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Haemodynamic effects of a 10-min treatment with a high inspired oxygen concentration in the emergency department: a prospective observational study

Renate Stolmeijer, Ellen van Ieperen, Heleen Lameijer, Paul van Beest, Jan Cornelis ter Maaten, Ewoud ter Avest

ABSTRACT

Previous studies show that prolonged exposure to a high inspired oxygen concentration (FiO₂) is associated with unfavourable haemodynamic effects. Until now, it is unknown if similar effects also occur after oxygen therapy of limited duration in the emergency department (ED).

**Objectives** To investigate the haemodynamic effects of a high FiO₂ administered for a limited duration of time in patients who receive preoxygenation for procedural sedation and analgesia (PSA) in the ED.

**Design, settings and participants** In a prospective cohort study, cardiac output (CO), stroke volume (SV) and systemic vascular resistance (SVR) were measured using the ClearSight non-invasive CO monitoring system in patients who received preoxygenation for PSA in the ED. Measurements were performed at baseline, after 5 min of preoxygenation via a non-rebreathing mask at 15 L/min and after 5 min of flush rate oxygen administration.

**Outcomes measures** The primary outcome was defined as the change in CO (L/min) from baseline after subsequent preoxygenation with 15 L/min and flush rate.

**Results** Sixty patients were included. Mean CO at baseline was 6.5 (6.0–6.9) L/min and decreased to 6.3 (5.8–6.8) L/min after 5 min of oxygen administration at a rate of 15 L/min, and to 6.2 (5.7–6.7) L/min after another 5 min at flush rate (p=0.037). Mean SV remained relatively constant during this period, whereas mean SVR increased markedly (from 781 (649–1067), to 1244 (936–1695) to 1337 (988–1738) dyn/s/cm⁵, p<0.001. Sixteen (27%) patients experienced a >10% decrease in CO.

**Conclusion** Exposure of patients to a high FiO₂ for 5–10 min results in a significant drop in CO in one out of four patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO₂ should be titrated based on deficit whenever this is feasible and high flow oxygen should not be given as a routine treatment.

BACKGROUND

Oxygen is frequently administered in the emergency department (ED) and in the prehospital setting by emergency medical services (EMS). It is used both to treat or prevent hypoxia in acutely ill patients and to preoxygenate (denitrogenate) patients for procedures such as rapid sequence induction (RSI) or procedural sedation and analgesia (PSA). Often, oxygen is administered at a flow of 15 L/min or even higher via a non-rebreathing mask (NRBM) in order to increase the end-expiratory oxygen fraction, and to denitrogenate the lungs, thereby increasing the save apnoea time for PSA or RSI.

Oxygen administration, however, may not be without risk. Previous studies show that prolonged exposure to a high inspired oxygen concentration (FiO₂) is associated with higher mortality rates in patients hospitalised with various conditions. This may be explained by a negative effect on cardiac output (CO), mediated by peripheral and coronary vasoconstriction, resulting from direct effects of oxygen on smooth muscle tone, and by the formation of reactive oxygen species that contribute to (vascular) oxidative stress.

As opposed to hospitalised patients, patients in the prehospital setting and in the...
ED normally receive high-flow oxygen only for a limited amount of time. Previous studies show nonetheless that this results in significant hyperoxaemia in many patients. The clinical relevance of this however is largely unknown, as until now the haemodynamic effects of exposure of patients in the ED to a high FiO₂ for only a limited duration of time have never been reported.

Therefore, in the present study, we aim to investigate the haemodynamic effects of a high FiO₂ administered for only a limited duration of time in patients who receive preoxygenation for PSA in the ED.

METHODS
Study setting and design
A single-centre prospective study was performed in a cohort of patients undergoing preoxygenation for PSA in the ED of the Medical Centre Leeuwarden (a teaching hospital in the Netherlands with an 27 000 ED visits yearly) between May 2018 to June 2019 (ClinicalTrials.gov (NCT03930979).

Patient and public involvement
No patients were involved in the design, recruitment or conduct of this study.

Study population
Patients were eligible for inclusion in the study if they were older than 18 years and were about to receive PSA to facilitate a procedure in ED. Patients were excluded if PSA was needed immediately according to the treating physician (no time to obtain informed consent and/or to perform necessary calibration of the system used to measure CO), if they were pregnant, if they presented with significant hypoxia (defined as an oxygen saturation<90% or a pO₂<8.0kPa), if they received oxygen suppletion preinclusion, if they had chronic obstructive pulmonary disease (COPD) GOLD I or II with hypercapnia (pCO₂>6.4kPa) or COPD GOLD III or IV, if they used bleomycine, if they presented with a cardiogenic shock (systolic blood pressure (SBP)<90 mm Hg) or if they needed PSA for electrocardioversion or pacing (for reasons of difficulty obtaining a reliable signal to measure CO). Patients could only be included once.

Study protocol
After informed consent was obtained from eligible patients, demographics, medical history and medication use, ECG at presentation and vital signs were obtained. Subsequently, the Clearsight non-invasive CO measurement system was attached to the patient and calibrated for continuous monitoring of blood pressure, CO, SV and SVR. Baseline values for these parameters were established as an average of three repeated measurements. Thereafter, oxygen was administered via a NRBM at a rate of 15L/min from a powered wall source, and measurements (CO, CI, SV and SVR) were repeated after 5 min. Thereafter, the rate of oxygen administration was increased to flush rate (30L/min) and after 5 min measurements were repeated. No other interventions than oxygen administration were performed during this period, and no medication or intravenous fluids were administered. Thereafter, care as usual was provided for the conduct of PSA. (figure 1)

Data collection
The following parameters were collected on a dedicated case report form for all included patients: patient demographics including (cardiac) medical history and use of alcohol, nicotine and medication, ECG abnormalities at presentation, ASA classification and indication for PSA, and vital parameters (heart rate (HR), non-invasively measured SBP, oxygen saturation (SpO₂), CO, SV and SVR).

Non-invasive CO measurements
CO was measured non-invasively using The ClearSight system (Edwards Lifesciences). The methodology of the ClearSight is based on Nexfin technology. This consists of pulsatile unloading of the finger arterial walls using an inflatable finger cuff with a built-in photoelectric plethysmograph that uses pressure to maintain a constant blood volume in the finger. ClearSight calculates beat-to-beat SV by dividing the area under the SBP curve (measured at 200 Hz) by the aortic input impedance (Zin). The value of Zin is determined from a three-element Windkessel model in which the nonlinear effect of MAP and the influence of the patient’s age, height, weight and gender on aortic mechanical properties are incorporated. Because the waveform at the finger shows a more undulatory appearance than the radial pressure waveform, the system transforms the finger waveform into a brachial waveform with a specific filter. ClearSight uses the integrated area under the pulsatile systolic waveform from the brachial pressure wave as an input to the model, which directly yields SV and produces CO by multiplying beat-to-beat SV by instantaneous HR. The Nexfin technology used in the ClearSight is validated in multiple studies. Measurements can reliably be performed in awake patients or during cardiac arrhythmias, but hypoperfusion of the finger (due to vasoconstriction) from shock, hypothermia, or the use of vasopressors may negatively impact signal reliability. All investigators received training given by a trainer of the manufacturer of Clearsight in how to operate the device before they were able to include patients for this study.
Outcomes
The primary outcome was defined as the absolute change in CO from baseline after, respectively, 5 min 15 L O₂/min and 5 min flush rate oxygenation via a NRBM.

Secondary outcomes were defined as:
- The absolute change in HR, SBP, SV and SVR from baseline after, respectively, 15 L O₂/min and flush rate oxygenation via NRBM.
- The number of subjects demonstrating a>10% change in CO* in response to oxygen administration (both 15 L/min and Flush rate).
* a 10% change in CO was deemed clinically relevant as this corresponds to the effect of a Vasalva manoeuvre and has been shown to be a detectable change using a (non-invasive) method based on pulse contour analysis.

Sample size
Based on previous literature, it was estimated that with a mean (SD) CO of 6.0 (0.8) L/min, 54 patients are necessary to allow the detection of a 10% decrease in CO as a result of procedural sedation with a power of 90% and a type I error rate of 5%. To allow for an attrition rate of 10%, we aimed to include 60 patients.

Statistical analysis
Continues variables are represented as mean (95% CI) or median (IQR) where appropriate. Repeated measures analysis of variance (ANOVA) with Greenhouse Geiser correction and post-hoc testing (Tukey Kramer) was used to analyse the difference in haemodynamic measurements at baseline and after preoxygenation with NRBM 15 L/min and flush rate oxygen. Comparisons between patients demonstrating a>10% decrease in CO and those who did not were made using Student’s t-test, Mann-Whitney U test, or Fisher’s exact test where appropriate. Mixed ANOVA was used to calculate oxygen dose-to-group interactions for these groups. Missing data were reported in the Results section according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. A p value<0.05 was considered statistically significant. All statistical analysis were done with SPSS V.23.0 for Apple statistical package (SPSS) and Vasarstats statistical software (Vassar College, Poughkeepsie, New York, USA).

RESULTS
Characteristics of study population
During the study period, a total of 91 patients were screened for eligibility. Thirty-one patients were excluded after screening due to various reasons (figure 2). Fourteen patients were excluded as no reliable signal for CO monitoring could be obtained. In 6/14 patients, this was due to identifiable patient factors (cold hands, tremor), whereas in the remaining 8 patients the system software failed.

Baseline characteristics of the study population are shown in table 1. Median (range) age of the included...
Non-invasively measured (haemodynamic) variables before and after preoxygenation with a high (FiO₂) for PSA in the ED (n=60)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline n=60</th>
<th>After 5min NRBM 15L/min n=60</th>
<th>After 5min flush rate oxygen n=59</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SpO₂ (%)</td>
<td>97 (97–98)</td>
<td>100 (100–100)</td>
<td>100 (100–100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.5 (6.0–6.9)</td>
<td>6.3 (5.8–6.8)</td>
<td>6.2 (5.7–6.7)</td>
<td>0.037</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>84 (77–89)</td>
<td>83 (75–89)</td>
<td>83 (75–90)</td>
<td>0.69</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>133 (123–151)</td>
<td>138 (125–164)</td>
<td>144 (132–162)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>78 (74–81)</td>
<td>76 (72–80)</td>
<td>76 (72–80)</td>
<td>0.064</td>
</tr>
<tr>
<td>SVR (dyn/s/cm⁻⁵)</td>
<td>781 (649–1067)</td>
<td>1244 (936–1695)</td>
<td>1337 (988–1738)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (95% CI) (CO, SV and HR) or median (IQR) (SpO₂, SBP, and SVR). Represented are P values for repeated measures ANOVA omnibus test.

*Denotes p<0.05 compared with baseline.
†Denotes p<0.05 compared with 15L/min.

CO, cardiac output; HR, heart rate; SBP, systolic blood pressure; SpO₂, oxygen saturation; SV, stroke volume; SVR, systemic vascular resistance.

DISCUSSION

In this study, we found that a short 10min exposure to a high FiO₂ is associated with a significant drop in mean CO. This stresses the importance of titrated oxygen administration in the ED and in prehospital care whenever this is feasible: clinicians should carefully balance the risk of hyperoxia against the risk of hypoxia when oxygen is administered, especially in patients with already compromised circulation.

The observed drop in mean CO in this study is in line with previous literature which shows that prolonged exposure to a high FiO₂ has a negative effect on CO, and (ultimately) on morbidity and mortality. The proposed pathophysiological mechanism mediating the relation between hyperoxia and CO is coronary vasoconstriction, resulting in a decrease in SV. The latter is in line with our finding that SV decreases with>10% in subjects who demonstrated >10% decrease in their CO, whereas HR remained unchanged. In these patients, we also observed a marked increase in SVR (afterload), which may have contributed to the reduction in CO. Although this may be the result of an increased sympathetic tone due to pain and/or stress, we did not observe a concomitant increase in HR. Alternatively, free oxygen radicals have been shown to modulate the tone of vascular smooth muscle both directly and indirectly by affecting the production or biological activity of vasoactive mediators. Furthermore, free radicals have the potential to damage (mitochondrial) DNA, lipids and proteins, and may cause irreversible damage. However, we can only speculate about the exact aetiology and the relative contribution of the above mentioned processes, as we did not measure free oxygen radicals and/or oxidative stress in our study.

One in four patients demonstrated >10% drop in CO. Changes of this magnitude are likely clinically relevant in patient who already have a reduced CO, as previous studies have demonstrated that even in healthy volunteers,
a sudden 10% drop in CO (comparable to the effect of a Valsalva manoeuvre) already causes symptoms, whereas a 20% decrease can result in syncope.\textsuperscript{32} 33 Besides, any drop in CO may be undesirable in critically ill patients who are also more prone to develop dysrhythmia’s such as atrial fibrillation, further compromising CO.\textsuperscript{33} It is worth mentioning, however, that not only the magnitude of the drop in CO, but also the duration are relevant for the ultimate effect. As medication for PSA was administered per protocol after the second period of preoxygenation, we could not monitor (speed of) recovery of CO in our current study, and therefore future studies should focus on reversibility of the observed changes.

As one in four patients demonstrates a>10% drop in CO, it seems reasonable to titrate oxygen administration on SpO\textsubscript{2} in patients, especially in patients with an already compromised circulation, even when oxygen is only administered for a short duration of time, as in the prehospital setting or in ED. This can be achieved relatively easy when oxygen is administered for the purpose of treating or preventing hypoxia. But it is more difficult to achieve when oxygen is administered for the purpose

### Table 3  Baseline patient characteristics stratified by the effect of preoxygenation with a high (Fi\textsubscript{O\textsubscript{2}}) for PSA in the ED (n=60)

<table>
<thead>
<tr>
<th>Demographics and history</th>
<th>Patients with a&gt;10% decrease in CO (n=16)</th>
<th>Other patients (n=44)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n)</td>
<td>5 (31%)</td>
<td>25 (57%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.5 (45.3–77.0)</td>
<td>60 (36.3–74.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>ASA III classification (n)</td>
<td>2 (13%)</td>
<td>11 (25%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Use of alcohol&lt;24 hours (n)</td>
<td>5 (31%)</td>
<td>12 (27%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Use of nicotine&lt;24 hours (n)</td>
<td>2 (13%)</td>
<td>13 (30%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Any cardiovascular medication use (n)</td>
<td>4 (25%)</td>
<td>12 (27%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Physical exam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO\textsubscript{2} (%)</td>
<td>97 (96–99)</td>
<td>97 (97–98)</td>
<td>0.98</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>77 (70–82)</td>
<td>78 (74–82)</td>
<td>0.72</td>
</tr>
<tr>
<td>SBP</td>
<td>138 (124–160)</td>
<td>133 (123–149)</td>
<td>0.63</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.6 (5.6–7.5)</td>
<td>6.4 (5.9–7.0)</td>
<td>0.73</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>86 (73–99)</td>
<td>83 (76–90)</td>
<td>0.59</td>
</tr>
<tr>
<td>SVR (dyn/s/cm\textsuperscript{5})</td>
<td>735 (637–1142)</td>
<td>846 (649–1042)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Values are mean (95% CI) (CO, SV and HR) or median (IQR) (SpO\textsubscript{2}, SBP, and SVR).

CO, cardiac output; HR, heart rate; SBP, systolic blood pressure; SpO\textsubscript{2}, oxygen saturation; SV, stroke volume; SVR, systemic vascular resistance.

Figure 3  Boxplots of stroke volume (SV) and systemic vascular resistance (SVR) as a function of oxygen administration in the emergency department (ED), stratified by response in cardiac output (CO) (>10% decrease or<10% decrease). Represented are median, IQR and ranges (with outliers). Grey boxes represent subjects with a>10% decrease in CO (n=16). White boxes represent subjects with a<10% decrease in CO during the course of the preoxygenation (n=44). Times on the x-axis are baseline, after 5 min and after 10.
of denitrogenation preceding PSA or RSI and thereby increasing save apnoeic time. In those instances, the risk of short duration hyperoxia should be balanced against the risk of the occurrence of hypoxic episodes when preoxy-
genation with a high FiO₂ is not provided. Although negative effects on CO are undesirable in patients undergoing PSA or RSI (who receive drugs affecting vascular tone and cardiac contractility), the risk of hypoxic episodes probably outweighs this risk in these patients and therefore high FiO₂ should still be given during preoxygenation. Early use of vasopressors to maintain perfusion pressures in the presence of a reduced CO can be considered under these circumstances.

In other patients, one should ideally aim for a high SpO₂ but at the same time a normal PaO₂ (9.5–13.5kPa). As continuous blood gas analysis is normally not feasible or appropriate in the prehospital or ED setting, future studies should investigate if there is a role for non-invasive tools to quantify (and prevent) hyperoxia, for example, by estimating the oxygen reserve index.⁶⁴ ⁶⁵ In the meantime, implementation of checklists, wherein the oxygen requirement and administration are discussed at handover from EMS in ED may increase awareness of the risks associated with hyperoxia and prevent administration of oxygen with a higher than necessary FiO₂.

**Limitations**

Our study has several limitations, inherent to the study design. First, although we observed lower CO and higher SVR values in patients undergoing PSA or RSI (who receive drugs affecting vascular tone and cardiac contractility), the risk of hypoxic episodes probably outweighs this risk in these patients and therefore high FiO₂ should still be given during preoxygenation. Early use of vasopressors to maintain perfusion pressures in the presence of a reduced CO can be considered under these circumstances.

<table>
<thead>
<tr>
<th>CO (L/min)</th>
<th>Other patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.6 (5.6–7.5)</td>
<td>6.4 (5.9–7.0)</td>
</tr>
<tr>
<td>Oxygen 15 L/min</td>
<td>6.2 (5.2–7.2)</td>
<td>6.3 (5.7–6.9)</td>
</tr>
<tr>
<td>Oxygen flush rate</td>
<td>5.4 (4.6–6.2)</td>
<td>6.5 (5.9–7.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SV (mL)</th>
<th>Other patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>86 (73–99)</td>
<td>83 (76–90)</td>
</tr>
<tr>
<td>Oxygen 15 L/min</td>
<td>80 (66–95)</td>
<td>84 (76–92)</td>
</tr>
<tr>
<td>Oxygen flush rate</td>
<td>76 (61–92)</td>
<td>86 (77–94)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SVR dyn/s/cm⁻⁵</th>
<th>Other patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>735 (637–1142)</td>
<td>846 (649–1042)</td>
</tr>
<tr>
<td>Oxygen 15 L/min</td>
<td>1248 (950–1954)</td>
<td>1244 (910–1658)</td>
</tr>
<tr>
<td>Oxygen flush rate</td>
<td>1482 (1129–2214)</td>
<td>1304 (982–1672)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HR (beats/min)</th>
<th>Other patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>77 (70–82)</td>
<td>78 (74–82)</td>
</tr>
<tr>
<td>Oxygen 15 L/min</td>
<td>75 (68–81)</td>
<td>77 (72–81)</td>
</tr>
<tr>
<td>Oxygen flush rate</td>
<td>75 (68–81)</td>
<td>77 (72–82)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>Other patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>138 (124–160)</td>
<td>133 (123–150)</td>
</tr>
<tr>
<td>Oxygen 15 L/min</td>
<td>147 (117–164)</td>
<td>137 (129–164)</td>
</tr>
<tr>
<td>Oxygen flush rate</td>
<td>148 (127–165)</td>
<td>144 (132–158)</td>
</tr>
</tbody>
</table>

Values are depicted as mean (95% CI) (CO, SV, HR) or median (IQR) (SBP, SVR). Represented P value are for the oxygen dose-to-group interaction in mixed ANOVA. T=5; value after 5 min of oxygen administration by NRBM at a rate of 15 L/min; T=10; value after an additional 5 min of oxygen administration by NRBM at flush rate.

CO, cardiac output; HR, heart rate; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance.
abuse of nicotine and/or alcohol can lead to cardiovascular impairment, for example, by decreasing coronary blood flow, this could also be a confounding factor. In addition, 25% of the patients included used cardiovascular medication that could have interacted with the body’s response to a drop in SV and CO from hyperoxia. However, this probably reflects the normal target population in the ED. Finally, generalisability of our results is limited due to the selection of our study population: none of our patients had significant cardiovascular comorbidity. Therefore, no conclusions can be drawn regarding how hyperoxia would affect patients with heart failure, especially when they already have a compromised CO.

CONCLUSION

Exposure of patients to a high FiO₂ for 5–10 min results in a significant drop in CO in one out of four patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO₂ should be titrated based on deficit and high flow oxygen should not be given as a routine treatment.

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Contributors RS and EJA conceived the study. EVA, RS and EJA acquired and interpreted the data. RS and EJA drafted the manuscript. NL, PB6 and JCCS revised the manuscript critically and gave final approval to submission of the manuscript. RS is the guarantor for the overall content.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by RTP Leeuwarden (protocol number nWMO 270). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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