SUPPLEMENTARY OXYGEN IN SURGICAL AND MEDICAL WARDS EVALUATED BY 30-DAY MORTALITY (SOSAM)

- FULL STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

INTRODUCTION

OBJECTIVE

The aim of this study is to investigate oxygen treatment and its correlation with morbidity and mortality in hospitalized medical and post-operative patients, the primary outcome being 30-day mortality.

Hyperoxia is hypothesized to increase 30-day mortality due to previous research indicating elevated arterial oxygenation as a negative predictor for mortality outcomes in various patient groups.

BACKGROUND

Supplementary oxygen is widely used to both treat and prevent hypoxia in a clinical hospital setting. In spite of the widespread use of oxygen, and the well-known malicious effects of hypoxia, little is known about the harmful effects of abundant oxygen supply during hospital admission. Several methods of action have been proposed for the mechanism of harmful effects of hyperoxia, and studies have found hyperoxia to be harmful on a cellular level[1,2]

Studies conducted on selected groups of patients have shown a harmful effect of short-term exposure of hyperoxia. Patients undergoing abdominal operations have been shown to have an increased long term-mortality when exposed to high levels of perioperative inspiratory oxygen[3,4] and patients with ST-elevation-myocardial infarction appear to have an increase in their level of myocardial injury after being randomized to high levels of supplementary oxygen.[5] It has been pointed out, that further research into this topic is of high relevance, seeing the current randomized controlled trials have focused mainly on the benefits of oxygen, rather than the potiential harmful effects of hyperoxia.[6,7]

METHODS

STUDY DESIGN

This study is designed as an observational retrospective cohort study, using a database consisting of data from the National Early Warning Score (EWS) from approximately 170.000 patients during hospitalization in the Capital Region of Denmark.

SETTING

Regular measurements of NEWS-values on patients admitted to a hospital in the Capital region of Denmark has been standard practice since 2013. Data from NEWS-recordings on patients admitted to hospital in the period from 1 January 2014 to 31 December 2014 in the Capital Region of Denmark have previously been critically assessed and sanitized for unreliable entries.[8] These sanitized recordings, combined with the primary diagnosis and 30-day mortality linked by the Danish CPR-number, are the primary datasets in this study.

Secondary analyses will be carried out on existing data for blood samples collected during hospital admission, and data for readmissions, ICU-admissions and reoperations.

PARTICIPANTS

INCLUDED PATIENTS

Patients are included according to the following criteria:

- Admission date (medical patients) or end of operation date (surgical patients) between 1st of January 2014 to 29th of December 2014.
- Age: ≥18
- Unique (first) admission for either:

Surgical Patients:

Admitted for:

- Major operation with significant perforation of the peritoneum (laparotomy)
- Admission diagnosis (primary diagnosis) of hip fracture (DS720-DS722) combined with a surgical procedure code starting with KNF (hip surgery) for the same admission.

DS720	Fracture of neck of femur
DS721	Pertrochanteric fracture
DS722	Subtrochanteric fracture

Medical patients:
Admitted under the primary diagnosis of:

- COPD with either acute exacerbation (DJ441) or acute lower respiratory infection (DJ440)

DJ440	Chronic obstructive pulmonary disease with acute lower respiratory infection
DJ441	Chronic obstructive pulmonary disease with acute exacerbation, unspecified

- Acute myocardial infarction (DI21X)

DI21	Acute myocardial infarction
DI210	Acute transmural myocardial infarction of anterior wall
DI210A	Anterior non-ST-elevation acute transmural myocardial infarction
DI210B	Anterior ST-elevation acute transmural myocardial infarction
DI211	Acute transmural myocardial infarction of inferior wall
DI211A	Inferior non-ST-elevation Acute transmural myocardial infarction
DI211B	Inferior ST-elevation Acute transmural myocardial infarction
DI212	Acute transmural myocardial infarction of other sites
DI213	Acute transmural myocardial infarction of unspecified site
DI214	Acute subendocardial myocardial infarction
DI219	Acute myocardial infarction, unspecified

EXCLUDED PATIENTS

Patients are excluded according to the following criteria:

- No data on saturation within 48 hours after
  - Admission (Medical patients)
  - Discharge from the post anaesthesia care unit, PACU (Surgical patients)
- No data on primary outcome (30-day mortality)

A patient inclusion diagram will be included in the final manuscript. See below figure for proposed illustration.

PATIENT INCLUSION DIAGRAM

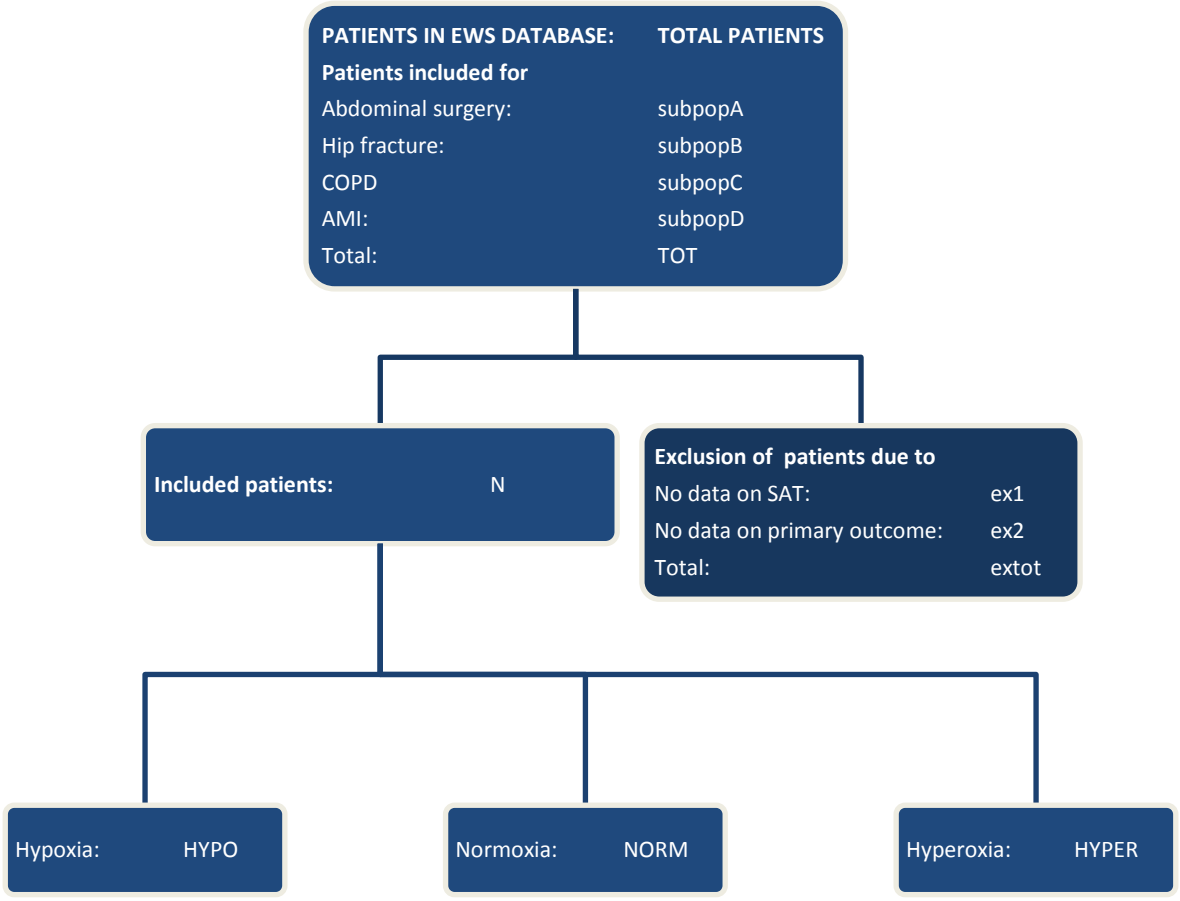


Figure 1 - Overview of patient inclusion

VARIABLES

As the majority of patients do not have a regular measurement of PaO_2, the exposure to hyperoxia will be estimated by combining the O_2-saturation (SpO2) as measured by pulse oximetry

and the amount of oxygen administration (measured in litres/min), both values obtained during the recording of EWS values.

Patients will be classified into three groups based on their oxygenation level. Patients will be assigned to the group according to which they spend the majority of time during the first 48 hours after either hospital admission for medical patients *or* discharge from the post anaesthesia care unit (PACU) for surgical patients. Patients previously diagnosed with COPD have a different setpoint for blood oxygenation, these patients are therefore classified according to the international guidelines for oxygenation in COPD-patients. Table 1 depicts the detailed classification of the three groups.

	Hypoxia	Normoxia	Hyperoxia
Non-COPD	SpO2 <94% irrespective of supplemental oxygen	SpO2 94-98% in combination with supplemental oxygen *Or* SpO2 ≥94% without supplemental oxygen.	SpO2 >98% in combination with supplemental oxygen
COPD	SpO2 <88% irrespective of supplemental oxygen	SpO2 88-92% in combination with supplemental oxygen *Or* SpO2 ≥88% without supplemental oxygen.	SpO2 >92% in combination with supplemental oxygen

Table 1 – Classification of oxygenation

Due to EWS measurements not being a function of time, a calculation will be done in order to estimate the weight of the individual EWS-measurement.

Based on the frequency of the EWS-measurements one measurement will be given a value corresponding to the fraction of time in the 48-hour period it covers, thus making it possible to estimate the oxemia status for the entire 48-hour period.

The normoxia group will serve as reference group for the analysis of the following outcome parameters in order to evaluate the effects of hyperoxia (primary analysis) and hypoxia (supplemental analysis):

The primary outcome is 30-day mortality, with secondary analysis of length of hospital stay, as well as the 30-day occurrence of admission to the Intensive Care Unit, re-operations and hospital readmission.

We will also assess associations of hyperoxia to organ-markers of disease severity: CRP (inflammation), creatinine (acute kidney injury) and troponin (myocardial injury), which will be analysed by the peak level of each organ marker within 30 days.
As a supplemental analysis, we will also assess the clinical effects among patients with at least one arterial blood gas analysis during the 48 hours observation window, in which we divide patients in groups of hypoxia (PaO2 <8 kPa), normoxia (PaO2 8-12 kPa) and hyperoxia (PaO2 ≥12 kPa), according to the highest measured PaO2 . We will also do a sensitivity analysis reassessing the effect when patients are reassigned to groups according to exposure to hypoxia ≥8 hours or hyperoxia ≥8 hours.

DATA SOURCES

This study will be based on data from a National Early Warning Score (EWS) database recorded on all patients hospitalized from 1 January 2014 to 31 December 2014 in the Capital Region. Data Protection approval and Ethics Committee waiver have been approved for these data. The data has been thoroughly validated for accurate entries and consists of data from approximately 170.000 unique hospital admissions in the Capital Region of Denmark.[8] Furthermore, the unique CPR registration of all Danish patients, enables the analysis of organ markers within 30-days as well as arterial blood gas in the previously defined 48-hour period.

BIASES

The measurements of patients EWS-scores have all been manually registered and entered in the EWS-database. Previous analyses of the EWS Database show inaccuracies in the entries with a bias towards “normalized” values of vital parameters. Furthermore, EWS-measuring in the capital region of Denmark was optional on patients at an “end of life pathway”, potentially distorting the data by not including the most critically ill patients.
The classification of patients according to their state of oxygenation was based on SpO2 measured on a plethysmograph. Although such measurements correlate with the actual saturation of the blood, factors such as peripheral circulation and nutritional status can effect this measurement and thus affect the initial data.

POWER CALCULATION

MORTALITY

The 30 day mortality in each of the four patient groups is estimated in order to calculate the power of the proposed study:

A - Acute myocardial infarction: $\mathrm{A} = 7{,}5$

Note: Estimated from a Prospective analysis on Danish patients with AMI. [9]

B - COPD with exacerbation: $\mathrm{B} = 10\%$

Note: Estimated from a Danish study on COPD patients admitted with exacerbation with or without pneumonia (8,3-12,1 %). [10]

C - Hip fracture and surgery: $\mathrm{C} = 10\%$

Note: Estimated from a nationwide, population-based cohort study using prospectively collected data from the Danish Multidisciplinary Hip Fracture Registry, reporting 7,3 – 10% 30- day mortality on all admissions for hip fracture. Due to selection of patients WITH surgery in the proposed study, the 30-day mortality is expected to be towards the higher end, maybe higher, than the range referenced in the study. [11]

D – Major abdominal surgery: $\mathrm{D} = 3{,}5\%$

Note: 30- day mortality estimated from the 30-day mortality in the PROXI-trial (2,9-4,4%).[12]

WEIGHTED AVERAGE OF 30-DAY MORTALITY:

Preliminary analysis suggests the following population sizes:

	A	B	C	D	TOTAL
Pop size (N_x)	$N_A = 2300$	$N_B = 3100$	$N_C = 2100$	$N_D = 4600$	12100
Mortality (P_x)	$P_A = 7{,}5\%$	$P_B = 10\%$	$P_C = 10\%$	$P_D = 3{,}5\%$	

Weighted average 30-day mortality:

$$\bar{P} = \frac{P_A * N_A + P_B * N_B + P_C * N_C + P_D * N_D}{N_A + N_B + N_C + N_D} \approx \mathbf{7}\%$$

POWER ON BASIS OF PRESUMED CLINICAL EFFICACY OF OXYGEN-GROUP

Values according to Figure 15.2, page 456 in "Practical Statistics for Medical Research"[13] See appendix 1.

Presumed difference in 30-day mortality between hyperoxia and normoxia (if N1-N2=0) $P_1 - P_2 = P$	Standardized difference $\frac{P_1 - P_2}{\sqrt{\bar{P}(1-\bar{P})}}$	Power at N=10.000 patients (derived from Figure 15.2, Appendix 1)
7,25% - 6,75% = 0,5%	0,0196	0,17
7,50% - 6,50% = 1,0%	0,0392	0,42
7,75% - 6,25% = 1,5%	0,0588	0,80
8,00% - 6,00% = 2,0%	0,0784	0,97
8,25% - 5,75% = 2,5%	0,0980	>0,995
8,50% - 5,50% = 3,0%	0,1176	>0,995

WEAKNESSES OF THIS POWER CALCULATION

The only patient population corresponding geographically to the currently proposed sample is the group from the PROXI trial used in group "D – major abdominal surgery". The other three mortality rates are from comparable but not exact same population base.

The power of the study was derived from a nomogram (Appendix 1) and not calculated with a formula, thus leaving room for reading errors.

Furthermore, the power calculation assumes the patient count in normoxia and hyperoxia are equal.

CONCLUSION

With 12000 patients included in this study we have 80% power to detect a statistically significant difference in 30-day mortality of absolute risk reduction of 1.5% (relative risk reduction 19%) assuming the average 30-day mortality of the study sample is 7%, a distribution of patients 1:1 in the two groups and a significance level of 5%.

PLAN FOR STATISTICAL ANALYSIS

SUGGESTED DESCRIPTIVE DATA

Descriptive data for the population will be presented in table 1. For each of the three exposure groups, the following will be reported to characterise the study population: Age (mean), sex (percentage female), admission-hospital distribution and patient inclusion group distribution. The average EWS value (adjusted for chronic values) will also be included in the population description table.

		Hypoxia	Normoxia	Hyperoxia
Age (yr)				
Sex (F%)				
Hospital				
	RH (%)			
	BFH (%)			
	GLO (%)			
	XX (%)			
Patient Group				
	MI (%)			
	COPD (%)			
	HIP (%)			
	ABD (%)			
Average EWS Value				

OUTCOME DATA

Outcome data will be presented in table 2. The table will contain the three exposure groups and outcome data as calculated for each of the groups.

The primary outcome, 30 day mortality, is a binary variable for the individual patient, and will be reported as a fraction of positives within the exposure group population.

Length of stay and highest values for organ markers during the 30-day period will be treated as continuous variables with a non-normal distribution, and thus the median, not the mean, will be reported for these outcomes.

30-day admission to ICU, 30-day reoperation and 30-day readmission will be reported as a fraction of positives within the exposure group population.

GROUP	Mortality 30 d	Length of stay	Adm. ICU 30 d	Reop. 30 d	Readm. 30 d	Blood 30 d
Hypoxia						CRP
						Creatinine
						Troponine
Normoxia						CRP
						Creatinine
						Troponine
Hyperoxia						CRP
						Creatinine
						Troponine

For patients with least one arterial blood gas analysis during the 48 hours observation window, a secondary table will be reported, in which patients are divided in groups of hypoxia (PaO2 <8 kPa), normoxia (PaO2 8-12 kPa) and hyperoxia (PaO2 ≥12 kPa), according to their highest measured PaO2 .

GROUP	Mortality 30 d	Length of stay	Adm. ICU 30	Reop. 30 d	Readm. 30 d	Blood 30 d
Hypoxia PaO2 <8 kPa						CRP
						Creatinine
						Troponine
Normoxia PaO2 8-12 kPa						CRP
						Creatinine
						Troponine
Hyperoxia PaO2 ≥12 kPa						CRP
						Creatinine
						Troponine

ANALYSES:

All outcome data will be compared in the normoxia vs. hyperoxia groups data and reported as an odds ratio in the primary analysis. 95% confidence intervals and the p-value will be reported for each outcome parameter. All values, including non-significant values, will be included in the final reporting.

	Normoxia	Hyperoxia	Odds Ratio (95% CI)	P value
Primary Outcome				
30 day mortality				
Secondary outcomes:				
Adm. ICU 30 d				
Reop. 30 d				
Readm. 30 d				
Blood 30 d				
CRP				
Creatinine				
Troponine				

OTHER ANALYSES

Secondary analyses will be carried out on normoxia vs hypoxia patients with the same outcome parameters as the primary analysis.

	Hypoxia	Normoxia	Odds Ratio (95% CI)	P value
Primary Outcome				
30 day mortality				
Secondary outcomes:				
Adm. ICU 30 d				
Reop. 30 d				
Readm. 30 d				
Blood 30 d				
CRP				
Creatinine				
Troponine				

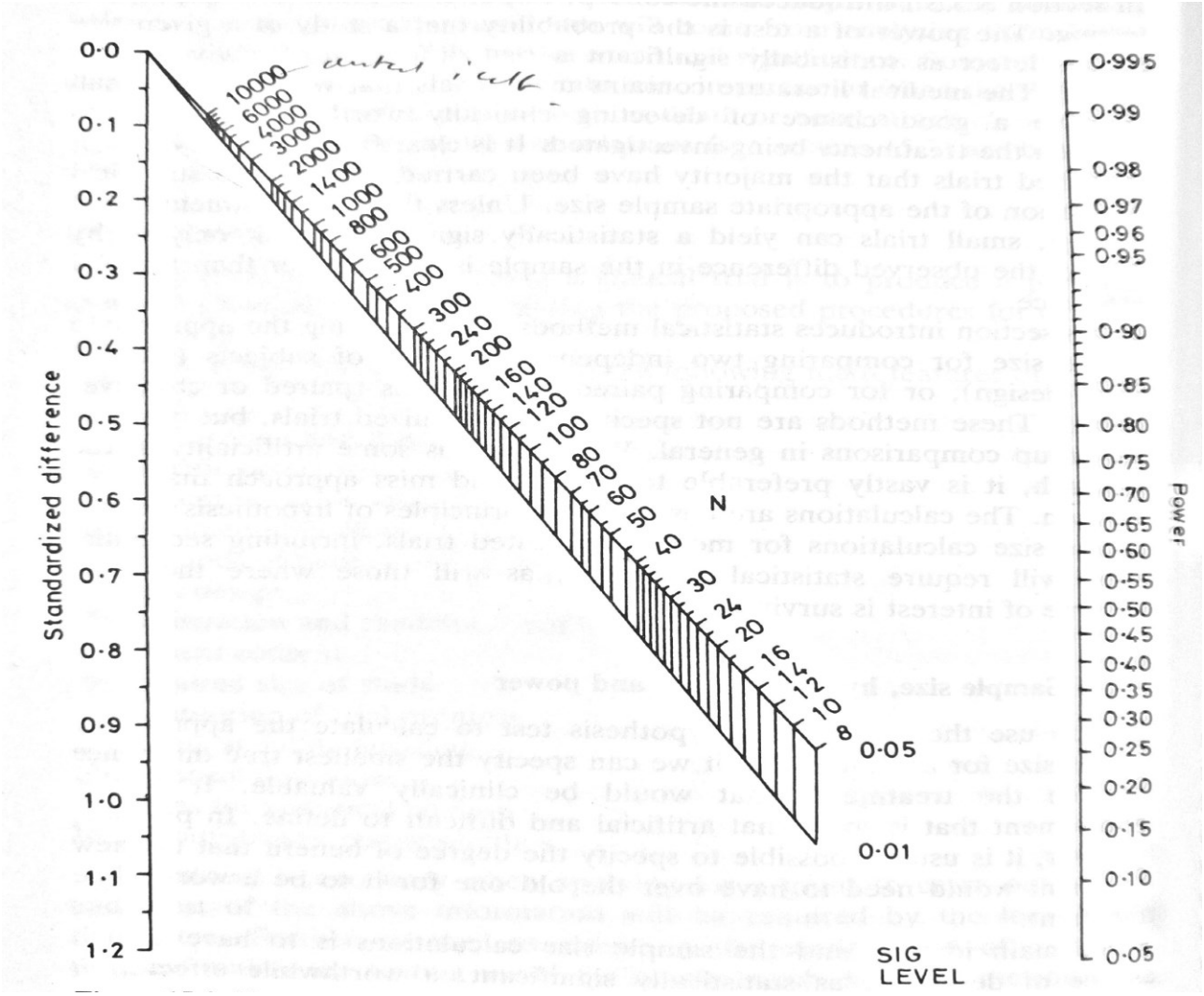
In order to assess the feasibility of the exposure groups, a supplementary sensitivity analysis will be made, reassessing the effect on outcome parameters when patients are reassigned to groups according to exposure to hypoxia ≥8 hours or hyperoxia ≥8 hours.

OTHER INFORMATION

FUNDING

This project has been funded by the internal grand for research projects at Bispebjerg and Frederiksberg Hospitals.

APPENDIX 1


Standardized difference
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Power

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