levels of $F_{IO2}$ on the autonomic nervous system have only been investigated in conscious volunteers. Considering the attention associated with HRV-based monitoring of stress and pain, the low number of studies mentioning the actual $F_{IO2}$ used is surprising. To our knowledge, previous studies have not considered oxygen as a confounding factor of HRV-based monitoring in general anaesthesia.

Time-domain analysis is a linear interpretation of fluctuations of successive RR intervals. SDNN and RMSSD values both reflect predominantly activity of the parasympathetic nervous system. Power spectral analysis of HRV is performed by an FFT. The HF power of the spectral band is thought to reflect mainly cardiac vagal activity. LF power contains components of both branches of the autonomic nervous system, but reflects basically sympathetic modulation when expressed in normalized units. The LF/HF ratio is commonly used to describe sympathovagal balance. General anaesthesia diminishes all components of the autonomic nervous system, leading to a general reduction in HRV, as shown in many studies (Table 1). Abating analgesia or rising stress levels are indicated by a decrease in the HF component and an increase in the LF:HF ratio, corresponding to a shift of the autonomic balance towards decreased vagal activity.

Our results show that the onset of HV leads to a significant increase in SDNN, RMSSD, TP, and HFnu in both groups, while LFnu and LF/HF decreased, indicating a shift in autonomic balance in terms of an increase in relative vagal influence on HRV during HV (Figs 1 and 2). Despite different baseline levels, changes in the normalized parameters (HFnu and
LFnu) reflect HV-induced alterations in a similar fashion in conscious volunteers and anaesthetized subjects (Fig 2), which were completely reversible within minutes after returning to room air levels. The HRV changes we observed during ventilation with pure oxygen uniformly indicate a change of the sympathetic-vagal balance towards a rise in vagal tone. This might be misinterpreted as a deepening of the level of anaesthesia or analgesia. As such, a reduction in inspiratory oxygen levels after induction of general anaesthesia might falsely indicate intraoperative stress and pain, and therefore result in administration of unnecessary doses of analgesics and anaesthetics.

Using our approach, we cannot identify the mechanisms causing the specific changes of HRV during ventilation with pure oxygen; however, several hypotheses can be deduced from volunteer data in the literature. It has been shown that hypoxia and the resulting low cellular O2 tension of the carotid body can affect sympathetic-vagal balance, resulting in a HR increase and a typical alteration of HRV (HR↑, RMSSD↓, HF↓).23,24 Changes in autonomic control in our model could be attributable to similar, but reciprocal effects of chemo-reflex activity induced by HV.25 Furthermore, stimulation of vascular baroreceptors might be responsible for the O2-induced changes in HRV. Hyperoxia reduces the basal release of NO, leading to endothelium-dependent peripheral vasoconstriction.26 The resulting increase in peripheral vascular resistance or central blood volume might activate carotid or cardiac baroreceptors inducing a reduction in HR and alteration in HRV.27 However, the majority of studies did not observe a significant increase in arterial pressure under HV.28 Presumably, the increase in vagal activity with a reduction in HR arises independently of the described vascular effects of HV, being triggered by different mechanisms.15

Although we described comparable alterations of HRV variables in spontaneous breathing volunteers and anaesthetized patients, a statistical comparison between both groups was not performed. Baseline characteristics of both groups were significantly different; differences in age, illness (healthy volunteers vs ASA I patients), sedation, and ventilation mode might influence study results. However, our data indicate that alterations in the level of inspiratory oxygen fractions similarly influence HRV monitoring in conscious volunteers and anaesthetized patients, although the two groups showed predictable sympathovagal changes during baseline measurements.

The patient medication used in our protocol was chosen to give haemodynamic stability; however, the combination of drugs used (propofol, remifentanil, midazolam for premedication) are known to decrease total spectral power, such as LF and HF power.22 Anaesthetics and analgesics were administered via an infusion syringe, so it is likely that narcotic and analgesic depth remained constant throughout the complete protocol. Considering our results, the influences of HV on the autonomic nervous system seem comparable for conscious volunteers and anaesthetized patients, despite the anaesthetic agents used. Therefore, we assume that changes of HRV in anaesthetized patients can be attributed to HV and not to the narcotics and analgesics used. Nevertheless, the missing of an additional electroencephalography-based monitoring to validate constant levels of narcosis is a limitation to this study. In addition, it is unclear whether the results observed in this study can be repeated if other anaesthetics, with other effects on the autonomic system, were used.

Both cohorts differed significantly in the ventilation mode. Volunteers breathed spontaneously with a pressure support of +2 mm Hg to compensate for resistance of the breathing system. In non-anaesthetized patients, the HF power was characterized by inspiratory cardiac acceleration (and expiratory cardiac deceleration), a phenomenon that sometimes be recognized in the clinical setting as respiratory sinus arrhythmia.12 Breathing frequency and tidal volume both have influences on the autonomic nervous system and particularly on HF power.12 29 However, these influences are of minor importance, and metronome-controlled breathing in conscious subjects is no longer recommended for HRV analysis.30 Therefore, we did not control the breathing frequency of volunteers.

Anaesthetized patients were ventilated mechanically with a pressure support of 16.5 (15/19) mm Hg and a PEEP of 5 mm Hg. The relationship of inspiratory cardiac acceleration and expiratory cardiac deceleration becomes inverted during positive pressure ventilation in anaesthetized subjects.31

Modern analysis tools simplify the application of complex mathematical algorithms to HRV analysis. In particular, multivariable approaches seem effective in complementing the perioperative monitoring of stress and analgesic depth. As perioperative FiO2 levels are sometimes difficult to control, oxygen has to be recognized as a possible confounding factor of HRV analysis during monitoring of analgesic depth. However, knowledge of this phenomenon can increase safety and efficacy of this diagnostic tool.

In conclusion, our findings indicate that ventilation with pure oxygen is associated with significant alterations of HRV in volunteers and anaesthetized, ventilated patients to a comparable extent. Therefore, HV profoundly changes HRV parameters that are crucial for monitoring perioperative stress and analgesic depth. To clarify these results and their clinical consequences, further studies are needed to identify the target of HV in sympathovagal balance and to test the effects of different levels of oxygen during changing levels of intraoperative stress and pain.

Declaration of interest
None declared.

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