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Haemodynamic effects of a 10-minute treatment with a high inspired oxygen concentration in the Emergency Department: a prospective observational study.

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Abstract

Previous studies have shown that prolonged exposure to a high inspired oxygen concentration (FiO_2) is associated with unfavourable hemodynamic 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 hemodynamic effects of a high FiO_2 administered for a limited duration of time in patients who are preoxygenated for 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 were pre-oxygenated for PSA in the ED. Measurements were performed at baseline, after 5 minutes of preoxygenation via a non-rebreathing mask at 15/L min and after 5-minutes 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 15L/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 minutes of oxygen administration at a rate of 15L/min, and to 6.2 (5.7-6.70) L/min after another 5 minutes at flush rate (p=0.037). Mean SV remained relatively constant during this period, whereas mean SVR increased markedly (from781 [649-1067], to 1244 [936-1695] to 1337 [988-1738] dyn/sec/cm^{-5} ,p<0.001. Sixteen (27%) patients experienced a >10% decrease in CO.

Conclusion. Exposure of patients to a high FiO_2 for 5-10 minutes results in a significant drop in CO in 1 out of 4 patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO_2 should be titrated based on deficit and high flow oxygen should not be given as a routine treatment.

Key words: hyperoxia, inspired oxygen concentration, hyperoxemia, emergency department, oxygen therapy, procedural sedation and analgesia.

Strengths and limitations of this study:

- This is the first prospective study to investigate the hemodynamic effects of treatment of patients in the ED with a high FiO_2 for a limited duration of time (10 minutes).
- Non-invasive monitoring of cardiac output, stroke volume and systemic vascular resistance was used before- and during pre-oxygenation to quantify hemodynamic effects.
- Findings are highly relevant to both prehospital- and ED care providers, who often treat patients for a relatively limited duration of time with high-flow oxygen.
- Generalizability of the findings is limited due to relative homogeneity of the subjects included in the study. No patients with known heart failure were included.

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 hypoxaemia in acutely ill patients and to pre-oxygenate (de-nitrogenate) patients for procedures such as rapid sequence induction (RSI) or procedural sedation and analgesia (PSA), (1-3). Often, oxygen is administered at a flow of 15 L/min or even higher (4) via a non-rebreathing mask (NRBM) in order to increase the end-expiratory oxygen fraction, and to de-nitrogenate the lungs, thereby increasing the save apnea time for PSA or RSI (5).

Oxygen administration, however, may not be without risk: Previous studies have shown that prolonged exposure to a high inspired oxygen concentration (FiO_2)is associated with higher mortality rate in patients hospitalised with various conditions (6-10). This may be explained by a negative effect on cardiac output mediated by peripheral- and coronary vasoconstriction resulting from direct effects of oxygen on smooth muscle tone (11,12), and by the formation of reactive oxygen species that contribute to (vascular) oxidative stress (13-16).

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 have nonetheless shown that this results in significant hyperoxemia in many patients (17). The clinical relevance of this however, is largely unknown, as until now, the hemodynamic effects of exposure of patients in the ED to a high FiO_2 for only a limited duration of time have never been reported.

Therefore, in the present study, we aim to investigate the hemodynamic effects of a high FiO_2 administered for only a limited duration of time in patients who are preoxygenated for PSA in the ED.

Methods

Study Setting and Design

A single centre prospective study was performed in a cohort of patients undergoing pre-oxygenation 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). Ethical approval was sought and obtained from the ethical committee of the RTPO Leeuwarden (protocol number nWMO 270).

Patient and public involvement

No patients were involved.

Study population

Patients were eligible for inclusion in the study if they were older than 18 years and were due 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< 8.0 kPa), if they received oxygen suppletion pre-inclusion, if they had chronic obstructive pulmonary disease (COPD) GOLD I or II with hypercapnia (pCO2 >6.4 kPa) or COPD GOLD III or IV, if they used bleomycine, if they presented with a cardiogenic shock (SBP<90 mmHg) 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 cardiac output 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 minutes. No other interventions than oxygen administration were performed during this period, and no medication was administered. Thereafter, the rate of oxygen administration was increased to flush rate (30L/min), and after 5 minutes measurements were repeated. 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 (CRF) for all included patients: patient demographics including (cardiac) medical history and alcohol- nicotine- and medication use, ECG abnormalities at presentation, ASA classification and indication for PSA, and vital parameters (heart rate (HR), non-invasively measured systolic blood pressure (SBP), oxygen saturation (SpO2), CO, SV and SVR).

Non-invasive cardiac output measurements

CO was measured non-invasively using The ClearSight® system (Edwards Lifesciences). The methodology of the ClearSight® is based on Nexfin technology 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 wave- form, 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 heart rate. The Nexfin technology used in the ClearSight® is validated in multiple studies (18,19). All investigators received a 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 minutes 15L O2/min and 5 minutes flush rate oxygenation via a NRBM.

Secondary outcomes were defined as:

- The absolute change in HR, SBP, SV and SVR from baseline after respectively 15L O2/min and flush rate oxygenation via NRBM.
- The number of subjects demonstrating a >10% change in CO* in response to oxygen administration (both 15L/min and Flush rate).

* a 10% change in CO was deemed clinically relevant as this corresponds to the effect of a Vasalva manoeuvre (20) and has been shown to be a detectable change using a (non-invasive) method based on pulse contour analysis (21).

Sample size

Based on previous literature (22) it was estimated that with a mean (SD) CO of 6.0 (0.8) L/min, 54 patients would be needed 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 ANOVA with Greenhouse Geiser correction and post-hoc testing (Tukey Kramer) was used to analyze the difference in hemodynamic measurements at baseline and after preoxygenation with NRBM 15L/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 STROBE guideline. A *p*-value <0.05 was considered statistically significant. All statistical analysis were done with SPSS 23.0 for Apple statistical package (SPSS Inc, Chicago, Illinois, USA) 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 for various reasons (figure 2). Fourteen patients were excluded as no reliable signal for cardiac output monitoring could be obtained with the Clearsight® system. 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 subjects was 62 (18-92) years, with an equal gender distribution. A total of 16 patients (26,7%) used one or more cardiovascular drugs on a daily basis. There were no patients with pre-existent heart failure or a pacemaker in situ. Other patient characteristics, pre-hospital treatments, and vital signs at presentation are represented in table 1.

Table 1. Baseline characteristics of patients pre-oxygenated with a high (FiO_2) for PSA in the ED (n=60).

Age in years, median (range)	62 (18-92)
Gender, n (%) Female Male	 30 (50) 30 (50)
Cardiovascular Medication use, n (%) Beta blocker ACE inhibitor or ATII receptor antagonist Spironolactone Calcium channel blockers	 10 (16,7) 12 (20) 1 (1,7) 0 (0)
Known heart failure, n (%)	0 (0)
Pacemaker, n (%)	0 (0)
Abnormality on ECG, n (%)*	3 (5)
ASA classification, n (%) I II III IV	 21 (35) 26 (43,4) 13 (21,7) 0 (0)
Use of alcohol < 24 hours, n (%)	17 (29,8)

Use of nicotine < 24 hours, n (%)	15 (26,3)
Indication PSA, n (%)	
Reduction dislocation	34 (56,7)
Reduction fracture	8 (13,3)
Incision and drainage abscess	17 (28,3)
Chest tube placement**	1 (1,7)

Legend table 1*. ACE, Angiotensin converting enzyme; ATII, angiotensin type 2; ECG, electrocardiogram; ASA, American Society of Anaesthesiologists; PSA, procedural sedation and analgesia. * atrial fibrillation. ** Indication for the chest tube was a large pneumothorax, without signs of hypoxia, or respiratory- or hemodynamic compromise.*

Main results

Oxygen administration at a rate of 15L/min during pre-oxygenation resulted in an increase in median oxygen saturation (from 97% to 100%), p< 0.0001. 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 minutes of oxygen administration by NRB at a rate of 15L/min, and to 6.2 (5.7-6.7) L/min after a further 5 minutes of flush rate oxygen suppletion (p=0.037). Mean SV remained relatively constant, whereas mean SVR increased markedly (table 2).

Table 2. Non-invasively measured (haemodynamic) variables before- and after pre-oxygenation with a high (FiO_2) for PSA in the ED (n=60).

	Baseline N = 60	**After 5 minutes NRBM 15L/min N = 60**	**After 5 minutes flush rate oxygen N = 59**	***p***
SpO2 (%)	97 (97 – 98)	100 (100 – 100)*	100 (100 – 100)*	<0.001
CO (L/min)	6.5 (6.0 - 6.9)	6.3 (5.8 - 6.8)	6.2 (5.7 - 6.7)*	0.037
SV (ml)	84 (77 – 89)	83 (75 – 89)	83 (75 – 90)	0.69
SBP (mmHg)	133 (123-151)	138 (125 – 164)*	144 (132 – 162)* ≠	<0.001
HR (bpm)	78 (74 – 81)	76 (72 – 80)	76 (72 – 80)	0.064
SVR ($dyn/sec/cm^{-5}$)	781 (649-1067)	1244 (936 – 1695)*	1337 (988 – 1738)* ≠	<0.001

Legend table 2*: Values are mean [95%CI] (CO, SV and HR) or median [IQR] (SpO_2, SBP, and SVR). Represented are P values for repeated measures ANOVA omnibus test. * denotes p<0.05 in post-hoc testing compared to baseline; ≠ denotes p<0.05 compared to 15L/min. CO, cardiac output;; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SpO2, oxygen saturation; SVR, systemic vascular resistance.*

A considerable proportion of the subjects (n=16, 27%) demonstrated a >10% decrease in CO in response to preoxygenation: In about a third of the subjects (n= 5) this was already apparent after the first 5 minutes of preoxygenation with a NRBM at a rate of 15L/min. Baseline patient characteristics were not significantly related to the occurrence of a > 10% decrease in CO (table 3).

Table 3. Patient characteristics stratified by the effect of pre-oxygenation with a high (FiO_2) for PSA in the ED (n=60).

	Patients with a >10 % decrease in CO (n = 16)	**Other patients (n = 44)**	***p***
Demographics and history			
Male (n)	5 (31%)	25 (57%)	0.14
Age (years)	67.5 (45.3 – 77.0)	60 (36.3 – 74.5)	0.45
ASA III classification (n)	2 (13%)	11 (25%)	0.48
Use of alcohol <24 hours (n)	5 (31%)	12 (27%)	0.76
Use of nicotine <24 hours (n)	2 (13%)	13 (30%)	0.31
Any cardiovascular medication use (n))	4 (25%)	12 (27%)	1.00
Physical exam			
SpO2 (%)	97 (96-99)	97 (97-98)	0.98
HR (bpm)	77 (70-82)	78 (74-82)	0.72
SBP	138 (124-160)	133 (123-149)	0.63
CO (L/min)	6.6 (5.6 – 7.5)	6.4 (5.9 – 7.0)	0.73
SV (ml)	86 (73 – 99)	83 (76 – 90)	0.59
SVR (dyn/sec/cm^{-5})	735 (637 – 1142)	846 (649 – 1042)	0.82

***Legend table 3**: Values are mean [95% CI] (CO, SV and HR) or median [IQR] (SpO_2, SBP, and SVR). CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SpO2, oxygen saturation; SVR, systemic vascular resistance.*

Patients who demonstrated a >10% decrease in CO had a significantly greater increase in SVR (from 735 dyn/sec/cm^{-5} at baseline to 1248 dyn/sec/cm^{-5} after 15L/min to 1482 dyn/sec/cm^{-5} after flush rate oxygen suppletion) compared to other patients (846, 1244 and 1304 dyn/sec/cm^{-5} respectively), p=0.025), figure 3 and table 4. Likewise, they demonstrated a significant decrease in SV (from 86 ml

to 80 ml and 76 ml respectively), whereas SV did not decrease in patient who did not demonstrate a clinically relevant decrease in CO (83, 84 and 86 ml respectively, p<0.001).

Table 4. Haemodynamic parameters as a function of oxygen administration, stratified by the response in CO (>10% decrease or < 10% decrease).

	>10% decrease in CO N = 16	Other patients N = 44	p
CO (L/min)			<0.001
Baseline	6.6 (5.6 – 7,5)	6.4 (5.9 – 7.0)	
Oxygen 15L/min	6.2 (5.2 – 7.2)	6.3 (5.7 – 6.9)	
Oxygen Flush rate	5.4 (4.6 – 6.2)	6.5 (5.9 – 7.1)	
SV (ml)			<0.001
Baseline	86 (73 – 99.)	83 (76 – 90)	
Oxygen 15L/min	80 (66 – 95)	84 (76 – 92)	
Oxygen Flush rate	76 (61 – 92)	86 (77 – 94)	
SVR dyn/sec/cm^{-5})			0.025
Baseline	735 (637 – 1142)	846 (649 – 1042)	
Oxygen 15L/min	1248 (950 – 1954)	1244 (910 – 1658)	
Oxygen Flush rate	1482 (1129 – 2214)	1304 (982 – 1672)	
HR (bpm)			0.85
Baseline	77 (70– 82)	78 (74 – 82)	
Oxygen 15L/min	75 (68 – 81)	77 (72 – 81)	
Oxygen Flush rate	75 (68 – 81)	77 (72 – 82)	
SBP (mmHg)			0.26
Baseline	138 (124 – 160)	133 (123 – 150)	
Oxygen 15L/min	147 (117 – 164)	137 (129 – 164)	
Oxygen Flush rate	148 (127 – 165)	144 (132 – 158)	

Legend table 4*. 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 minutes of oxygen administration by NRBM at a rate of 15L/min; T=10; value after an additional 5 minutes of oxygen administration by NRBM at flush rate. CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SVR, systemic vascular resistance.*

Discussion

In this study, we found that a short 10-minute exposure to a high FiO_2 is associated with a significant drop in mean CO. This stresses the importance of titrated oxygen administration in the ED and in prehospital care.

The observed drop in mean CO in this study is in line with previous literature, wherein it has been shown that prolonged exposure to a high FiO2 has a negative effect on CO (13-16), and (ultimately) on morbidity and mortality (23). The proposed pathophysiological mechanism mediating the relation between hyperoxia and CO is coronary vasoconstriction (13-16), resulting in a decrease in SV. The latter is in line with our finding that SV decreased with >10% in subjects who demonstrated a >10% decrease in their CO, whereas HR remained unchanged. In these patients we also observed a marked increase in SVR (afterload), which may also 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 (24,25). Furthermore, free radicals have the potential to damage (mitochondrial) DNA, lipids and proteins, and may cause irreversible damage (23,26-28). However, we can only speculate about the exact aetiology and the relative contribution of the above mentioned processes however, as we did not measure free oxygen radicals and/or oxidative stress in our study.

One in four patients demonstrated a >10% drop in CO. Changes of this magnitude might be of relevance to patients who have an already decreased baseline CO. It is worth mentioning however, that not only the magnitude- but also the duration of the drop are relevant for the ultimate effect. As per protocol medication for PSA was administered after the second period of pre-oxygenation, 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 1 in 4 patients demonstrates a >10% drop in CO, it seems reasonable to titrate oxygen administration on SpO2 in all patients, especially in patients with an already compromised circulation, and 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 easily 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 of denitrogenation preceding PSA or RSI. In those instances, the risk of short duration hyperoxia should be balanced against the risk of the occurrence of hypoxic episodes when pre-oxygenation with a high FiO_2 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.

Ideally, one should aim for a high SpO_2 but at the same time avoid a (too) high PaO_2. 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 (29,30).

Limitations

Our study has several limitations, inherent to the study design. First, although we observed lower CO and higher SVR values with flush-rate oxygen administration than with 15L/min, we cannot exclude that this is a time-dependent rather than a dose dependent effect, as flush rate oxygen was administered immediately after 5 minutes of 15L/min were administered. Second, we did not perform arterial blood gas analysis after pre-oxygenation to establish the presence (and the amount of) hyperoxia. However, the presence of hyperoxemia is highly likely, as SpO_2 increased to 100% in all participating subjects, and previous studies with comparable oxygen administration strategies have demonstrated the presence of both a high expired oxygen fraction (3, 31) and a high PaO2. In addition, 14 patients had to be excluded as no reliable Clearsight® signal could be obtained, sometimes for unknown reasons, which could have contributed to selection bias. Also, at least a quarter of the patients used alcohol (n=15) or nicotine (n=17) in the last 24 hours. Since chronic 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 (32,33). Finally, generalizability of our results is limited due to

the selection of our study population: None of our patients had significant cardiovascular co-morbidity. 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 FiO_2 for 5-10 minutes results in a significant drop in CO in 1 out of 4 patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO_2 should be titrated based on deficit and high flow oxygen should not be given as a routine treatment.

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Declarations

Competing interests: The authors declare that they have no competing interests.

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Ethics approval and consent to participate: Regionale toetsingscommissie patiëntgebonden onderzoek (RTPO) Leeuwarden, protocol number nWMO 270. Written consent to participate was obtained.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions: All authors fulfilled the ICMJE criteria for authorship. RS and EtA conceived the study. EvI, RS and EtA acquired and interpreted the data. RS and EtA drafted the manuscript. All authors revised the manuscript critically and gave final approval to submission of the manuscript.

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Figures:

Figure 1. Study Overview

Legend Figure 1: Arrows indicate moments of measurement of haemodynamic parameters.

Figure 2. Patient inclusion

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 CO (>10% decrease or < 10% decrease).

Legend figure 3*: 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 pre-oxygenation (n=44). Times on the x-axis are baseline, after 5 minutes and after 10.*

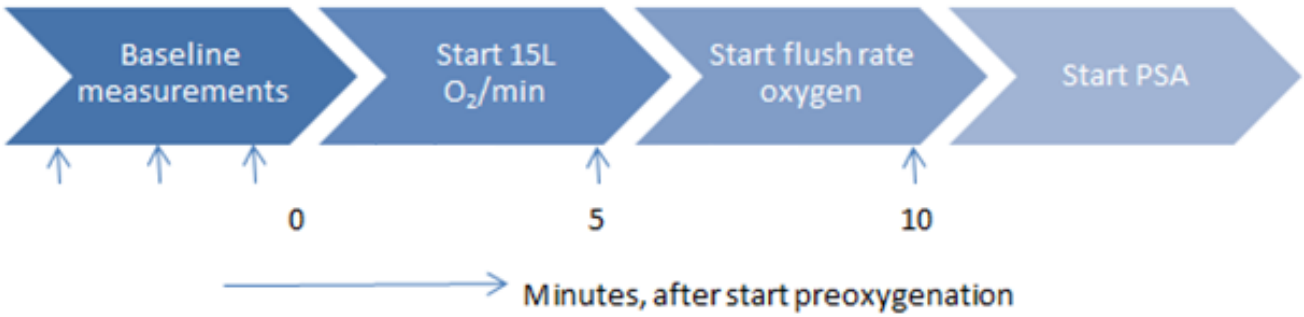
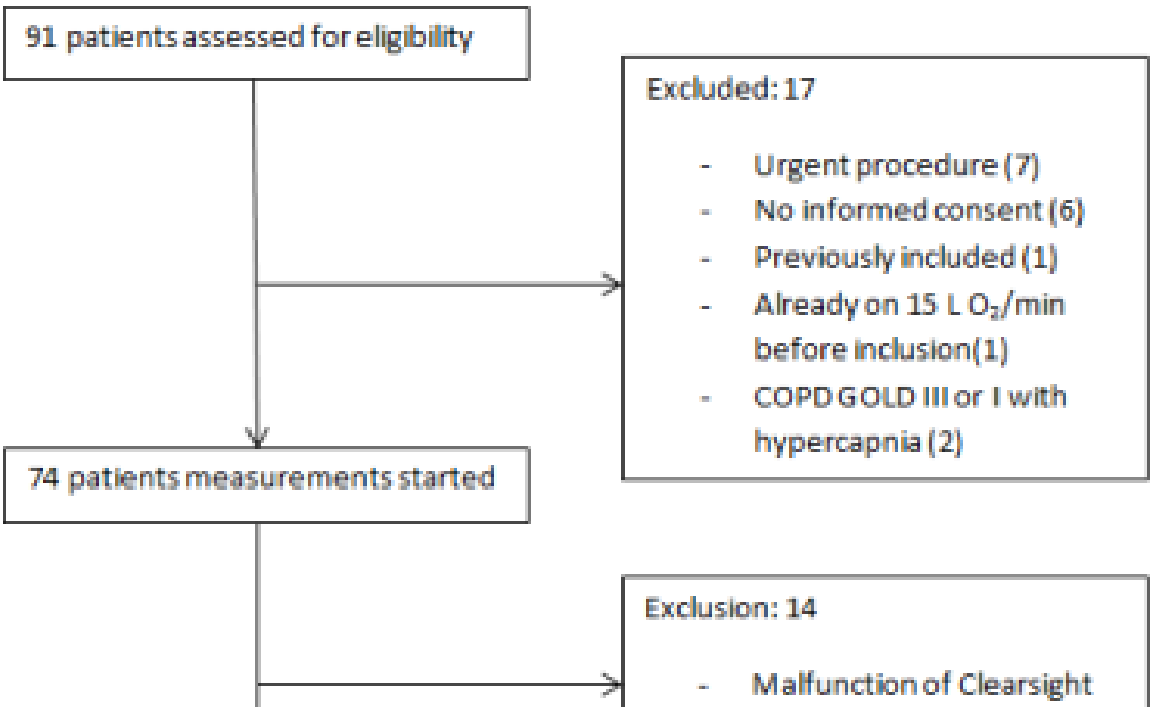
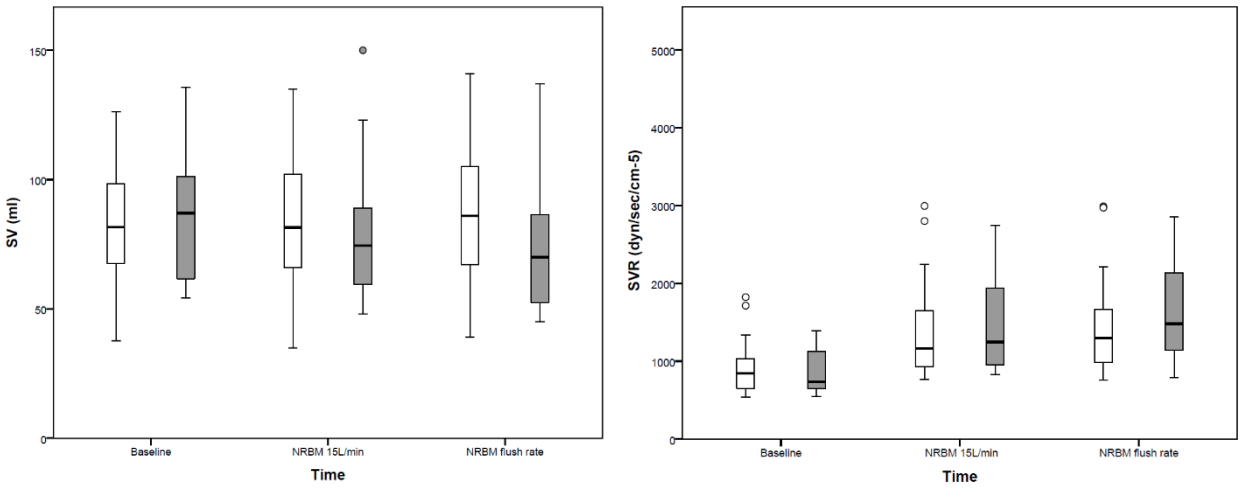


Figure 2. Patient inclusion





STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7	
Bias	9	Describe any efforts to address potential sources of bias	6-7	
Study size	10	Explain how the study size was arrived at	7	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Haemodynamic effects of a 10-minute treatment with a high inspired oxygen concentration in the Emergency Department: a prospective observational study.

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Haemodynamic effects of a 10-minute treatment with a high inspired oxygen concentration in the Emergency Department: a prospective observational study.

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Short title: The effects of short term hyperoxia on cardiac output in the ED.

Word count: 3786

Abstract

Previous studies show that prolonged exposure to a high inspired oxygen concentration (FiO_2) is associated with unfavourable hemodynamic 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 hemodynamic effects of a high FiO_2 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 minutes of preoxygenation via a non-rebreathing mask at 15/L min and after 5-minutes 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 15L/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 minutes of oxygen administration at a rate of 15L/min, and to 6.2 (5.7-6.70) L/min after another 5 minutes 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/sec/cm^{-5} ,p<0.001. Sixteen (27%) patients experienced a >10% decrease in CO.

Conclusion. Exposure of patients to a high FiO_2 for 5-10 minutes results in a significant drop in CO in 1 out of 4 patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO_2 should be titrated based on deficit whenever this is feasible and high flow oxygen should not be given as a routine treatment.

Key words: hyperoxia, inspired oxygen concentration, hyperoxemia, emergency department, oxygen therapy, procedural sedation and analgesia.

Strengths and limitations of this study:

- This prospective study investigates the hemodynamic effects of treatment of patients in the emergency department with a high inspired oxygen concentration for a limited duration of time (10 minutes).
- Non-invasive monitoring of cardiac output, stroke volume and systemic vascular resistance was used before- and during pre-oxygenation to quantify hemodynamic effects.
- Generalizability this study is limited due to relative homogeneity of the subjects included in the study.

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 pre-oxygenate (de-nitrogenate) patients for procedures such as rapid sequence induction (RSI) or procedural sedation and analgesia (PSA), (1-3). Often, oxygen is administered at a flow of 15 L/min or even higher (4) via a non-rebreathing mask (NRBM) in order to increase the end-expiratory oxygen fraction, and to de-nitrogenate the lungs, thereby increasing the save apnea time for PSA or RSI (5).

Oxygen administration however, may not be without risk. Previous studies show that prolonged exposure to a high inspired oxygen concentration (FiO_2) is associated with higher mortality rates in patients hospitalised with various conditions (6-10). 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 (11,12), and by the formation of reactive oxygen species13 that contribute to (vascular) oxidative stress (13-16).

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 hyperoxemia in many patients (17). The clinical relevance of this however is largely unknown, as until now the hemodynamic effects of exposure of patients in the ED to a high FiO_2 for only a limited duration of time have never been reported.

Therefore, in the present study, we aim to investigate the hemodynamic effects of a high FiO_2 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 pre-oxygenation 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). Ethical approval was sought and obtained from the ethical committee of the RTPO Leeuwarden (protocol number nWMO 270).

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< 8.0 kPa), if they received oxygen suppletion pre-inclusion, if they had chronic obstructive pulmonary disease (COPD) GOLD I or II with hypercapnia (pCO2 >6.4 kPa) or COPD GOLD III or IV, if they used bleomycine, if they presented with a cardiogenic shock (SBP<90 mmHg) 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 cardiac output 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 minutes. Thereafter, the rate of oxygen administration was increased to flush rate (30L/min) and after 5 minutes 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 (CRF) for all included patients: patient demographics including (cardiac) medical history and alcohol- nicotine- and medication use, ECG abnormalities at presentation, ASA classification and indication for PSA, and vital parameters (heart rate (HR), non-invasively measured systolic blood pressure (SBP), oxygen saturation (SpO2), CO, SV and SVR).

Non-invasive cardiac output 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 heart rate. The Nexfin technology used in the ClearSight® is validated in multiple studies (18,19). 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 minutes 15L O2/min and 5 minutes flush rate oxygenation via a NRBM.

Secondary outcomes were defined as:

- The absolute change in HR, SBP, SV and SVR from baseline after respectively 15L O2/min and flush rate oxygenation via NRBM.
- The number of subjects demonstrating a >10% change in CO* in response to oxygen

administration (both 15L/min and Flush rate).

* a 10% change in CO was deemed clinically relevant as this corresponds to the effect of a Vasalva manoeuvre (20) and has been shown to be a detectable change using a (non-invasive) method based on pulse contour analysis (21).

Sample size

Based on previous literature (22) 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 ANOVA with Greenhouse Geiser correction and post-hoc testing (Tukey Kramer) was used to analyze the difference in hemodynamic measurements at baseline and after preoxygenation with NRBM 15L/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 was reported in the results section according to the STROBE guideline. A *p*-value <0.05 was considered statistically significant. All statistical analysis were done with SPSS 23.0 for Apple statistical package (SPSS Inc, Chicago, Illinois, USA) 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 cardiac output 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 subjects was 62 (18-92) years, with an equal gender distribution. A total of 16 patients (26,7%) used one or more cardiovascular drugs on a daily basis. There were no patients with pre-existent heart failure or a pacemaker in situ. Other patient characteristics, and vital signs at presentation are represented in table 1. None of the patients received intravenous fluids before arrival in hospital. Sometimes they did receive analgesics administered by EMS; fentanyl (n=25 (41,7%)), ketamine (n=12 (20%)) or other opioids (n=4 (6,7%)).

Table 1. Baseline characteristics of patients pre-oxygenated with a high (FiO_2) for PSA in the ED (n=60).

Age in years, median (range)	62 (18-92)
Gender, n (%) Female Male	 30 (50) 30 (50)
Cardiovascular Medication use, n (%) Beta blocker ACE inhibitor or ATII receptor antagonist	 10 (16,7) 12 (20)

Spironolactone Calcium channel blockers	1 (1,7) 0 (0)
Known heart failure, n (%)	0 (0)
Pacemaker, n (%)	0 (0)
Abnormality on ECG, n (%)*	3 (5)
ASA classification, n (%) I II III IV	 21 (35) 26 (43,3) 13 (21,7) 0 (0)
Use of alcohol < 24 hours, n (%)	17 (29,8)
Use of nicotine < 24 hours, n (%)	15 (26,3)
Indication PSA, n (%) Reduction dislocation Reduction fracture Incision and drainage abscess Chest tube placement**	 34 (56,7) 8 (13,3) 17 (28,3) 1 (1,7)

***Legend table 1**. ACE, Angiotensin converting enzyme; ATII, angiotensin type 2; ECG, electrocardiogram; ASA, American Society of Anaesthesiologists; PSA, procedural sedation and analgesia. * atrial fibrillation. ** Indication for the chest tube was a large pneumothorax, without signs of hypoxia, or respiratory- or hemodynamic compromise.*

Main results

Oxygen administration at a rate of 15L/min during pre-oxygenation resulted in an increase in median oxygen saturation (from 97% to 100%), p< 0.0001. Mean (95% CI) 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 minutes of oxygen administration by NRB at a rate of 15L/min, and to 6.2 (5.7-6.7) L/min after a further 5 minutes of flush rate oxygen suppletion (p=0.037). Mean SV remained relatively constant, whereas mean SVR increased markedly (table 2).

Table 2. Non-invasively measured (haemodynamic) variables before- and after pre-oxygenation with a high (FiO_2) for PSA in the ED (n=60).

	Baseline **N = 60**	**After 5 minutes NRBM 15L/min** **N = 60**	**After 5 minutes flush rate oxygen** **N = 59**	***p***
SpO2 (%)	97 (97 – 98)	100 (100 – 100)*	100 (100 – 100)*	<0.001
CO (L/min)	6.5 (6.0 - 6.9)	6.3 (5.8 - 6.8)	6.2 (5.7 - 6.7)*	0.037
SV (ml)	84 (77 – 89)	83 (75 – 89)	83 (75 – 90)	0.69
SBP (mmHg)	133 (123-151)	138 (125 – 164)*	144 (132 – 162)* ≠	<0.001
HR (bpm)	78 (74 – 81)	76 (72 – 80)	76 (72 – 80)	0.064
SVR ($dyn/sec/cm^{-5}$)	781 (649-1067)	1244 (936 – 1695)*	1337 (988 – 1738)* ≠	<0.001

***Legend table 2**: Values are mean [95%CI] (CO, SV and HR) or median [IQR] (SpO_2, SBP, and SVR). Represented are P values for repeated measures ANOVA omnibus test. * denotes p<0.05 in post-hoc testing compared to baseline; ≠ denotes p<0.05 compared to 15L/min. CO, cardiac output;; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SpO2, oxygen saturation; SVR, systemic vascular resistance.*

A considerable proportion of the subjects (n=16, 27%) demonstrated a >10% decrease in CO in response to preoxygenation: In about a third of the subjects (n= 5) this was already apparent after the first 5 minutes of preoxygenation with a NRBM at a rate of 15L/min. Baseline patient characteristics were not significantly related to the occurrence of a > 10% decrease in CO (table 3).

Table 3. Baseline patient characteristics stratified by the effect of pre-oxygenation with a high (FiO_2) for PSA in the ED (n=60).

	Patients with a >10 % decrease in CO (n = 16)	Other patients (n = 44)	*p*
Demographics and history			
Male (n)	5 (31%)	25 (57%)	0.14
Age (years)	67.5 (45.3 – 77.0)	60 (36.3 – 74.5)	0.45
ASA III classification (n)	2 (13%)	11 (25%)	0.48
Use of alcohol <24 hours (n)	5 (31%)	12 (27%)	0.76
Use of nicotine <24 hours (n)	2 (13%)	13 (30%)	0.31
Any cardiovascular medication use (n))	4 (25%)	12 (27%)	1.00
Physical exam			
SpO2 (%)	97 (96-99)	97 (97-98)	0.98
HR (bpm)	77 (70-82)	78 (74-82)	0.72
SBP	138 (124-160)	133 (123-149)	0.63
CO (L/min)	6.6 (5.6 – 7.5)	6.4 (5.9 – 7.0)	0.73
SV (ml)	86 (73 – 99)	83 (76 – 90)	0.59
SVR (dyn/sec/cm^{-5})	735 (637 – 1142)	846 (649 – 1042)	0.82

***Legend table 3**: Values are mean [95% CI] (CO, SV and HR) or median [IQR] (SpO_2, SBP, and SVR). CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SpO2, oxygen saturation; SVR, systemic vascular resistance.*

Patients who demonstrated a >10% decrease in CO had a significantly greater increase in SVR (from 735 dyn/sec/cm^{-5} at baseline to 1248 dyn/sec/cm^{-5} after 15L/min to 1482 dyn/sec/cm^{-5} after flush rate oxygen suppletion) compared to other patients (846, 1244 and 1304 dyn/sec/cm^{-5} respectively), p=0.025), figure 3 and table 4. Likewise, they demonstrated a significant decrease in SV (from 86 ml to 80 ml and 76 ml respectively), whereas SV did not decrease in patient who did not demonstrate a clinically relevant decrease in CO (83, 84 and 86 ml respectively, p<0.001).

Table 4. Haemodynamic parameters as a function of oxygen administration, stratified by the response in CO (>10% decrease or < 10% decrease).

	>10% decrease in CO N = 16	Other patients N = 44	p

CO (L/min)			<0.001
	Baseline	6.6 (5.6 – 7,5)	6.4 (5.9 – 7.0)
	Oxygen 15L/min	6.2 (5.2 – 7.2)	6.3 (5.7 – 6.9)
	Oxygen Flush rate	5.4 (4.6 – 6.2)	6.5 (5.9 – 7.1)
SV (ml)			<0.001
	Baseline	86 (73 – 99.)	83 (76 – 90)
	Oxygen 15L/min	80 (66 – 95)	84 (76 – 92)
	Oxygen Flush rate	76 (61 – 92)	86 (77 – 94)
SVR dyn/sec/cm^{-5})			0.025
	Baseline	735 (637 – 1142)	846 (649 – 1042)
	Oxygen 15L/min	1248 (950 – 1954)	1244 (910 – 1658)
	Oxygen Flush rate	1482 (1129 – 2214)	1304 (982 – 1672)
HR (bpm)			0.85
	Baseline	77 (70– 82)	78 (74 – 82)
	Oxygen 15L/min	75 (68 – 81)	77 (72 – 81)
	Oxygen Flush rate	75 (68 – 81)	77 (72 – 82)
SBP (mmHg)			0.26
	Baseline	138 (124 – 160)	133 (123 – 150)
	Oxygen 15L/min	147 (117 – 164)	137 (129 – 164)
	Oxygen Flush rate	148 (127 – 165)	144 (132 – 158)

***Legend table 4**. 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 minutes of oxygen administration by NRBM at a rate of 15L/min; T=10; value after an additional 5 minutes of oxygen administration by NRBM at flush rate. CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SVR, systemic vascular resistance.*

Discussion

In this study, we found that a short 10-minute exposure to a high FiO_2 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 showsthat prolonged exposure to a high FiO2 has a negative effect on CO (13-16), and (ultimately) on morbidity and mortality (23). The proposed pathophysiological mechanism mediating the relation between hyperoxia and CO is coronary vasoconstriction (13-16), resulting in a decrease in SV. The latter is in line with our finding that SV decreases with >10% in subjects who demonstrated a >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 (24,25). Furthermore, free radicals have the potential to damage (mitochondrial) DNA, lipids and proteins, and may cause irreversible damage (23,26-28). 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 a >10% drop in CO. Changes of this magnitude might be of relevance to patients who already have a decreased baseline COIt is worth mentioning however, that not only the magnitude, but also the duration of the drop are relevant for the ultimate effect. As medication for PSA was administered per protocol after the second period of pre-oxygenation, 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 1 in 4 patients demonstrates a >10% drop in CO, it seems reasonable to titrate oxygen administration on SpO2 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 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 pre-oxygenation with a high FiO_2 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 FiO_2 should still be given during preoxygenation

In other patients, one should ideally aim for a high SpO_2 but at the same time a normal PaO_2 (9,5 – 13,5 kPa). 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 (29,30).

Limitations

Our study has several limitations, inherent to the study design. First, although we observed lower CO and higher SVR values with flush-rate oxygen administration than with 15L/min, we cannot exclude that this is a time-dependent rather than a dose dependent effect, as flush rate oxygen was administered immediately after 5 minutes of 15L/min were administered. Secondly, we did not perform arterial blood gas analysis after pre-oxygenation to establish the presence (and the amount

of) hyperoxia. Nonetheless, the presence of hyperoxemia is highly likely, as SpO_2 increased to 100% in all participating subjects, and previous studies with comparable oxygen administration strategies have demonstrated the presence of both a high expired oxygen fraction (3, 31) and a high PaO2. In addition, 14 patients had to be excluded as no reliable Clearsight® signal could be obtained, sometimes for unknown reasons, which could have contributed to selection bias. Also, at least a quarter of the patients used alcohol (n=15) or nicotine (n=17) in the last 24 hours. Since chronic 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 (32,33). 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, generalizability of our results is limited due to the selection of our study population: None of our patients had significant cardiovascular co-morbidity. 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 FiO_2 for 5-10 minutes results in a significant drop in CO in 1 out of 4 patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO_2 should be titrated based on deficit and high flow oxygen should not be given as a routine treatment.

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Declarations

Competing interests: The authors declare that they have no competing interests.

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Ethics approval and consent to participate: Regionale toetsingscommissie patiëntgebonden onderzoek (RTPO) Leeuwarden, protocol number nWMO 270. Written consent to participate was obtained.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions: All authors fulfilled the ICMJE criteria for authorship. RS and EtA conceived the study. EvI, RS and EtA acquired and interpreted the data. RS and EtA drafted the manuscript. All authors revised the manuscript critically and gave final approval to submission of the manuscript.

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Figures:

Figure 1. Study Overview

Legend Figure 1: Arrows indicate moments of measurement of haemodynamic parameters.

Figure 2. Patient inclusion

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 CO (>10% decrease or < 10% decrease).

Legend figure 3*: 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 pre-oxygenation (n=44). Times on the x-axis are baseline, after 5 minutes and after 10.*

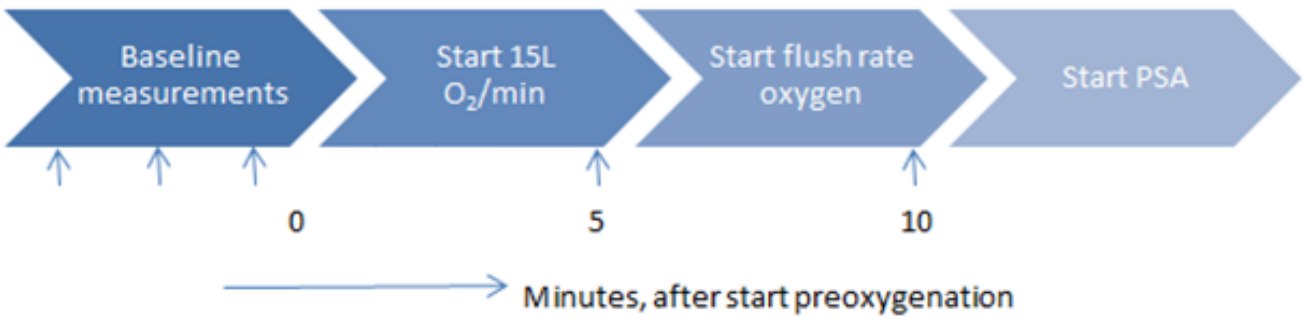
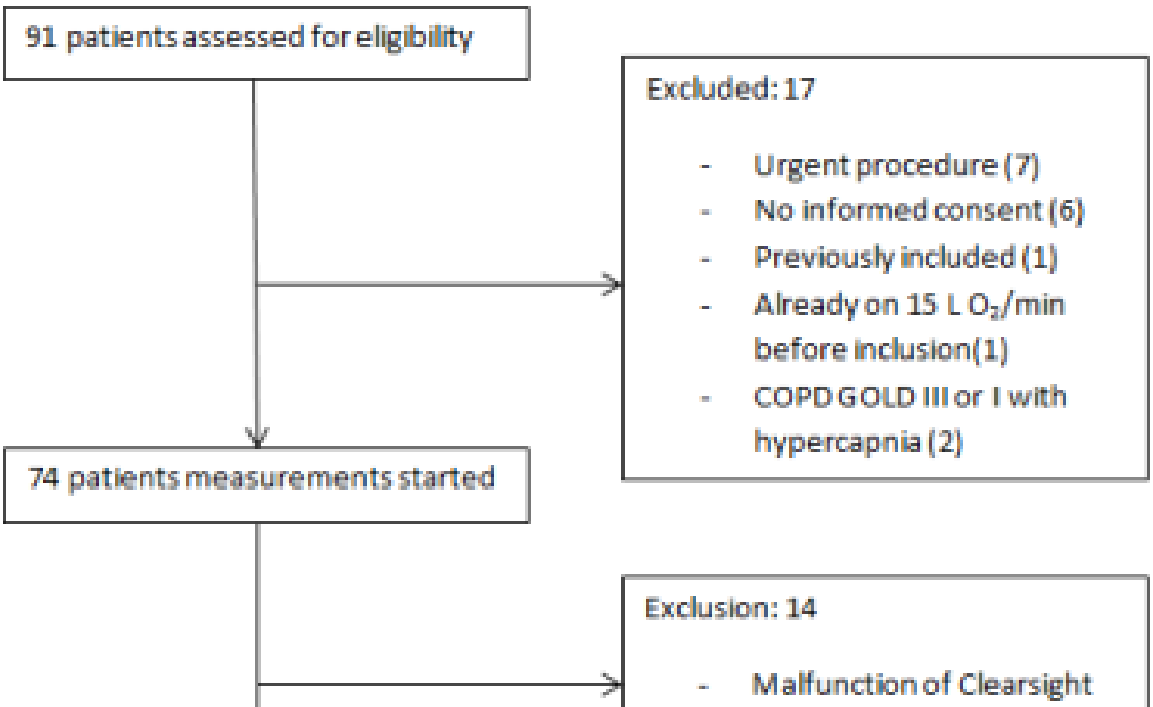
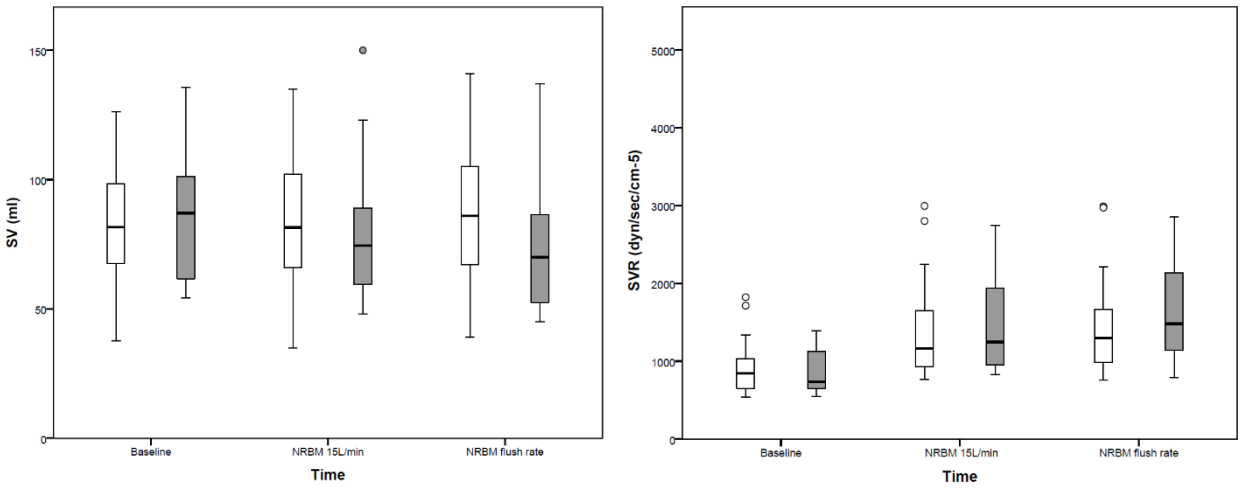


Figure 2. Patient inclusion





STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7	
Bias	9	Describe any efforts to address potential sources of bias	6-7	
Study size	10	Explain how the study size was arrived at	7	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Haemodynamic effects of a 10-minute treatment with a high inspired oxygen concentration in the Emergency Department: a prospective observational study.

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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Anaesthesia
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE

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Haemodynamic effects of a 10-minute treatment with a high inspired oxygen concentration in the Emergency Department: a prospective observational study.

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Short title: The effects of short term hyperoxia on cardiac output in the ED.

Word count: 3949

Abstract

Previous studies show that prolonged exposure to a high inspired oxygen concentration (FiO_2) is associated with unfavourable hemodynamic 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 hemodynamic effects of a high FiO_2 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 minutes of preoxygenation via a non-rebreathing mask at 15/L min and after 5-minutes 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 15L/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 minutes of oxygen administration at a rate of 15L/min, and to 6.2 (5.7-6.70) L/min after another 5 minutes 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/sec/cm^{-5} ,p<0.001. Sixteen (27%) patients experienced a >10% decrease in CO.

Conclusion. Exposure of patients to a high FiO_2 for 5-10 minutes results in a significant drop in CO in 1 out of 4 patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO_2 should be titrated based on deficit whenever this is feasible and high flow oxygen should not be given as a routine treatment.

Key words: hyperoxia, inspired oxygen concentration, hyperoxemia, emergency department, oxygen therapy, procedural sedation and analgesia.

Strengths and limitations of this study:

- This prospective study investigates the hemodynamic effects of treatment of patients in the emergency department with a high inspired oxygen concentration for a limited duration of time (10 minutes).
- Non-invasive monitoring of cardiac output, stroke volume and systemic vascular resistance was used before- and during pre-oxygenation to quantify hemodynamic effects.
- Generalizability this study is limited due to relative homogeneity of the subjects included in the study.

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 pre-oxygenate (de-nitrogenate) patients for procedures such as rapid sequence induction (RSI) or procedural sedation and analgesia (PSA), (1-3). Often, oxygen is administered at a flow of 15 L/min or even higher (4) via a non-rebreathing mask (NRBM) in order to increase the end-expiratory oxygen fraction, and to de-nitrogenate the lungs, thereby increasing the save apnea time for PSA or RSI (5).

Oxygen administration however, may not be without risk. Previous studies show that prolonged exposure to a high inspired oxygen concentration (FiO_2) is associated with higher mortality rates in patients hospitalised with various conditions (6-10). 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 (11,12), and by the formation of reactive oxygen species13 that contribute to (vascular) oxidative stress (13-16).

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 hyperoxemia in many patients (17). The clinical relevance of this however is largely unknown, as until now the hemodynamic effects of exposure of patients in the ED to a high FiO_2 for only a limited duration of time have never been reported.

Therefore, in the present study, we aim to investigate the hemodynamic effects of a high FiO_2 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 pre-oxygenation 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). Ethical approval was sought and obtained from the ethical committee of the RTPO Leeuwarden (protocol number nWMO 270).

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< 8.0 kPa), if they received oxygen suppletion pre-inclusion, if they had chronic obstructive pulmonary disease (COPD) GOLD I or II with hypercapnia (pCO2 >6.4 kPa) or COPD GOLD III or IV, if they used bleomycine, if they presented with a cardiogenic shock (SBP<90 mmHg) 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 cardiac output 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 minutes. Thereafter, the rate of oxygen administration was increased to flush rate (30L/min) and after 5 minutes 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 (CRF) for all included patients: patient demographics including (cardiac) medical history and alcohol- nicotine- and medication use, ECG abnormalities at presentation, ASA classification and indication for PSA, and vital parameters (heart rate (HR), non-invasively measured systolic blood pressure (SBP), oxygen saturation (SpO2), CO, SV and SVR).

Non-invasive cardiac output 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 heart rate. The Nexfin technology used in the ClearSight® is validated in multiple studies (18,19). Measurements can reliably be performed in awake patients or during cardiac arrhythmias (20-22), but hypoperfusion of the finger (due to vasoconstriction) from shock, hypothermia, or the use of vasopressors may negatively impact signal reliability (18,19). 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 minutes 15L O2/min and 5 minutes flush rate oxygenation via a NRBM.

Secondary outcomes were defined as:

- The absolute change in HR, SBP, SV and SVR from baseline after respectively 15L O2/min and

flush rate oxygenation via NRBM.

- The number of subjects demonstrating a >10% change in CO* in response to oxygen administration (both 15L/min and Flush rate).

* a 10% change in CO was deemed clinically relevant as this corresponds to the effect of a Vasalva manoeuvre (23) and has been shown to be a detectable change using a (non-invasive) method based on pulse contour analysis (24).

Sample size

Based on previous literature (25) 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 ANOVA with Greenhouse Geiser correction and post-hoc testing (Tukey Kramer) was used to analyze the difference in hemodynamic measurements at baseline and after preoxygenation with NRBM 15L/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 was reported in the results section according to the STROBE guideline. A *p*-value <0.05 was considered statistically significant. All statistical analysis were done with SPSS 23.0 for Apple statistical package (SPSS Inc, Chicago, Illinois, USA) 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 cardiac output 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 subjects was 62 (18-92) years, with an equal gender distribution. A total of 16 patients (26,7%) used one or more cardiovascular drugs on a daily basis. There were no patients with pre-existent heart failure or a pacemaker in situ. Other patient characteristics, and vital signs at presentation are represented in table 1. None of the patients received intravenous fluids before arrival in hospital. Sometimes they did receive analgesics administered by EMS; fentanyl (n=25 (41,7%)), ketamine (n=12 (20%)) or other opioids (n=4 (6,7%)).

Table 1. Baseline characteristics of patients pre-oxygenated with a high (FiO_2) for PSA in the ED (n=60).

Age in years, median (range)	62 (18-92)
Gender, n (%) Female Male	 30 (50) 30 (50)
Cardiovascular Medication use, n (%)	

Beta blocker	10 (16,7)
ACE inhibitor or ATII receptor antagonist	12 (20)
Spironolactone	1 (1,7)
Calcium channel blockers	0 (0)
Known heart failure, n (%)	0 (0)
Pacemaker, n (%)	0 (0)
Abnormality on ECG, n (%)*	3 (5)
ASA classification, n (%)	
I	21 (35)
II	26 (43,3)
III	13 (21,7)
IV	0 (0)
Use of alcohol < 24 hours, n (%)	17 (29,8)
Use of nicotine < 24 hours, n (%)	15 (26,3)
Indication PSA, n (%)	
Reduction dislocation	34 (56,7)
Reduction fracture	8 (13,3)
Incision and drainage abscess	17 (28,3)
Chest tube placement**	1 (1,7)

***Legend table 1**. ACE, Angiotensin converting enzyme; ATII, angiotensin type 2; ECG, electrocardiogram; ASA, American Society of Anaesthesiologists; PSA, procedural sedation and analgesia. * atrial fibrillation. ** Indication for the chest tube was a large pneumothorax, without signs of hypoxia, or respiratory- or hemodynamic compromise.*

Main results

Oxygen administration at a rate of 15L/min during pre-oxygenation resulted in an increase in median oxygen saturation (from 97% to 100%), p< 0.0001. Mean (95% CI) 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 minutes of oxygen administration by NRB at a rate

of 15L/min, and to 6.2 (5.7-6.7) L/min after a further 5 minutes of flush rate oxygen suppletion (p=0.037). Mean SV remained relatively constant, whereas mean SVR increased markedly (table 2).

Table 2. Non-invasively measured (haemodynamic) variables before- and after pre-oxygenation with a high (FiO_2) for PSA in the ED (n=60).

	Baseline **N = 60**	**After 5 minutes NRBM 15L/min** **N = 60**	**After 5 minutes flush rate oxygen** **N = 59**	***p***
SpO2 (%)	97 (97 – 98)	100 (100 – 100)*	100 (100 – 100)*	<0.001
CO (L/min)	6.5 (6.0 - 6.9)	6.3 (5.8 - 6.8)	6.2 (5.7 - 6.7)*	0.037
SV (ml)	84 (77 – 89)	83 (75 – 89)	83 (75 – 90)	0.69
SBP (mmHg)	133 (123-151)	138 (125 – 164)*	144 (132 – 162)* ≠	<0.001
HR (bpm)	78 (74 – 81)	76 (72 – 80)	76 (72 – 80)	0.064
SVR ($dyn/sec/cm^{-5}$)	781 (649-1067)	1244 (936 – 1695)*	1337 (988 – 1738)* ≠	<0.001

***Legend table 2**: Values are mean [95%CI] (CO, SV and HR) or median [IQR] (SpO_2, SBP, and SVR). Represented are P values for repeated measures ANOVA omnibus test. * denotes p<0.05 in post-hoc testing compared to baseline; ≠ denotes p<0.05 compared to 15L/min. CO, cardiac output;; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SpO2, oxygen saturation; SVR, systemic vascular resistance.*

A considerable proportion of the subjects (n=16, 27%) demonstrated a >10% decrease in CO in response to preoxygenation: In about a third of the subjects (n= 5) this was already apparent after the first 5 minutes of preoxygenation with a NRBM at a rate of 15L/min. Baseline patient characteristics were not significantly related to the occurrence of a > 10% decrease in CO (table 3).

Table 3. Baseline patient characteristics stratified by the effect of pre-oxygenation with a high (FiO_2) for PSA in the ED (n=60).

	Patients with a >10 % decrease in CO (n = 16)	Other patients (n = 44)	*p*
Demographics and history			
Male (n)	5 (31%)	25 (57%)	0.14
Age (years)	67.5 (45.3 – 77.0)	60 (36.3 – 74.5)	0.45
ASA III classification (n)	2 (13%)	11 (25%)	0.48
Use of alcohol <24 hours (n)	5 (31%)	12 (27%)	0.76
Use of nicotine <24 hours (n)	2 (13%)	13 (30%)	0.31
Any cardiovascular medication use (n))	4 (25%)	12 (27%)	1.00
Physical exam			
SpO2 (%)	97 (96-99)	97 (97-98)	0.98
HR (bpm)	77 (70-82)	78 (74-82)	0.72
SBP	138 (124-160)	133 (123-149)	0.63
CO (L/min)	6.6 (5.6 – 7.5)	6.4 (5.9 – 7.0)	0.73
SV (ml)	86 (73 – 99)	83 (76 – 90)	0.59
SVR (dyn/sec/cm^{-5})	735 (637 – 1142)	846 (649 – 1042)	0.82

***Legend table 3**: Values are mean [95% CI] (CO, SV and HR) or median [IQR] (SpO_2, SBP, and SVR). CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SpO2, oxygen saturation; SVR, systemic vascular resistance.*

Patients who demonstrated a >10% decrease in CO had a significantly greater increase in SVR (from 735 dyn/sec/cm^{-5} at baseline to 1248 dyn/sec/cm^{-5} after 15L/min to 1482 dyn/sec/cm^{-5} after flush rate oxygen suppletion) compared to other patients (846, 1244 and 1304 dyn/sec/cm^{-5} respectively), p=0.025), figure 3 and table 4. Likewise, they demonstrated a significant decrease in SV (from 86 ml to 80 ml and 76 ml respectively), whereas SV did not decrease in patient who did not demonstrate a clinically relevant decrease in CO (83, 84 and 86 ml respectively, p<0.001).

Table 4. Haemodynamic parameters as a function of oxygen administration, stratified by the response in CO (>10% decrease or < 10% decrease).

	>10% decrease in CO N = 16	Other patients N = 44	p
CO (L/min)			<0.001
Baseline	6.6 (5.6 – 7,5)	6.4 (5.9 – 7.0)	
Oxygen 15L/min	6.2 (5.2 – 7.2)	6.3 (5.7 – 6.9)	
Oxygen Flush rate	5.4 (4.6 – 6.2)	6.5 (5.9 – 7.1)	
SV (ml)			<0.001
Baseline	86 (73 – 99.)	83 (76 – 90)	
Oxygen 15L/min	80 (66 – 95)	84 (76 – 92)	
Oxygen Flush rate	76 (61 – 92)	86 (77 – 94)	
SVR dyn/sec/cm^{-5})			0.025
Baseline	735 (637 – 1142)	846 (649 – 1042)	
Oxygen 15L/min	1248 (950 – 1954)	1244 (910 – 1658)	
Oxygen Flush rate	1482 (1129 – 2214)	1304 (982 – 1672)	
HR (bpm)			0.85
Baseline	77 (70– 82)	78 (74 – 82)	
Oxygen 15L/min	75 (68 – 81)	77 (72 – 81)	
Oxygen Flush rate	75 (68 – 81)	77 (72 – 82)	
SBP (mmHg)			0.26
Baseline	138 (124 – 160)	133 (123 – 150)	
Oxygen 15L/min	147 (117 – 164)	137 (129 – 164)	
Oxygen Flush rate	148 (127 – 165)	144 (132 – 158)	

***Legend table 4**. 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 minutes of oxygen administration by NRBM at a rate of 15L/min; T=10; value after an additional 5 minutes of oxygen administration by NRBM at flush rate. CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; SVR, systemic vascular resistance.*

Discussion

In this study, we found that a short 10-minute exposure to a high FiO_2 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 (13-16), and (ultimately) on morbidity and mortality (26). The proposed pathophysiological mechanism mediating the relation between hyperoxia and CO is coronary vasoconstriction (13-16), resulting in a decrease in SV. The latter is in line with our finding that SV decreases with >10% in subjects who demonstrated a >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 (27,28). Furthermore, free radicals have the potential to damage (mitochondrial) DNA, lipids and proteins, and may cause irreversible damage (26,29-31). 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 a >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 (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 (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 pre-oxygenation, 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 1 in 4 patients demonstrates a >10% drop in CO, it seems reasonable to titrate oxygen administration on SpO2 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 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 pre-oxygenation with a high FiO_2 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 FiO_2 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 SpO_2 but at the same time a normal PaO_2 (9,5 – 13,5 kPa). 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 (34,35). 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 FiO_2.

Limitations

Our study has several limitations, inherent to the study design. First, although we observed lower CO and higher SVR values with flush-rate oxygen administration than with 15L/min, we cannot exclude that this is a time-dependent rather than a dose dependent effect, as flush rate oxygen was administered immediately after 5 minutes of 15L/min were administered. Secondly, we did not perform arterial blood gas analysis after pre-oxygenation to establish the presence (and the amount of) hyperoxia. Nonetheless, the presence of hyperoxemia is highly likely, as SpO_2 increased to 100% in all participating subjects, and previous studies with comparable oxygen administration strategies have demonstrated the presence of both a high expired oxygen fraction (3, 36) and a high PaO2. In addition, 14 patients had to be excluded as no reliable Clearsight® signal could be obtained, sometimes for unknown reasons, which could have contributed to selection bias. Also, at least a quarter of the patients used alcohol (n=15) or nicotine (n=17) in the last 24 hours. Since chronic 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 (37,38). 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, generalizability of our results is limited due to the selection of our study population: None of our patients had significant cardiovascular co-morbidity. 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 FiO_2 for 5-10 minutes results in a significant drop in CO in 1 out of 4 patients. Therefore, even in the ED and in prehospital care, where oxygen is administered for a limited amount of time, FiO_2 should be titrated based on deficit and high flow oxygen should not be given as a routine treatment.

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Declarations

Competing interests: The authors declare that they have no competing interests.

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Ethics approval and consent to participate: Regionale toetsingscommissie patiëntgebonden onderzoek (RTPO) Leeuwarden, protocol number nWMO 270. Written consent to participate was obtained.

Consent for publication: not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions: All authors fulfilled the ICMJE criteria for authorship. RS and EtA conceived the study. EvI, RS and EtA acquired and interpreted the data. RS and EtA drafted the manuscript. HL, PvB and JtM revised the manuscript critically and gave final approval to submission of the manuscript.

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Figures:

Figure 1. Study Overview

Legend Figure 1: Arrows indicate moments of measurement of haemodynamic parameters.

Figure 2. Patient inclusion

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 CO (>10% decrease or < 10% decrease).

Legend figure 3*: 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 pre-oxygenation (n=44). Times on the x-axis are baseline, after 5 minutes and after 10.*

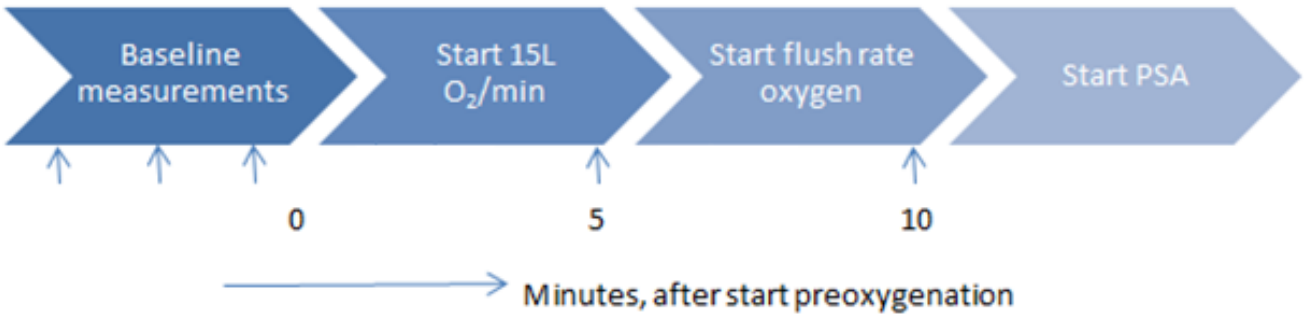
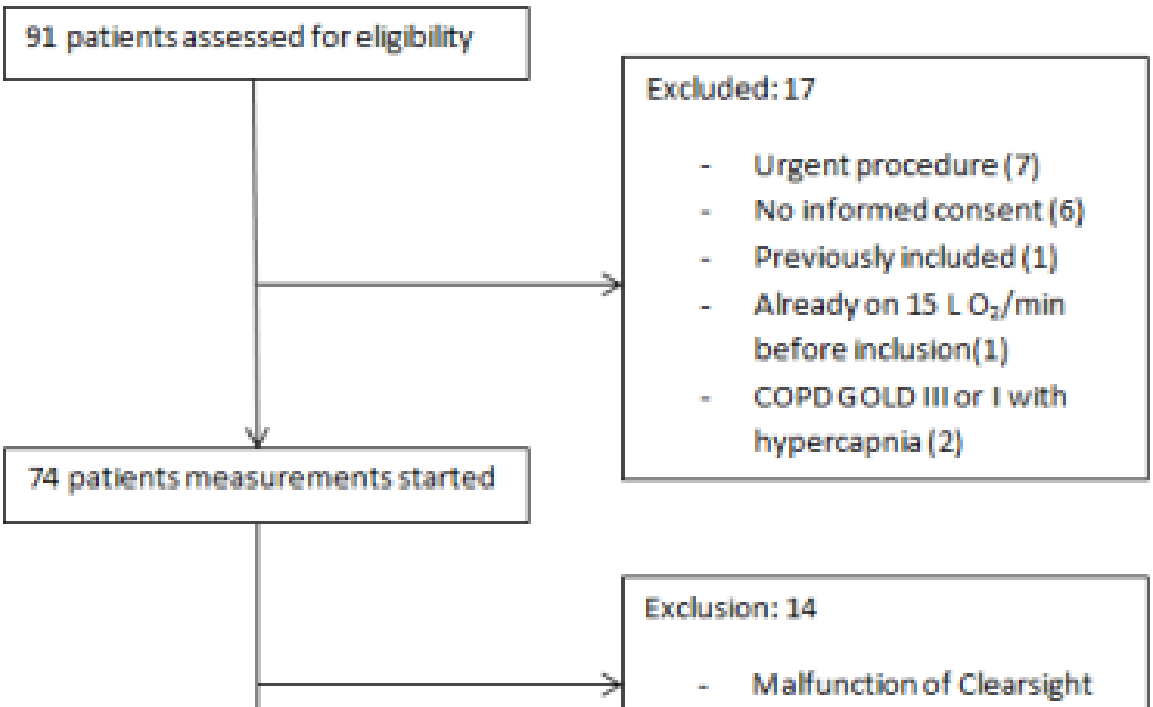
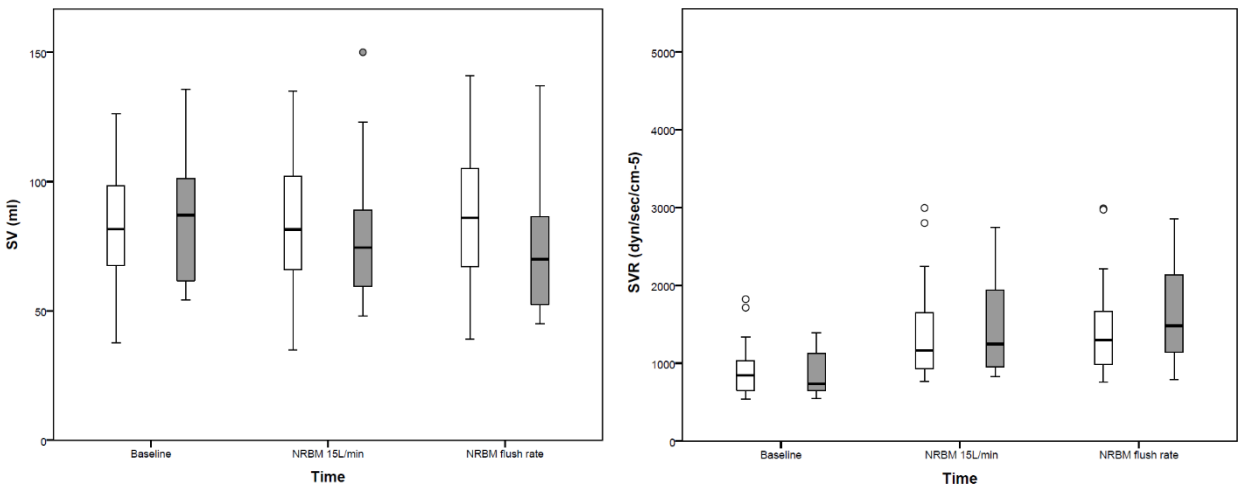


Figure 2. Patient inclusion





STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7	
Bias	9	Describe any efforts to address potential sources of bias	6-7	
Study size	10	Explain how the study size was arrived at	7	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.