Journal of Clinical Anesthesia 73 (2021) 110379

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Perioperative supplemental oxygen and NT-proBNP concentrations after major abdominal surgery – A prospective randomized clinical trial

Christian Reiterer, MD [a], Barbara Kabon, MD [a,*], Alexander Taschner, medical student [a], Markus Falkner von Sonnenburg, MD [a], Alexandra Graf, PhD [b], Nikolas Adamowitsch, medical student [a], Patrick Starlinger, MD [c], Julius Goshin, MD [a], Melanie Fraunschiel, Msc [d], Edith Fleischmann, MD [a]

[a] Department of Anaesthesia, General Intensive Care Medicine and Pain Medicine, Medical University of Vienna, 1090 Vienna, Austria
[b] Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, 1090 Vienna, Austria
[c] Department of Surgery, Medical University of Vienna, 1090 Vienna, Austria
[d] IT Systems and Communications, Medical University of Vienna, 1090 Vienna, Austria

ARTICLE INFO

Keywords:
NT-proBNP
Supplemental oxygen
MINS
Cardiovascular risk
Major abdominal surgery

ABSTRACT

Study objective: Supplemental oxygen is a simple method to improve arterial oxygen saturation and might therefore improve myocardial oxygenation. Thus, we tested whether intraoperative supplemental oxygen reduces the risk of impaired cardiac function diagnosed with NT-proBNP and myocardial injury after noncardiac surgery (MINS) diagnosed with high-sensitivity Troponin T.

Design: Parallel-arm double-blinded single-centre superiority randomized trial.

Setting: Operating room and postoperative recovery area.

Patients: 260 patients over the age of 45 years at-risk for cardiovascular complications undergoing major abdominal surgery.

Intervention: Administration of 80% *versus* 30% oxygen throughout surgery and for the first two postoperative hours.

Measurements: The primary outcome was the postoperative maximum NT-proBNP concentration in both groups, which was assessed within 2 h after surgery, and on the first and third postoperative day. The secondary outcome was the incidence of MINS in both groups.

Main results: 128 patients received 80% oxygen and 130 received 30% oxygen throughout surgery and for the first two postoperative hours. There was no significant difference in the median postoperative maximum NT-proBNP concentration between the 80% and the 30% oxygen group (989 pg.mL^{-1} [IQR 499; 2005] and 810 pg.mL^{-1} [IQR 409; 2386], effect estimate: 159 pg.mL^{-1}, 95%CI -123, 431, $p = 0.704$). There was no difference in the incidence of MINS between both groups. ($p = 0.703$).

Conclusions: There was no beneficial effect of perioperative supplemental oxygen administration on postoperative NT-proBNP concentration and MINS. It seems likely that supplemental oxygen has no effect on the release of NT-proBNP in patients at-risk for cardiovascular complications undergoing major abdominal surgery.

Trial registration: ClinicalTrials.gov: NCT 03366857.
https://clinicaltrials.gov/ct2/results?cond=NCT+03366857&term=&cntry=&state=&city=&dist=

1. Introduction

Major cardiovascular complications occur in about 8% of all patients older than 45 years undergoing inpatient noncardiac surgery [1,2]. Surgery is a stressful event that is associated with an endogenous release of catecholamines that increases heart rate and blood pressure, which negatively affects myocardial oxygenation [3,4].

Beside other trigger factors such as inflammation, surgical stress and

* Corresponding author at: Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria.
E-mail address: barbara.kabon@meduniwien.ac.at (B. Kabon).

https://doi.org/10.1016/j.jclinane.2021.110379
Received 4 March 2021; Received in revised form 7 May 2021; Accepted 7 May 2021

hypercoagulability, perioperative hypoxia can lead to myocardial ischemia, which is mostly caused by oxygen demand and supply mismatch [3,5]. Intraoperative administration of supplemental oxygen is a simple method to increase arterial oxygen partial pressure and also increase tissue oxygen tension [6]. It might also increase oxygen delivery and reduce the risk of myocardial injury [6–8]. Especially, patients with significant cardiovascular comorbidities might benefit from enhanced oxygen delivery through supplemental oxygen.

Although the effect of intraoperative supplemental oxygen on postoperative surgical site infection was studied intensively, the effect on the cardiovascular systems is still not entirely clear [6–10]. A post-hoc analysis of the PROXI (Effect of High Perioperative Fraction on Surgical Site Infection and Pulmonary Complications after Abdominal Surgery) trial indicated that intraoperative administration of 80% oxygen concentration might increase the risk of long-term myocardial infarction or other heart diseases [11]. On the other hand, another post-hoc analysis showed that the administration of 80% oxygen did not significantly effect postoperative cardiovascular complications [12]. Even more, supplemental oxygen decreases heart rate and thus reduces myocardial oxygen consumption which might in turn increase myocardial oxygen supply [13]. This might result in a reduced risk for myocardial oxygen demand and supply mismatch [14–16]. Interestingly, it has been shown in a previous trial that nocturnal oxygen therapy significantly reduced the brain natriuretic peptide concentration and prevented the progression of congestive heart failure in patients with central sleep apnea [17].

Whether supplemental oxygen decreases the release of cardiac biomarkers as N-terminal pro brain natriuretic peptide (NT-proBNP) and Troponin T also perioperatively remains unknown. Elevated perioperative NT-proBNP is a strong predictor for cardiovascular complications and mortality after noncardiac surgery and can be used as a surrogate parameter for cardiac function as well [18–20]. Elevated Troponin T defines myocardial injury after noncardiac surgery (MINS), which is a common and serious complication [1,21]. Troponin T is an additional predictor for postoperative mortality [1].

Therefore, we tested the primary hypothesis that perioperative 80% oxygen administration changes postoperative maximum NT-proBNP concentration as compared to 30% oxygen administration in patients at-risk for cardiovascular complications undergoing major abdominal surgery. Additionally, we tested the secondary hypothesis that perioperative 80% oxygen administration changes the incidence of MINS as defined by postoperative high-sensitivity troponin T measurement. We also evaluated the effect of supplemental oxygen on the incidence of cardiac failure, myocardial infarction, new onset of cardiac arrhythmias and death during hospitalization and up to 30 days after surgery. Furthermore, we evaluated the influence of various morphometric and demographic factors on NT proBNP and Troponin T.

2. Materials and methods

2.1. Study design and participants

This parallel-arm double-blinded single-center superiority randomized trial was conducted at the Medical University of Vienna. The trial was approved by the local Institutional Review Board and was registered at ClinicalTrials.gov (NCT 03388957) and at the European Clinical Trial Database (EudraCT 2017-003714-68). The protocol was published previously [22].

Study staff screened and obtained written informed consent from eligible patients before randomization on the day before surgery. A data and safety monitoring board oversaw the conduct of the study and reviewed the blinded safety data. We evaluated patients scheduled for moderate- to high-risk abdominal surgery expected to last at least 2 h. Eligible patients were aged over 45 years and underwent major abdominal surgery under general anesthesia. Patients had to meet one or more of the following criteria: 1. History of coronary artery disease; 2. History of peripheral arterial disease; 3. History of stroke OR 4. Any three of the following six criteria (a-f): a) age over 70 years; b) undergoing major surgery; c) history of congestive heart failure; d) history of transient ischemic attack; e) diabetes and currently taking an oral hypoglycemic agent or insulin; f) history of hypertension. We excluded patients meeting one of the following criteria: 1. Sepsis, 2. Preoperative inotropic therapy, 3. Oxygen dependent patients, 4. History of severe heart failure (defined as ejection fraction <30%).

2.2. Randomization and masking

We randomized patients 1:1 using a web-based randomization program (Randomizer, Medical University of Graz, Graz, Austria, https://www.meduniwien.ac.at/randomizer/web). Randomization sequence was generated by the study statistician using permutated blocks. Each block had a size of 6 numbers, of which all investigators were unaware. There was no stratification of randomization.

A trained study physician evaluated eligibility, obtained informed consent, and then on the day of surgery, shortly before induction of anesthesia, enrolled patients by accessing the web-bases randomization system. The attending anesthesiologist was then informed of the allocation. Study staff responsible for randomization were not involved in postoperative blood sampling and outcome assessment.

Blood sampling on the first and third postoperative day, as well as phone follow up at 30-day after surgery was performed by blinded research personnel. Blinded research personnel received no information about the randomized allocation. They had further no access for electronic anesthesia documentation.

We randomized patients to receive either 80% or 30% inspired oxygen concentration throughout surgery, and for two hours postoperatively. After endotracheal intubation patients in the 80% oxygen group received an inspired oxygen fraction of 0.8 throughout surgery and 8 L/min oxygen *via* facemask with reservoir for the first two postoperative hours. Patients in the 30% oxygen group received an inspired oxygen fraction of 0.3 throughout surgery and 3 L/min oxygen *via* facemask without a reservoir for the first two postoperative hours. If necessary, oxygen fraction was increased at the discretion of the attending anesthesia team according to a predefined algorithm. (Online supplement, Appendix B, Appendix C) Postoperative pain management was performed according to standard of clinical care. (Online Supplement, Appendix A).

2.3. Protocol

Anesthesia was standardized. We performed esophageal doppler goal-directed fluid management in all patients according to a previously published algorithm [23,24]. Detailed description of intraoperative anesthesia, hemodynamic and fluid management is provided in the online supplement (Appendix A). The trial was conducted in accordance with the original protocol.

2.4. Measurements

We recorded demographic data including age, sex, BMI, American Society of Anesthesiologists (ASA) physical status, comorbidities, long-term medication, type of surgery and preoperative laboratory values. We also recorded routine intraoperative variables including duration of anesthesia and surgery, fluid and anesthesia management, and hemodynamic data. We performed blood gas analysis hourly. Blood pressure and oxygen saturation were recorded intraoperatively and during the postoperative study period. Intraoperative core temperature was measured at the distal esophagus.

Blinded research personnel drew all study specific pre- and postoperative blood samples. In all patients NT-proBNP (Roche) and Troponin T (high-sensitivity 5th generation Troponin T, Roche) was assessed shortly before induction of anesthesia, within two hours after

end of surgery and on the first and third postoperative day. All laboratory measurements were performed by the department for laboratory medicine at the Medical University of Vienna.

The primary outcome was the postoperative maximum NT-proBNP concentration (maximum values measured at 2 h postoperatively, on the first and third day after surgery) between the 80% and the 30% perioperative oxygen group in patients at-risk for cardiovascular complications undergoing major abdominal surgery. We defined maximum NT-proBNP as the highest measured value within 2 h after surgery, and on the first and third postoperative day.

Our secondary outcome the incidence of MINS between the 80% *versus* 30% oxygen group in patients at-risk for cardiovascular complications undergoing major abdominal surgery. We measured Troponin T concentrations within 2 h after surgery, and on the first and third postoperative day. For MINS diagnosis we used the highest available value measured during these time points. We used the following MINS thresholds: a) troponin T of 20 to <65 ng/L with an absolute change of at least 5 ng/L or b) troponin T level > 65 ng/L. Patients, whose Troponin T concentration was adjudicated for nonischemic etiology (*e.g.* sepsis, pulmonary embolism), were not considered as having MINS [25].

Our exploratory outcomes included cardiac failure, myocardial infarction, new onset of cardiac arrhythmias, unplanned ICU admission, re-operation, respiratory failure, bleeding, and death within 30 days after surgery. Blinded research team evaluated for exploratory outcomes within the first three days after surgery and further screened the hospital discharge letters for postoperative complications. At 30-day after surgery blinded study personnel performed follow-up interviews *via* phone. In the case of new complications, hospital records were checked. Outcomes were adjudicated by the outcome adjudication committee chaired by Barbara Kabon, MD. Outcome definitions were provided in the online supplement appendix D.

2.5. Data management

Blinded research personnel obtained all data. All data were recorded and stored in the data management system 'Clincase', v2.7.0.12 hosted by IT Systems & Communications, Medical University of Vienna, Vienna, Austria.

2.6. Statistical analysis

Patients were analyzed on an intention-to-treat basis according to their randomized group. Continuous variables are presented using median and quartiles [25th percentile; 75th percentile]. Descriptive statistics are given for both randomization groups separately as well as overall.

Categorical variables were summarized using absolute and percent values, separately for the two groups as well as overall.

For our primary outcome, the postoperative maximum NT-proBNP concentration, we performed a two-sided Wilcoxon Rank Sum test to evaluate the difference between both oxygen groups. To investigate the effect in more detail and due to the skew distribution, we furthermore used a median regression model using bootstrap to calculate estimates and confidence intervals for the difference between groups. We furthermore performed post-hoc analyses to evaluate the influence of the following baseline covariates on postoperative maximum NT-proBNP concentrations: preoperative NT-proBNP, preoperative Troponin T, age, sex, BMI, ASA physical status, coronary artery disease, peripheral artery disease, stroke, congestive heart failure, transient ischemic attack, diabetes, and hypertension on postoperative maximum NT-proBNP using univariable median regression models. Furthermore, for all influencing parameters that were significant in the univariable models ($p < 0.05$), we performed a multiple median regression model.

For our secondary outcome we first performed a univariable logistic regression model (using firths correction) to analyze the influence of supplemental oxygen on the incidence of MINS. MINS was defined using the following perioperative high-sensitive Troponin T thresholds: a) troponin T of 20 to <65 ng.L^{-1} with an absolute change of at least 5 ng.L^{-1} or b) Troponin T level > 65 ng.L^{-1} [21]. Furthermore, in patients whose Troponin T concentration was adjudicated from nonischemic etiology (*e.g.* sepsis, pulmonary embolism), were not considered as having MINS [25].

We additionally performed univariable logistic regression models to investigate the following baseline covariates on the occurrence of MINS: preoperative Troponin T, preoperative NT-proBNP, age, sex, BMI, ASA physical status, coronary artery disease, peripheral artery disease, stroke congestive heart failure, transient ischemic attack, diabetes, and hypertension. For all parameters which were significant in the univariable models ($p < 0.05$), a multiple logistic regression model was performed.

For our exploratory outcomes, to investigate the differences in the incidence of cardiac failure, myocardial infarction, new onset of cardiac arrhythmias, unplanned ICU admission, re-operation, respiratory failure, bleeding, and death, within 30 days after surgery between both groups, we present numbers and percentages. For death, we performed a fisher exact test.

All p-values <0.05 were considered as statistically significant. All analyses were performed using R, release 3.3.3.

We further performed a post-hoc subanalysis to investigate the difference in maximum NT-proBNP as well as well as the difference between preoperative NT-proBNP and postoperative maximum NT-proBNP. We calculated Wilcoxon tests overall, as well as for several subgroups. The subgroups were based on the tertiles of age, BMI, preoperative NT-proBNP, estimated glomerular filtration rate (eGFR), hemoglobin as well as based on ASA physical status and sex.

Due to 19 subgroup analysis, the significance level for the subgroup analysis was set to $0.05/19 = 0.0026$ using Bonferroni correction to correct for multiple testing.

2.7. Sample size

Based on previous data we observed a fourfold increase of NT-proBNP (preoperative 129.05 ± 160.13 to postoperative 482.49 ± 538.78 ng.L^{-1}) in patients undergoing moderate- to major open abdominal surgery [26]. Therefore, we assumed a postoperative maximum NT-proBNP of 482.49 ± 538.78 ng.L^{-1} in the 30% oxygen group. A previous study showed a 40% reduction in BNP concentration after the administration of supplemental oxygen [17]. Thus, we planned this study to detect a reduction of the postoperative maximum NT-proBNP of about 40%, which was based on previous trials and assumed to be clinically relevant, in the 80% oxygen group (assuming the same standard deviation). These assumptions correspond to a probability of about 0.4 that an observation in one group is less than an observation in the other group. Using a two-sided Wilcoxon rank-sum test with significance level 0.05, we calculated a needed sample size of 130 per group (260 in total) to detect the assumed effect with 80% power.

3. Results

260 over the age of 45 years at-risk for cardiovascular complications undergoing elective moderate- to high-risk noncardiac surgery were enrolled between December 2017 and December 2019 at the Medical University of Vienna. 130 patients were randomized to receive 80% oxygen and 130 patients to receive 30% oxygen. We ceased enrollment when our target sample size of 260 patients was obtained. Two patients in the 80% oxygen group were excluded from the study after randomization because surgery was postponed. (Fig. 1) Thus, 258 patients were included in the final analysis.

Patient characteristics and morphometric data, ASA physical status, comorbidities, long-term medication, type of surgery and preoperative laboratory parameters were similar between the two groups. (Table 1).

Similarly, intraoperative and postoperative characteristics including

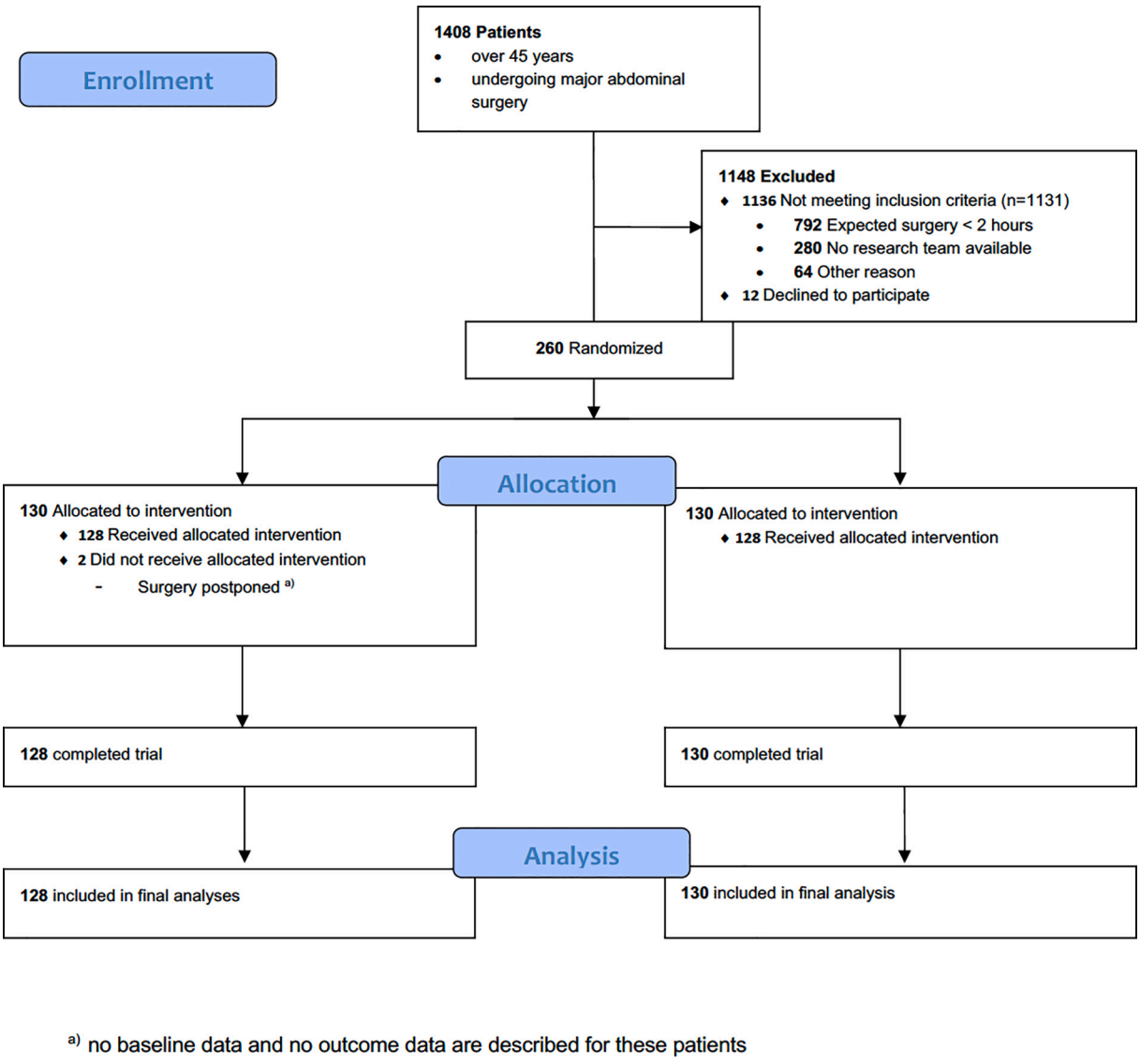

Fig. 1. Consort 2010 Flow Diagram.

duration of anesthesia and surgery, fluid management, anesthesia management, hemodynamic parameters, arterial blood gas analysis and postoperative characteristics were similar. (Table 2).

3.1. NT-proBNP

There was no significant difference of the postoperative NT-proBNP concentration between 80% and the 30% oxygen group ($p = 0.704$). The median maximum NT-proBNP concentration was 989 pg.dL^{-1} [499; 2005] in the 80% oxygen group as compared to 810 pg.dL^{-1} [409; 2386] in the 30% oxygen group (estimated effect: 159 pg.mL^{-1}, 95%CI -123, 431). (Table 4; Online supplement Appendix Fig. E2) One patient in the 80% oxygen group died within the first 3 days after surgery. The patients' maximum NT-proBNP value equaled the maximum measurable value of 35,000 pg.dL^{-1}.

3.2. Myocardial injury after noncardiac surgery (MINS)

The incidence of MINS was 20.2% (26 patients) in the 80% oxygen group and 18.3% (23 patients) in the 30% oxygen group (OR 0.887, 95% CI 0.475, 1.646; $p = 0.703$). One patient died within the first 3 days. The maximum Troponin T value for this patient was set to 10,000.

The median postoperative maximum Troponin T concentration was 20 ng.L^{-1} [14; 36] in the 80% oxygen group as compared to 19 ng.L^{-1} [14; 31] in the 30% oxygen group ($p = 0.361$). (Table 3) One patient developed pulmonary embolism and one patient developed deep surgical site infection within the study period (both patients were allocated to the 30% oxygen group). They were not categorized as having MINS.

3.3. Exploratory outcomes

The 30-day follow-up rate in the 80% oxygen group was 92.3% (4 patients died; 6 patients were lost to follow-up). The 30-day follow-up rate in the 30% oxygen group was 94.6% (2 patients died; 3 patients were lost to follow-up). Medical records were reviewed on 30 day after surgery. There was no difference in our exploratory outcomes during hospitalization and on 30-day after surgery. (Table 5). Because of the small number of events, no univariate and multiple regression models were performed.

There was no significant difference in the probability of death within 30 days between the 80% and 30% oxygen group. ($p = 0.684$). There was also no difference in the incidence of adverse events between the groups. (Table 5).

Table 1
Patient baseline characteristics.

	80% Oxygen (n = 128)		30% Oxygen (n = 130)	
Age, *yrs*	74	[70; 78]	74	[70; 78]
Among those >70 yrs	75	[72; 79]	76	[72; 79]
> 70 years, *no (%)*	103	(80.5)	100	(76.9)
Height, *cm*	171	[165; 176]	172	[168; 178]
Weight, *kg*	80	[69; 90]	78	[70; 90]
BMI, $kg.m^{-2}$	26.7	[24.0; 30.7]	25.8	[23.7; 29.1]
Sex, n (%)				
Women	47	(36.7)	38	(29.2)
Men	81	(63.3)	92	(70.8)
ASA physical status, n (%)				
I[a]	1	(0.8)	0	(0.0)
II	29	(22.7)	46	(35.4)
III	96	(75.0)	84	(64.6)
IV	2	(1.6)	0	(0.0)
Comorbidities, n (%)				
Hypertension	120	(93.8)	120	(92.3)
Coronary artery disease	33	(25.8)	31	(23.8)
Peripheral artery disease	19	(14.8)	20	(15.4)
Stroke	12	(9.4)	10	(7.7)
Congestive heart failure	8	(6.3)	10	(7.7)
Transient ischemic attack	3	(2.3)	8	(6.2)
Diabetes	39	(30.2)	35	(27.1)
Insulin use	12	(9.4)	8	(6.2)
Long-term medication, n (%)				
Beta blockers	62	(48.4)	65	(50.0)
ACE-I/ARB	70	(54.7)	73	(56.2)
Dihydropyridine	39	(30.4)	33	(25.4)
Thiazide	25	(19.5)	24	(18.5)
Loop diuretic	9	(7.2)	16	(12.3)
K^+ sparing	5	(3.9)	8	(6.2)
Statins	53	(41.4)	57	(43.8)
Thienopyridines/ASA	26	(20.3)	34	(26.2)
Oral anticoagulant	49	(38.3)	36	(27.7)
Alpha 2aAgonist	5	(3.9)	5	(3.9)
Type of Surgery, (%)				
Hepatobiliary	13	(10.2)	13	(10.0)
Colorectal	29	(22.7)	27	(20.8)
Pancreatic	17	(13.3)	20	(15.4)
Kidney	19	(14.8)	25	(19.2)
Prostate	13	(10.2)	18	(13.8)
Cystectomy	15	(11.7)	10	(7.7)
Gynecological	7	(5.5)	3	(2.3)
Other	15	(11.7)	13	(10.0)
Laboratory parameters				
Hemoglobin, *g/dL*	12.3	[10.8; 13.5]	12.8	[11.3; 13.9]
C-reactive protein, *mg/dL*	0.34	[0.11; 1.24]	0.27	[0.11; 0.74]
Creatinine, *mg/dL*	0.9	[0.8; 1.1]	0.9	[0.8; 1.1]
Natrium, *mmol/L*	140	[138; 142]	140	[138; 142]
Albumin, *g/dL*	37.5	[35.1; 40.4]	38.4	[35.1; 40.5]

Table 1**:** Summary characteristics are presented as counts, percentages of patients, and median, quartiles [25th percentile; 75th percentile]. BMI, body mass index; ASA physical status, American Society of Anaesthesiologists physical status; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] ASA physical status was corrected from II to I after enrollment into the study.

3.4. Univariate and multiple regression model

3.4.1. NT-proBNP

Preoperative NT-proBNP, preoperative Troponin T, age, sex, BMI, ASA physical status and diabetes were significant in the univariable regression model (Table 4). In the multiple logistic regression only preoperative NT-proBNP concentration and ASA physical remained significant. (online Supplement, Table E1).

3.4.2. MINS

Detailed results of the univariable logistic regression model are shown in the online supplement (Table E2). Preoperative Troponin T, preoperative NT-proBNP, age, BMI, and hypertension were significant in the univariable logistic regression model and were therefore included in the multiple logistic regression model. (online Supplement, Table E3) In the multiple logistic regression only preoperative Troponin T concentration remained significant. ($p < 0.001$).

The uni- (Table E4) and multiple (Table E5) regression models for the maximum Troponin T are provided in the online Supplement. (Fig. E3).

Table 2
Perioperative variables.

	80% Oxygen (n = 128)		30% Oxygen (n = 130)		p-value
Intraoperative					
Duration of anesthesia, min	268	[178; 363]	253	[194; 323]	0.684
Duration of surgery, *min*	194	[136; 255]	195	[128; 286]	0.926
Fluid management					
Crystalloid, *mL*	2173	[1382; 3298]	2373	[1611; 3315]	0.494
Blood Loss, *mL*	175	[0; 550]	200	[0; 500]	0.631
Urine Output, *mL*	245	[50; 400]	300	[200; 400]	0.071
Anesthesia management					
Fentanyl, *mcg*	1000	[800; 1400]	1000	[800; 1419]	0.744
Propofol, *mg*	150	[80; 193]	150	[100; 200]	0.266
Phenylephrine, *mcg*	0.28	[0.10; 0.54]	0.22	[0.08; 0.44]	0.233
Noradrenalin, *mg*	0.1	[0.0; 0.7]	0.2	[0.0; 0.7]	0.883
etSevo, *%*	1.2	[1.1;1.4]	1.2	[1.0;1.4]	0.364
FiO_2, *%*	80	[80;81]	33	[30;32]	
$etCO_2$, *mmHg*	35	[33;37]	35	[33;36]	0.147
Core temp, *C°*	36.3	[36.0; 36.6]	36.4	[36.1; 36.7]	0.194
Hemodynamic parameters					
HR, $beats.min^{-1}$	64	[58; 72]	65	[58; 71]	0.701
MAP, *mmHg*	81	[76; 86]	82	[78; 87]	0.254
SV, *mL*	71	[58; 79]	70	[59; 81]	0.245
CO, $L.min^{-1}$	4.4	[3.4; 5.3][a]	4.4	[3.7; 4.9][b]	0.535
CVP, *mmHg*	12	[9; 15]	11	[9; 13]	0.183
Arterial blood gas analysis					
pO_2, *mmHg*	314	[263; 356]	131	[108; 160]	<0.001
pCO_2, *mmHg*	42	[40; 45]	41	[39; 42]	<0.001
pH	7.37	[7.34; 7.40]	7.39	[7.37; 7.42]	0.002
BE	−0.7	[−1.9; 0.9]	−0.3	[−1.8; 1.1]	0.329
Hb, $g.dL^{-1}$	11.7	[10.3; 12.7]	11.8	[10.4; 12.9]	0.518
Lactate, $mmol.L^{-1}$	0.9	[0.7; 1.2]	0.9	[0.7; 1.1]	0.663
Glucose, $mg.dL^{-1}$	134	[117; 156]	126	[112; 148]	0.063
Postoperative Hemodynamic parameters					
HR, $beats.min^{-1}$	74	[64; 86]	73	[65; 84]	0.912
MAP, *mmHg*	93	[78; 95]	86	[84; 103]	< 0.001
Pain management					
Piritramide, *mg*	9	[6; 15]	11	[6; 15]	0.606
Arterial blood gas analysis					
pO_2, *mmHg*	166	[126; 226]	121	[101; 139]	< 0.001
Hb, $g.dL^{-1}$	11.6	[10.2; 12.7]	11.7	[10.6; 13.0]	0.272
Lactate, $mmol.L^{-1}$	1.2	[0.9; 1.7]	1.2	[0.9; 1.7]	0.910

Table 2**:** Summary characteristics of intraoperative measurements presented as medians [25th percentile; 75th percentile]. All p-values are for two-tailed Mann-Whitney-*U* tests. etSevo, end-tidal Sevoflurane concentration, FiO_2, fraction of inspired oxygen; $etCO_2$, end-tidal carbon dioxide concentration; HR, heart rate; MAP, mean arterial pressure, SV, stroke volume; CO, cardiac output; CVP, central venous pressure; pO_2, oxygen partial pressure; pCO_2, carbon dioxide partial pressure; BE, base excess; Hb, hemoglobin.

[a] Cardiac output of our patients was 85.2% of the time during surgery between 3.0 and 7.0 $L.min^{-1}$.

[b] Cardiac output of our patients was 87.3% of the time during surgery between 3.0 and 7.0 $L.min^{-1}$.

Table 3
Primary and secondary outcomes.

	Baseline		Postoperative		Postoperative day 1		Postoperative day 3		*Maximum NT-proBNP*	
NT-proBNP, pg.dL^{-1}										
80% Oxygen group	219	[93; 516]	229	[112; 514]	568	[301; 947]	779	[386; 1933]	989	[499; 2005]
30% Oxygen group	194	[93; 689]	201	[92; 707]	560	[248; 1185]	694	[309; 1768]	810	[409; 2387]
p-Values	0.667		0.612		0.842		0.351		0.704	
Troponin T, ng.dL^{-1}										
									MINS, n (%)	
n (80%/30%)										
80% Oxygen group	13	[9; 19]	13	[8; 20]	18	[12;27]	16	[11;26]	23	(18.3)
30% Oxygen group	14	[9; 21]	14	[8;21]	18	[12;29]	15	[10;23]	26	(20.3)
p-Values	0.652		0.350		0.953		0.184		0.703	
n (80%/30%)[a]	(127/130)		(126/127)		(124/122)		(115/115)			

Table 3**:** Summary characteristics are presented as counts and percentages for patients, median [25th percentile; 75th percentile]. All p-values are for logistic regression model (MINS) and for two-tailed Mann-Whitney-U tests (NT-proBNP, Troponin T) as appropriate.
[a] Number of patients with complete measurements according to their randomization.

Table 4
Maximum NT-proBNP – univariable regression models.

Variable	Comparison	Estimate	Lower CI	Upper CI	*p*-value
Random. group	80% *vs.* 30%	159.4	−112.633	431.433	0.252
Pre-Op NT-proBNP		1.236	0.768	1.704	<0.001
Pre-Op Troponin T		58.742	34.393	83.091	<0.001
Age		39.118	21.628	56.608	<0.001
Sex	Men *vs.* Women	−462.9	−867.097	−58.703	0.026
BMI		−35.306	−57.848	−12.764	0.002
BMI categorical	Overweight *vs.* Normal	−205.4	−535.673	124.873	0.224
	Obese *vs.* Normal	−392.9	−769.869	−15.931	0.042
	Obese *vs.* Overweight	−187.5	−508.177	133.177	0.253
ASA	3,4 *vs.* 1,2	359.7	144.299	575.101	0.001
Coronary artery disease	No *vs.* Yes	−406.9	−959.481	145.681	0.15
Peripheral arterial disease	No *vs.* Yes	14.3	−274.584	303.184	0.923
Stroke	No *vs.* Yes	213.5	−370.99	797.99	0.475
Congestive heart failure	No *vs.* Yes	−152.9	−2279.156	1973.356	0.888
Transient ischemic attack	No *vs.* Yes	−101.9	−1522.032	1318.232	0.888
Diabetes	No *vs.* Yes	270.6	32.616	508.584	0.027
Hypertension	No *vs.* Yes	−219.8	−602.985	163.385	0.262

Table 4: The regression coefficients (column estimate) and confidence intervals (columns Lower CI and Upper CI) were estimated using univariable median regression models. The corresponding p-values are presented. Random. group, randomization group; Pre-Op, preoperative; BMI, body mass index; ASA, American Society of Anaesthesiologists physical status.

3.5. Subgroup analysis

Detailed results of post-hoc subgroup analysis were provided in the online Supplement (Table E7, eFigure E1).

4. Discussion

Previous studies indicated that supplemental oxygen significantly affects hemodynamic parameters [13]. Specifically, supplemental oxygen leads to a significant decrease in heart rate, a significant decrease in stroke volume and cardiac output, and significantly increases blood pressure due to vasoconstriction [13]. However, this data is based on relatively small studies including healthy volunteers, patients undergoing cardiac surgery, as well as septic patients [13]. In contrast to this previous data, we included cancer patients at-risk for cardiovascular complications undergoing major abdominal surgery. We did not observe a significant effect of 80% *versus* 30% oxygen on intraoperative hemodynamic data; in detail, we there was no significant difference in intraoperative heart rate, blood pressure or cardiac output between both groups.

Table 5
Exploratory outcomes.

	80% Oxygen[a]		30% Oxygen[b]		*p*-value
Complication within hospitalization					
Cardiac failure	3	2.34	3	2.33	>0.999
Myocardial infarction	2	1.56	0	0.00	0.247
New onset of cardiac arrhythmias	5	3.91	4	3.10	0.749
Unplanned ICU admission	10	7.81	12	9.30	0.658
Reoperation	12	9.38	15	11.54	0.364
Respiratory failure	1	0.78	5	3.85	0.263
Bleeding	5	3.91	5	3.85	0.980
Complications after discharge within 30-days after surgery[b]					
Cardiac failure	2	1.64	0	0.00	0.239
Myocardial infarction	0	0.00	0	0.00	
New onset of cardiac arrhythmias	0	0.00	0	0.00	
Death at day 30	2	1.64	4	3.15	0.684

Table 5: Summary characteristics are presented as counts and percentages of patients. All p-values are for chi-squared tests.
[a] 80% oxygen group includes 122 patients (6 patients were lost to follow up on day 30 after surgery).
[b] 30% oxygen group includes 127 patients (3 patients were lost to follow up on day 30 after surgery).

Furthermore, perioperative administration of 80% *versus* 30% oxygen did not affect postoperative maximum NT-proBNP concentration and the incidence of MINS in high-risk patients undergoing major abdominal surgery. Maximum NT-proBNP concentration was greatly elevated postoperatively but similar between the 80% and 30% oxygen groups.

NT-proBNP concentrations on the first and third postoperative day increased up to 400% compared to baseline values in both groups. In contrast NT-proBNP values within 2 h after surgery were similar to preoperative baseline values in both groups. This might be explained that we performed standardized goal-directed fluid therapy according to a previously published algorithm [23], which might have reduced the risk of extensive fluid overload in perioperative period. On the other hand, fluid management on the ward was not controlled. We also controlled intraoperative blood pressure and avoided a mean arterial pressure < 65 mmHg [27]. In contrast we did not control postoperative blood pressure. It has been shown recently that patients experience prolonged and often severe hypotension or hypertension during the

postoperative period on the ward [28].

It is further well known that surgical stress leads to an increased inflammatory state postoperatively [29–31]. While the association between inflammation and cardiovascular events has been well studied in the non-surgical setting [32–35], the correlation between the postoperative inflammatory response and the release of cardiac biomarkers is not well studied yet. Therefore, it might be possible that inflammatory stress, specifically in the postoperative period, is a further important substrate for the formation and release of natriuretic peptides and Troponin T. We did not evaluate the association between postoperative blood pressure and inflammation on the release of postoperative cardiac biomarkers; therefore, we cannot rule out that these affected our results.

We also evaluated the effect of 80% *versus* 30% oxygen administration on the incidence of myocardial injury after noncardiac surgery (MINS). 80% oxygen did not significantly decrease the incidence of MINS in high-risk surgical patients. Our results are comparable with a sub-analysis of 1647 patients of an alternating interventional trial that included over 5000 patients (average age of 52 ± 17 years) and evaluated the effect of supplemental oxygen on surgical site infections (SSIs) as the primary outcome [8,12]. In this sub-analysis the authors did not detect any effect of supplemental oxygen on the composite outcome of MINS, cardiac arrest and 30-day mortality [12]. In contrast, a sub-analysis of 1386 patients of the PROXI trial, showed that intraoperative supplemental oxygen increased the long-term risk of acute coronary syndrome and furthermore increased the risk of myocardial injury [7,11]. The most apparent differences between the PROXI trial and our study addresses the intraoperative anesthesiologic management. In the PROXI trial perioperative fluid therapy was relatively restrictive [36]. In contrast, we performed goal-directed fluid therapy, that was shown in a previous study to be associated with a significant increase in microcirculatory blood flow and tissue oxygen tension [37]. Furthermore, perioperative hemodynamic data such as blood pressure and cardiac output were not reported in the PROXI trial, therefore it is difficult to determine whether these patients were hypotensive intraoperatively [7]. We tightly controlled intraoperative blood pressure, resulting in a median MAP of around 80 mmHg in both groups. This might explain that we did not observe a significant difference in MINS between our groups.

Nevertheless, there are studies indicating that the administration of higher oxygen concentrations has harmful effects [38,39]. For example a recent meta-analysis including over 16,000 acutely ill patients, showed that a liberal oxygen therapy increased mortality [38]. Another study showed that the administration of supplemental oxygen significantly increased the infarct size in normoxic patients having ST-elevated myocardial infarction [39]. The most important differences of these studies as compared to our trial were the study population, the study setting and the time-point of oxygen administration. Specifically, critically ill (including sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, and patients who had emergency surgery) and patients with acute signs of ST-elevated myocardial infarction were included [38,39]. Even of more importance might be the fact that oxygen was administered when cardiovascular injury was already present. In contrast, we gave supplemental oxygen immediately after intubation, at a time before oxygen supply and demand mismatch occurred. That this might be one reason that supplemental oxygen has different effects in critically ill patients as compared to the surgical setting. In this context, it seems very important to differentiate between acute critically ill patients and patients undergoing surgery. Therefore, we strongly assumed that a preemptive supplemental oxygen administration might result in a reduced incidence of myocardial injury.

We mainly included elderly patients with mostly more than one cardiovascular risk factor, which might explain our fairly high rate of MINS (18.3% in the 80% group *vs* 20.3% in the 30% group; $p = 0.703$). Overall, 70% of our study population was over 70 years of age and more than 90% had preoperative hypertension requiring medical treatment. Several, mainly retrospective, studies in recent years point out that perioperative hyper- or hypotension increases the incidence of postoperative MINS [40,41]. Moreover, bleeding is a major risk factor for myocardial injury [42]. Our rate of postoperative clinically relevant bleedings (defined as requiring reoperation) was approximately 4% of the patients in both groups, which is consistent with a previous study [43]. However, all of our patients were cancer patients and approximately half of our patients showed preoperative mild anemia (defined as hemoglobin level < 12 g/dL) [44]. In this context a recent retrospective study has shown that a preoperative hemoglobin level of lower than 12.2 g/dL was significantly associated with a higher rate of MINS [45]. In our study there was no significant difference in preoperative hemoglobin levels between both groups, thus it might not have influenced our results. Moreover, our preoperative hemoglobin levels reflect clinical routine. Nevertheless, the effect of preoperative correction of anemia still needs to be studied.

Our multiple regression analysis showed that patients with an ASA physical status classification of III or IV had significantly higher postoperative NT-proBNP values and an increased risk for MINS as compared to patients with ASA physical status I or II. Furthermore, elevated preoperative NT-proBNP concentration is associated with significantly higher postoperative NT-proBNP concentrations. Also, the risk of MINS significantly increased when preoperative Troponin T values were elevated, which is consistent with previous studies [1,20]. This emphasizes the importance of preoperative cardiac biomarker assessment specifically in high-risk surgical patients.

A recent study showed that acute postoperative pain was significantly associated with the incidence of MINS [46]. Specifically, high TWA pain scores during the first three postoperative days significantly increased the risk of myocardial ischemia [46]. In our study, pain was controlled according to local clinical standard of care. In detail, at the end of surgery all patients received metamizole or a non-steroidal anti-inflammatory drug; when visual analog pain score (VAS) was >4, piritramide was administered additionally. At the PACU there was no significant difference in postoperative heart rate between the groups. Furthermore, we did not observe a significant difference in postoperative opioid requirements between the 80% and 30% oxygen group. However, mean arterial pressure was significantly higher in the 80% oxygen group, which might be explained by the vasoconstricting effects of supplemental oxygen [13]. Pain treatment on the ward was performed by the attending physician and was not recorded. However, postoperative pain management was no part of our study protocol, consequently we did not evaluate and record VAS. Therefore, we cannot rule that postoperative pain management might have affected our results.

Our study has several limitations. We did not measure NT-proBNP and Troponin T values on the second day after surgery. The VISION trial (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation), the to-date largest perioperative study in 40,000 patients, indicated that 80% of MINS events occur during the first 48 h after surgery [1]. It is possible that we missed some patients with MINS on the second postoperative day. However, our incidence of MINS is fairly high and our rate of postoperative complications as well as our mortality rate are consistent with previous studies [1]. Furthermore, we did neither control nor record blood pressure and fluid management on the ward, which might have influenced our results. It is fairly well established that the incidence of postoperative hypotension is high, and that postoperative hypotension is an important risk factor for MINS [40]. As our study is a randomized trial postoperative hypotension most likely was similar in both study groups.

Furthermore, our clinicians in the operating rooms were not blinded to the allocated oxygen concentration, which could have influenced intraoperative anesthetic management. However, anesthesia and fluid management were standardized and most importantly were similar in both groups. Furthermore, postoperative blood samples and outcomes were evaluated by separate teams of investigators, who were blinded to randomization and oxygen administration.

Last but not least we evaluated the effect of supplemental oxygen on surrogate parameters for cardiac function and myocardial perfusion. It might of great interest to test the effect of oxygen on a composite outcome of cardiovascular complications. We observed no significant effect on our exploratory outcomes. However, our sample size was too small to draw further conclusions. Nevertheless, our data provide a valuable overview on the effect of oxygen on the perioperative course on cardiac biomarkers and might serve as a basis for future well-powered outcome studies.

In summary, perioperative administration of 80% oxygen did not significantly decrease maximum NT-proBNP concentration within the first three postoperative days. Additionally, there was no significant difference in the incidence of MINS between 80% and 30% oxygen administration. Therefore, it is unlikely that the administration of supplemental oxygen has an effect on the postoperative release of cardiac biomarkers in patients at-risk for cardiovascular complications undergoing major abdominal surgery.

Authors statement

Christian Reiterer: Conceptualization, Methodology, Funding acquisition, Writing – original draft, Writing – review & editing.

Barbara Kabon: Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Alexander Taschner: Data Acquisition, Writing – review & editing.

Markus Falkner von Sonnenburg: Data Curation, Investigation, Writing – review & editing.

Alexandra Graf: Formal analysis, Software, Visualization.

Nikolas Adamowitsch: Data curation, Investigation, Writing – review & editing.

Patrick Starlinger: Conceptualization, Writing – review & editing.

Julius Goshin: Data curation, Investigation.

Melanie Fraunschiel: Data curation, Software.

Edith Fleischmann: Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Reproducible science

Full protocol available at: barbara.kabon@meduniwien.ac.at. Raw data available at: barbara.kabon@meduniwien.ac.at

Disclosures

Medical-Scientific Fund of the Mayor of Vienna (Nr. 18058).
Medical University of Vienna.
The authors declare no competing interests.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110379.

References

[1] Devereaux PJ, Biccard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA J Am Med Assoc 2017;317(16):1642–51. https://doi.org/10.1001/jama.2017.4360.

[2] Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA Cardiol 2017. https://doi.org/10.1001/jamacardio.2016.4792.

[3] Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. Br J Anaesth 2004;93(1):9–20. https://doi.org/10.1093/bja/aeh147.

[4] Weissmann C. The metabolic response to stress: an overview and update. Anesthesiology. 1990;73:308–27.

[5] Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. Cmaj. 2005;173(6):627–34. https://doi.org/10.1503/cmaj.050011.

[6] Greif R, Akca O, Horn E-P, Kurz A, Sessler DI. Group for the OR. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342(3):161–7. https://doi.org/10.1056/nejm200001203420303. Accessed August 16, 2013.

[7] Meyhoff C, Wetterslev J, Jorgensen L, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery the PROXI trial. JAMA J Am Med Assoc 2009;302(14):1543–50. http://jama.ama-assn.org/content/302/14/1543.short. Accessed August 20, 2013.

[8] Kurz A, Kopyeva T, Suliman I, et al. Supplemental oxygen and surgical-site infections: an alternating intervention controlled trial. Br J Anaesth 2018;120(1):117–26. https://doi.org/10.1016/j.bja.2017.11.003.

[9] Belda JF, Aguilera L, Garcia De La Asuncion J, et al. Supplemental perioperative oxygen and the risk of surgical wound infection. JAMA J Am Med Assoc 2005;294(16):2035–42. http://jama.ama-assn.org/content/294/16/2035.short. [Accessed 20 August 2013].

[10] Pryor KO, Fahey TJI, Lien CA, Goldstein PA. Surgical site infection and the routine use of perioperative Hyperoxia in a general surgical population - a randomized controlled trial. JAMA J Am Med Assoc 2004;291(1):79–87.

[11] Fonnes S, Gögenur I, Søndergaard ES, et al. Perioperative hyperoxia - long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial. Int J Cardiol 2016;215:238–43. https://doi.org/10.1016/j.ijcard.2016.04.104.

[12] Ruetzler K, Cohen B, Leung S, et al. Supplemental intraoperative oxygen does not promote acute kidney injury or cardiovascular complications after noncardiac surgery: subanalysis of an alternating intervention trial. Anesth Analg 2019;130(4):933–40. https://doi.org/10.1213/ane.0000000000004359.

[13] Smit B, Smulders YM, van der Wouden JC, Oudemans-van Straaten HM, Spoelstra-de Man AME. Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis. Crit Care 2018;22(1):1–10. https://doi.org/10.1186/s13054-018-1968-2.

[14] Kemming GI, Meisner FG, Meier J, et al. Hyperoxic ventilation at the critical hematocrit: effects on myocardial perfusion and function. Acta Anaesthesiol Scand 2004;48(8):951–9. https://doi.org/10.1111/j.0001-5172.2004.00460.x.

[15] Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J 2009;158(3):371–7. https://doi.org/10.1016/j.ahj.2009.05.037.

[16] Meier J, Kemming GI, Kisch-Wedel H, Wölkhammer S, Habler OP. Hyperoxic ventilation reduces 6-hour mortality at the critical hemoglobin concentration. Anesthesiology. 2004;100(1):70–6. https://doi.org/10.1097/00000542-200401000-00014.

[17] Shigemitsu M, Nishio K, Kusuyama T, Itoh S, Konno N, Katagiri T. Nocturnal oxygen therapy prevents progress of congestive heart failure with central sleep apnea. Int J Cardiol 2007;115(3):354–60. https://doi.org/10.1016/j.ijcard.2006.03.018.

[18] Rodseth RN, Biccard BM, Le Manach Y, et al. The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patien. J Am Coll Cardiol 2014;63(2):170–80. https://doi.org/10.1016/j.jacc.2013.08.1630.

[19] Rodseth RN, Biccard BM, Chu R, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. Anesthesiology. 2013;119(2):270–83. https://doi.org/10.1097/ALN.0b013e31829083f1.

[20] Duceppe E, Patel A, Chan MTV, et al. Preoperative N-terminal pro-B-type natriuretic peptide and cardiovascular events after noncardiac surgery: a cohort study. Ann Intern Med 2019:1–10. https://doi.org/10.7326/M19-2501.

[21] Botto F, Alonso-Coello P, Chan MTV, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014;120:564–78. https://doi.org/10.1097/ALN.0000000000000113.

[22] Reiterer C, Kabon B, von Sonnenburg MF, et al. The effect of supplemental oxygen on perioperative brain natriuretic peptide concentration in cardiac risk patients - a protocol for a prospective randomized clinical trial. Trials. 2020;21(1):400. https://doi.org/10.1186/s13063-020-04336-9.

[23] Gan TJ, Sooitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology. 2002;97(4):820–6.

[24] Feldheiser A, Conroy P, Bonomo T, Cox B, Ruiz Garces T, Spies C. Development and feasibility study of an algorithm for intraoperative goaldirected haemodynamic management in noncardiac surgery. J Int Med Res 2012;40(4):1227–41. https://doi.org/10.1177/147323001204000402.

[25] The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION). Writing Group on behalf of TV events I noncardiac S patIents cOhort evaluatioN (VISION) I. Myocardial injury after noncardiac surgery. Anesthesiology 2014;120:56. https://doi.org/10.1097/aco.0000000000000336.

[26] Reiterer C, Kabon B, Taschner A, Zotti O, Kurz A, Fleischmann E. A comparison of intraoperative goal-directed intravenous administration of crystalloid versus colloid solutions on the postoperative maximum N-terminal pro brain natriuretic peptide in patients undergoing moderate- to high-risk noncardiac surgery. BMC Anesthesiol 2020;20(1):1–9. https://doi.org/10.1186/s12871-020-01104-9.
[27] Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery a retrospective cohort analysis. Anesthesiology. 2017;1:47–65.
[28] Turan A, Chang C, Cohen B, et al. Incidence, Severety, and detection of blood pressure perturbations after abdominal surgery - a prospective blinded observational study. Anesthesiology. 2019;130(4):550–9.
[29] Gaudino M, Andreotti F, Zamparelli R, et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation 2003;108(10 Suppl). https://doi.org/10.1161/01.cir.0000087441.48566.0d.
[30] Rettig TCD, Verwijmeren L, Dijkstra IM, Boerma D, Van De Garde EMW, Noordzij PG. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. Ann Surg 2016;263(6):1207–12. https://doi.org/10.1097/SLA.0000000000001342.
[31] Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg 2006;93(9):1069–76. https://doi.org/10.1002/bjs.5454.
[32] Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. N Engl J Med 2000;343(16):1139–47. https://doi.org/10.1056/nejm200010193431602.
[33] Ridker PM, Lüscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J 2014;35(27):1782–91. https://doi.org/10.1093/eurheartj/ehu203.
[34] Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet. 2018;391(10118):319–28. https://doi.org/10.1016/S0140-6736(17)32814-3.
[35] Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. N Engl J Med 2020;383(19):1838–47. https://doi.org/10.1056/nejmoa2021372.
[36] Meyhoff CS, Wetterslev J, Jorgensen LN, et al. Perioperative oxygen fraction - effect on surgical site infection and pulmonary complications after abdominal surgery: a randomized clinical trial. Rationale and design of the PROXI-trial. Trials. 2008;9:1–13. https://doi.org/10.1186/1745-6215-9-58.
[37] Kimberger O, Arnberger M, Brandt S, et al. Goal-directed colloid administration improves the microcirculation of healthy and perianastomotic colon. Anesthesiology. 2009;110(3):496–504. https://doi.org/10.1097/ALN.0b013e31819841f6.
[38] Chu DK, Kim LHY, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018;391(10131):1693–705. https://doi.org/10.1016/S0140-6736(18)30479-3.
[39] Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation. 2015;131(24):2143–50. https://doi.org/10.1161/CIRCULATIONAHA.114.014494.
[40] Sessler DI, Meyhoff CS, Zimmerman NM, et al. Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: a substudy of the POISE-2 trial. Anesthesiology. 2018;128(2):317–27. https://doi.org/10.1097/ALN.0000000000001985.
[41] Maheshwari K, Turan A, Mao G, et al. The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. Anaesthesia. 2018;73(10):1223–8. https://doi.org/10.1111/anae.14416.
[42] Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery a cohort study. Ann Intern Med 2011;154:523–8.
[43] Devereaux PJ, Duceppe E, Guyatt G, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. Lancet. 2018;391(10137):2325–34. https://doi.org/10.1016/S0140-6736(18)30832-8.
[44] Muñoz M, Gómez-Ramírez S, Campos A, Ruiz J, Liumbruno GM. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus 2015;13(3):370–9. https://doi.org/10.2450/2015.0014-15.
[45] Kwon J-H, Park J, Lee S-H, et al. Pre-operative anaemia and myocardial injury after noncardiac surgery. Eur J Anaesthesiol 2021. https://doi.org/10.1097/eja.0000000000001421.
[46] Turan A, Leung S, Bajracharya GR, et al. Acute postoperative pain is associated with myocardial injury after noncardiac surgery. Anesth Analg 2020;131(3):822–9. https://doi.org/10.1213/ANE.0000000000005033.