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Decrease in Tissue Oxygenation as Predictor for Myocardial Injury in Patients Undergoing Major Spine Surgery: A Prospective Cohort Study

Katrine Feldballe Bernholm, MD[1,2], Christian S. Meyhoff, MD, PhD[2,3,4], Philip Bickler, MD, PhD[1]*

[1]Department of Anesthesia and Perioperative Care, University of California, San Francisco, USA

[2]Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

[3]Copenhagen Center for Translational Research, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark

[4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

* Corresponding author. Email: bernholm3@hotmail.com

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Abstract

Objective: To describe the association between intraoperative tissue oxygenation and postoperative troponin elevation in patients undergoing major spine surgery. We hypothesized that a decrease in intraoperative muscle tissue oxygenation (SmO_2) was associated with the peak postoperative cardiac troponin value.

Design: This is a prospective cohort study.

Setting: Single-center, University of California San Francisco Medical Center.

Participants: Seventy adult patients undergoing major elective spine surgery.

Primary and secondary outcome measures: High-sensitivity troponin T (hsTnT) was measured in plasma pre-operatively and on the first and second day after surgery to assess the primary outcome of peak postoperative hsTnT. Secondary outcomes included MINS and intensive care unit (ICU) admission within 30 days. Cerebral (ScO_2) and muscle (SmO_2) tissue oxygenation was measured continuously with near-infrared spectroscopy during surgery. The primary exposure variable was time-weighted area under the curve (TW AUC) for SmO_2.

Results: Mean age was 65 (33-85) years and 59% were female. No significant association was found between TW AUC for SmO_2 and peak hsTnT (Spearman's correlation, r_s=0.17, p=0.16). A total of 28 (40%) patients had MINS. ICU admission occurred in 14 (40%) in lower vs. 25 (71%) in upper half of patients based on TW AUC for SmO_2, p=0.008.

Conclusions: Decrease in SmO_2 was not a statistically significant predictor for peak troponin value following major spine surgery but is a potential predictor for other postoperative complications.

Trial registration: Clinicaltrials.gov identifier: NCT03518372.

Article Summary

Strengths and limitations of this study

- Prospective observational study including 70 patients undergoing major spine surgery
- Contributing knowledge to potential predictors for myocardial injury and clinical implications of tissue oxygenation monitoring
- Applying muscle tissue oxygenation as primary predictor, decreasing risk of autoregulation modification of outcomes
- There is no clinical consensus of absolute threshold for tissue hypoxemia, thus population median for muscle tissue oxygenation was used as cut-off in this study.

Introduction

Major non-cardiac surgery is associated with significant risks of postoperative complications which are sometimes asymptomatic such as covert stroke[1] and myocardial infarction and injury.[2] Cardiovascular events are the leading cause of morbidity and mortality[3] with myocardial injury after non-cardiac surgery (MINS) being a major contributor to further postoperative complications.[4–7] MINS can be diagnosed from elevated postoperative high-sensitivity cardiac troponin, in the absence of non-ischemic factors for troponin elevation.[8] The 30-day mortality is increased up to eight-fold in patients with covert stroke compared to matched controls[9] and stroke occurs in 9% of patients with MINS, making it a substantial public health problem.[10] Peak postoperative cardiac troponin has a linear association with 30-day mortality.[7] Each year, 8 million surgical patients worldwide suffer from MINS but there is sparse knowledge about triggering causes and contributing factors to the magnitude of peak postoperative cardiac troponin.[5,11]

Intraoperative tissue desaturation is common in patients undergoing major spine surgery[12] probably because of the substantial blood loss and hemodynamic changes that occur in this type of operation. Tissue oxygenation (StO_2) can be measured non-invasively with near-infrared spectroscopy (NIRS). Previous studies found that a decrease in intraoperative StO_2 was associated with wound infection, stroke and renal failure,[13] and that decrease in muscle tissue oxygenation (SmO_2) was a stronger predictor for these complications than cerebral tissue oxygenation (ScO_2) in spine surgery.[12] However, current knowledge of how tissue oxygenation affects other important clinical outcomes, including MINS, is lacking. In this prospective cohort study we hypothesized that a decrease in SmO_2 was associated with higher peak postoperative high-sensitivity Troponin T (hsTnT). The primary exposure variable was time-weighted area under the curve (TW AUC) for SmO_2 and the primary outcome was peak postoperative hsTnT. This study was conducted with the aim of examining the association

between intraoperative tissue oxygenation and postoperative troponin elevation in patients undergoing major spine surgery.

Methods

This prospective cohort study was conducted at the University of California, San Francisco (UCSF) with Clinicaltrials.gov identifier: NCT03518372. The study was approved by the local Institutional Review Board (IRB 14-12996) and both verbal and written consent was obtained from all participants before surgery. This manuscript adheres to the applicable STROBE guidelines.

Patients

The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018. The surgeries selected were scheduled to last for more than two hours and included instrumentation. Exclusion criteria were: American Society of Anesthesiologists Physical Status Classification System score (ASA)>IV, surgery for tumor or infection, emergent or urgent surgery.

Data collection

Patient characteristics, comorbidities, preoperative physical status and postoperative complications were extracted from the electronical medical record (KFB). Data was collected at two time-points: Prior to surgery and 30 days after surgery. A follow-up phone call to the patient was made 30 days after surgery to verify postoperative outcomes. Baseline values were defined as the pre-incision value. Intraoperative values were defined as data from incision to end of procedure when last suture was placed. Study data were managed using the REDCap electronic data capture tools hosted at UCSF.

Tissue oximetry

Tissue oxygenation was monitored using a tissue oximeter based on near-infrared spectroscopy (NIRS) (FORE-SIGHT Elite, CASMED, Inc., Branford, Connecticut, USA). Cerebral and leg muscle oxygenation was monitored via two cables connected to adhesive probes provided by the manufacturer. Probes were placed after tracheal intubation and a baseline was measured from placing of probe to incision. One probe was placed on the left side on the upper forehead to monitor one-sided frontal cortex ScO_2. The second probe was placed on the left tibialis anterior muscle, four fingers below the tibial tuberosity and two fingers lateral to the anterior edge of the tibial shaft, to monitor the SmO_2 of the lower leg muscle. The oximeter generated a data point every 2 seconds. The anesthesia team was blinded to the oximeter. Data from the oximeter were used for tissue oxygenation indices derivation. Indices were maximum, minimum, median and time-weighted area under the curve (TW AUC) for SmO_2 and ScO_2 respectively. The primary exposure variable was TW AUC for SmO_2. TW AUC was calculated for each participant as the area below the intraoperative median for the study population and divided by length of surgery. This was chosen because there is no international consensus on a universal baseline level or normal range for tissue oxygenation.

Troponin measurements

A total of three blood samples for hsTnT were drawn. First sample was drawn by the anesthesiologist in the operating room after placement of the arterial line prior to surgery. Second and third sample were drawn by a phlebotomist or nurse the first and second day after surgery, respectively. After the blood was drawn, the sample was centrifuged immediately and the plasma was divided into two cryo collecting tubes and placed in a -80 ºCelsius freezer for storage. All plasma samples were sent to a specialized laboratory at Hennepin Medical Center (Minneapolis, MN, USA) to be analyzed for the Roche 5th generation, Elecsys hsTnT

assay after the study was completed. The data collector was blinded to the results of hsTnT and laboratory personnel analyzing the blood samples were blinded to patient data. Medical records and perioperative information (e.g. ECG, laboratory values) were reviewed for patients with troponin elevation, to exclude a non-ischemic etiology.[8]

Outcomes

The primary outcome was defined as postoperative peak high-sensitivity cardiac troponin T (hsTnT). A secondary related outcome was MINS, initially defined as hsTnT ≥14 ng/L[14] with factors for non-ischemic etiology excluded (e.g. sepsis, kidney failure, heart failure). This MINS definition was registered at clinicaltrials.gov, but during the course of the study and prior to hsTnT analysis of the blood samples, new data was published, where MINS was defined as an elevated postoperative hsTnT (i.e. 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L) with factors for non-ischemic etiology excluded (e.g. sepsis, kidney failure, heart failure).[8] We therefore updated the protocol to the latter and current MINS definition. Other secondary outcomes were myocardial infarction, non-fatal cardiac arrest, new-onset arrhythmia (defined as new atrial fibrillation or other treatment requiring arrhythmia), heart failure, transient cerebral ischemia, symptomatic stroke, sepsis, surgical site infection, pulmonary complications (including pulmonary infection, pneumothorax, atelectasis, pulmonary embolus and other pulmonary complication), creatinine elevation (>1.3 mg/dL for men and >1.1 mg/dL for women), intensive care unit (ICU) admission, length of hospital stay and mortality, all within 30 days after surgery. In addition, we analyzed a composite outcome that consisted of all above mentioned postoperative complications.

Sample size

Sample size calculations were based on clinical data and previous studies investigating tissue oxygenation as an outcome for postoperative complications.[12,13] These studies evaluated all types of complications as primary outcome. Mean (SD) TW AUC for SmO_2 was 1.59 %*min*h^{-1} (2.35).[12] We estimated a minimal clinically relevant difference to be a 36% increase in TW AUC for SmO_2 for participants with high peak hsTnT (with a cut-off of 14 ng/L based on the 99th percentile of a healthy population[15]) compared to participants with low peak hsTnT. Using a power of 80% and a significance level of 0.05, a sample size of 68 participants for this study was needed. We anticipated a low number of drop-outs, as the study design was observational, resulting in a total sample size of 70 participants.

Statistical analysis

Results are presented as mean±SD and median (interquartile range, IQR) when appropriate. Postoperative outcomes were compared stratifying the study population in two groups by median TW AUC for SmO_2. Comparison between groups were based on Chi-squared tests for categorical variables, ANOVA and Wilcoxon rank sum test.

The primary analysis of the association between TW AUC for SmO_2 and peak hsTnT was tested by Spearman correlation analysis. Univariable and multivariable logistic regression models were used in secondary analyses to examine the associations of baseline characteristics, intraoperative variables and StO_2 indices with higher peak hsTnT which was dichotomized in high/low categories using median peak hsTnT in the study population as cut-off. Univariable and multivariable logistic regression was used to test the association between StO_2 indices and MINS and the adjusted prediction for TW AUC for SmO_2 and MINS was calculated. Variables for adjustment in the multivariable analyses were age, sex, body mass index (BMI), smoking, diabetes, hypertension, previous stroke, chronic lung disease,

arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate.

Stata Statistical Software (release 15; StataCorp LP, College Station, TX, USA) was used for all analyses.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

Results

A total of 70 patients undergoing spine surgery was included in this prospective cohort study. Mean age was 65 (33-85) years and 41 (59%) participants were female. The median estimated blood loss was 753 (IQR 400;1400) mL. A summary of patient characteristics, medical history, surgical information and values for tissue oxygenation are found in Table 1.

Incidence of MINS and major outcomes

The median peak hsTnT was 19 (IQR 10;30) ng/L and based on a hsTnT of 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L, 28 (40%) participants had MINS (Table 2). The number of participants with any postoperative complications were 41 (59%) and when MINS was included as a complication, 52 (74%) of participants had one or more postoperative complications (Table 2). Estimated blood loss and length of surgery was associated with MINS (odds ratio, OR (95% confidence interval, CI): 1.001 (1.000-1.002), p=0.002 and 1.007 (1.002-1.011), p=0.004, respectively).

Relationships of tissue oxygenation to MINS and other outcomes

In the univariable correlation analysis of TW AUC for SmO_2 and peak hsTnT, no significant association was found (r_s=0.17, p=0.16, Figure 1). There was a statistically significant association between higher TW AUC for SmO_2 and the composite outcome of postoperative complications (participants in lower half: 21 (60%) vs. participants in upper half: 31 (89%), p=0.006, Table 2) but when logistic regression was performed, this association was not significant. Furthermore, a statistically significant association between higher TW AUC for SmO_2 and ICU admission was found (participants in lower half: 14 (40%) vs. participants in upper half: 25 (71%), p=0.008, Table 2). There were no other statistically significant differences in outcomes between the two groups based on median TW AUC for SmO_2. When

testing the StO_2 indices as predictors for higher peak hsTnT by logistic regression, the univariable analysis found that for every one percent increase in median and maximum SmO_2, the odds of having high peak hsTnT decreased (OR (95% CI): 0.93 (0.87-0.996), p-value=0.039 and 0.92 (0.85-0.99), p=0.025, respectively, Table 3). After multivariable adjustment for baseline and clinical variables, median and maximum SmO_2 were not independent predictors for higher peak hsTnT (Table 3). None of the StO_2 indices were found to be significant predictors for MINS (Table 3). Adjusted predicted probability was calculated based on univariable logistic regression and showed increasing probability for MINS with increasing TW AUC for SmO_2 (Figure 2) albeit this was not statistically significant (OR (95% CI): 1.00 (0.99-1.01), p=0.74). Although this was not systematically assessed for the purpose of this study, only one participant presented with ischemic symptoms on the first two postoperative days according to medical records. This patient was not diagnosed with clinical myocardial infarction after examination, although hsTnT was 31 ng/L.

Discussion

In a prospective cohort study of 70 participants, we investigated intraoperative tissue oxygenation as predictor for myocardial injury after spine surgery. We found that muscle and cerebral tissue oxygenation were not independent predictors for elevated high-sensitivity troponin T or MINS. However, in exploratory analyses, some other indices for SmO_2 were associated with higher peak hsTnT, whereas ScO_2 indices were not.

Tissue oxygenation is a result of the oxygen supply and demand of the specific tissue and is determined by multiple physiological factors including oxygen saturation, hemoglobin concentration and cardiac output.[16] Measurement of tissue oxygenation with NIRS has been investigated in previous studies as predictor for a number of different outcomes. Several studies have examined cerebral oxygenation in patients undergoing cardiac surgery, whereas few studies have investigated muscle tissue oxygenation as predictor for clinical outcomes. In patients undergoing cardiac surgery, ScO_2 was found to be associated with stroke, cognitive decline, length of hospital stay and mortality.[17,18] One study found that decrease in ScO_2 was not a predictor for delirium in elderly patients.[19] A recent meta-analysis of 10 trials with a total of 1466 patients, found that NIRS-based algorithms for ScO_2 did not reduce mortality or organ injury affecting the heart, brain or kidneys.[20] Despite the lack of evident benefit for ScO_2-guided clinical algorithms, ScO_2 monitoring is routinely used in cardiac surgery. Cerebral and muscle tissue have different physiological characteristics. *Meng et al.*[12] found that SmO_2 was a stronger predictor than ScO_2 for composite postoperative outcomes, including myocardial injury, stroke, pulmonary complications and creatinine elevation. Although findings in the current study were statistically insignificant, the exploratory analyses yielded a stronger association between SmO_2 and outcomes as compared to ScO_2. This aligns with the theory that SmO_2 is a leading indicator for global desaturation due to low

autoregulation in muscle tissue compared with the higher level of autoregulation in cerebral tissue.[21] The importance of preserved cerebral autoregulation is substantial. Brain tissue is more sensitive to hypoxia than skeletal muscle.[16] One study showed that impaired cerebrovascular autoregulation was associated with increased morbidity and mortality within 30 days from surgery in patients undergoing major non-cardiac surgery.[22] A study in healthy subjects suggested SmO_2 to be an early indicator for impending cardiovascular collapse and showed that SmO_2 declined in parallel with stroke volume.[23] Perfusion of muscle tissue follows the same linearity in decline with decreasing cardiac output whereas cerebral tissue perfusion only decreases approximately one third of cardiac output.[24] This study found TW AUC for SmO_2 to be almost three times larger than TW AUC for ScO_2 (98 vs. 33 %*min*h^{-1}) indicating autoregulation in brain tissue. Of note, spine surgery patients at UCSF almost all receive anesthetics that include very low amounts of inhalational anesthetics, probably preserving brain autoregulation of blood flow. Despite these findings, the clinical implications of SmO_2 monitoring is still yet to be determined.

StO_2 was not statistically significant associated with MINS in the current study but other indicators of supply-demand mismatch, i.e. estimated blood loss and length of surgery, were significantly associated with MINS and peak hsTnT. These are established predictors for MINS[25] and contributes to the understanding of the pathophysiology for elevated troponin.[26] In general, the majority of MINS are undetected (80%) as patients do not have ischemic symptoms.[4,10] In this study only one participant presented with ischemic symptoms. The type of surgery the participants underwent was comprehensive and many participants were treated with strong analgesics postoperatively which could be a contributing factor to the lack of ischemic symptoms in the participants with MINS. The incidence of MINS among the participants in this study was 40%. In comparison the general incidence of MINS in patients undergoing non-cardiac surgery is 8%[4] but this is not restricted to major surgery only.

Study limitations

As this was an observational cohort study it was not designed to determine causality between tissue oxygenation and postoperative myocardial injury. The study was not powered for all secondary outcomes, as we based the power calculation on a study with the outcome composite postoperative complications that included less severe complications (constipation, oliguria etc.).[12]

We found a high incidence of MINS in this study but the number of serious outcome events (e.g. death, stroke, non-fatal cardiac, myocardial infarction) were sparse in the 30-day follow-up period. The participants underwent spine surgery which was not emergent, conducted as cancer treatment/tumor resection or indicated by any life-threatening condition. Thus, it is possible that participants were in a better physical condition when scheduled for this type of elective surgery than for other major non-cardiac surgical procedures.

The NIRS method is non-invasive and tracks tissue oxygenation continuously. However, limitations in regards to the technology has been presented and includes bias regarding skin pigmentation, gender and assumed mixture of venous and arterial blood.[27] Inter-individual differences in saturation contributes to the difficulty of determining an absolute threshold for tissue hypoxia. In the calculation of the primary predictor of TW AUC for SmO_2 we used the population median for intraoperative SmO_2 as cut-off. The choice of cut-off should be considered when interpreting results of studies investigating the impact of tissue oxygenation.

In summary, tissue oxygenation was not a statistically significant predictor for peak postoperative high-sensitivity troponin but is a potential predictor for other postoperative complications. Future studies should focus on determining a threshold for tissue oxygenation taking inter-individual factors into account. The frequency of MINS was high (40%) and related to blood loss, suggesting supply-demand mismatch etiology in spine surgery. Tissue

oxygenation did not have the power to predict myocardial injury but other intraoperative indicators for supply-demand mismatch should be considered as potential predictors for MINS in future studies.

Author contributions

KFB: Conception and design, acquisition, analysis and interpretation of data, drafting, critical revision and final approval of the manuscript. CSM: Conception and design, analysis and interpretation of data, critical revision and final approval of the manuscript. PB: Conception and design, analysis and interpretation of data, critical revision and final approval of the manuscript.

Declaration of interests

Christian S. Meyhoff has received institutional direct and indirect research funding from Boehringer Ingelheim, Ferring Pharmaceuticals, Radiometer and Merch, Sharp & Dohme, as well as lecture fees from Radiometer, all outside submitted work. The remaining authors declare that they have no conflict of interest.

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Data availability statement

Anonymised data will be made available upon reasonable request.

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Table 1. Participant characteristics and intraoperative data.

Variables	*Participants n=70*
Demographics	
Age, years	65 (33-85)
Sex, female	41 (59%)
BMI, kg/m^2	28.8 (24.4;32.9)
ASA	
I	1 (1%)
II	37 (53%)
III	31 (44%)
IV	1 (1%)
Smoking	
Never	37 (53%)
Current	3 (4%)
Former	30 (43%)
Medical history	
Stroke	5 (7%)
TCI	3 (4%)
Hypertension	36 (51%)
Diabetes mellitus	8 (11%)
Chronic lung disease[a]	15 (21%)
Sleep apnea	16 (23%)
Arrhythmia	11 (16%)
Valvular disease	6 (9%)
Coronary artery disease	8 (11%)
Creatinine elevation	2 (3%)
Surgical information	
Length of surgery, minutes	264 (201;405)

2.

Osteotomy performed	35 (50%)
Estimated blood loss, mL	753 (400;1400)
Mean arterial pressure, mmHg	83±9
Heart rate, bpm	69±11
Tissue oximetry	
SmO_2 median, %	75 (70;79)
SmO_2 minimum, %	66 (61;70)
SmO_2 maximum, %	84 (78;88)
TW AUC for SmO_2, %*min*h^{-1}	98 (9;298)
ScO_2 median, %	66 (62;71)
ScO_2 minimum, %	60 (56;65)
ScO_2 maximum, %	77 (72;82)
TW AUC for ScO_2, %*min*h^{-1}	33(0.06;131)

Data are mean (standard deviation) for normally distributed variables and median (interquartile range) for variables with skewed distributions. [a]Includes asthma and chronic obstructive pulmonary disorder (COPD). BMI=body mass index, ASA= American Society of Anesthesiologists Physical Status Classification System score, TCI=transient cerebral ischemia, SmO_2=muscle tissue oxygenation, TW AUC=time-weighted area under the curve, ScO_2=cerebral tissue oxygenation.

Table 2. Summary of postoperative outcomes within 30 days after spinal surgery.

Postoperative complications	Lower half TW AUC for SmO_2, N=35	Upper half TW AUC for SmO_2, N=35	p-value
TW AUC for SmO2, (%*min*h^{-1})	9 (1;53)	298 (189;586)	<0.001
Peak hsTnT, ng/L	17 (9;26)	24 (10;33)	0.15
MINS	12 (34%)	16 (46%)	0.33
Myocardial infarction	0	0	-
Non-fatal cardiac arrest	0	0	-
New-onset arrhythmia	1 (3%)	2 (6%)	0.56
Heart failure	0	0	-
TCI	0	0	-
Stroke	0	0	-
Sepsis	1 (3%)	1 (3%)	1.00
Surgical site infection	2 (6%)	2 (6%)	1.00
Pulmonary complications	4 (11%)	3 (9%)	0.69
Creatinine elevation	1 (3%)	1 (3%)	1.00
ICU admission	14 (40%)	25 (71%)	0.008
Length of postoperative hospitalization	6 (4;7)	6 (6;8)	0.056
Mortality	0	0	-
Composite outcome	21 (60%)	31 (89%)	0.006

Data are mean (standard deviation) for normally distributed variables and median (interquartile range) for variables with skewed distributions). P-values are based on chi^2-tests, ANOVA and Wilcoxon rank sum tests. TW AUC=time-weighted area under the curve, SmO_2=muscle tissue oxygenation, hsTnT=high-sensitivity Troponin T, MINS=myocardial injury after non-cardiac surgery, TCI=transient cerebral ischemia, ICU=intensive care unit.

Table 3. Tissue oxygenation measures as predictors for higher peak hsTnT and MINS.

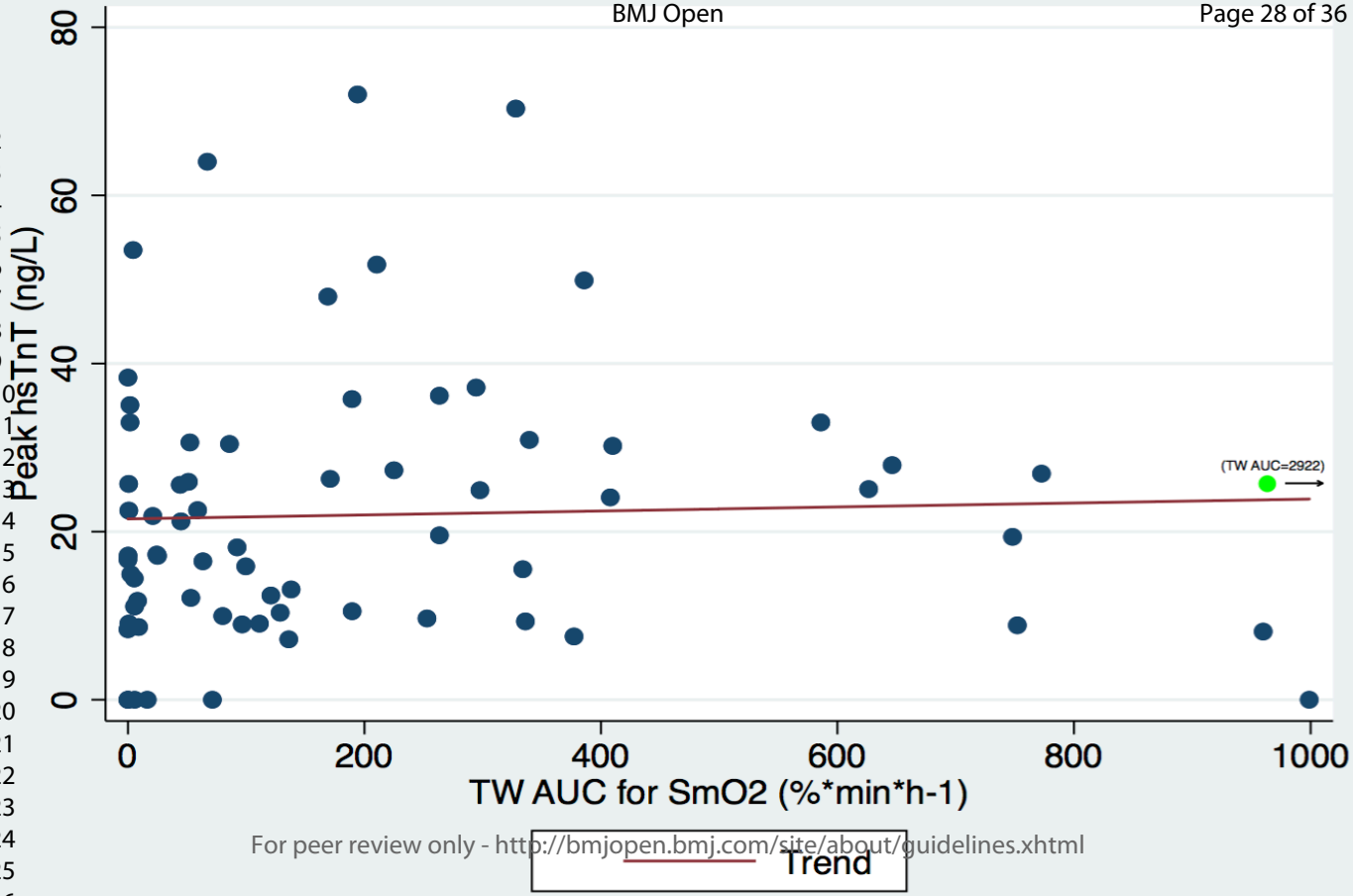
	High peak hsTnT vs. low peak hsTnT				MINS vs. no MINS	
StO_2 indices	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value	Univariable OR (95% CI)	p-value
Median SmO_2, %	0.93 (0.87-0.996)	0.039	0.92 (0.82-1.04)	0.18	0.96 (0.76-1.21)	0.75
Minimum SmO_2, %	0.97 (0.92-1.01)	0.16	0.94 (0.86-1.03)	0.20	0.95 (0.75-1.22)	0.70
Maximum SmO_2, %	0.92 (0.85-0.99)	0.025	0.90 (0.80-1.02)	0.11	0.90 (0.70-1.15)	0.41
TW AUC SmO_2, %*min*h^{-1}	1.00 (1.00-1.00)	0.15	1.00 (1.00-1.01)	0.22	1.00 (0.99-1.01)	0.74
Median ScO_2, %	0.99 (0.91-1.06)	0.70	0.92 (0.79-1.06)	0.24	0.79 (0.59-1.07)	0.13
Minimum ScO_2, %	0.96 (0.91-1.03)	0.26	0.83 (0.69-0.98)	0.030	0.10 (0.00-5.34)	0.26
Maximum ScO_2, %	0.97 (0.90-1.05)	0.47	0.99 (0.94-1.05)	0.82	1.01 (0.96-1.06)	0.76
TW AUC ScO_2, %*min*h^{-1}	1.00 (1.00-1.01)	0.32	1.00 (1.00-1.01)	0.33	1.00 (1.00-1.01)	0.32

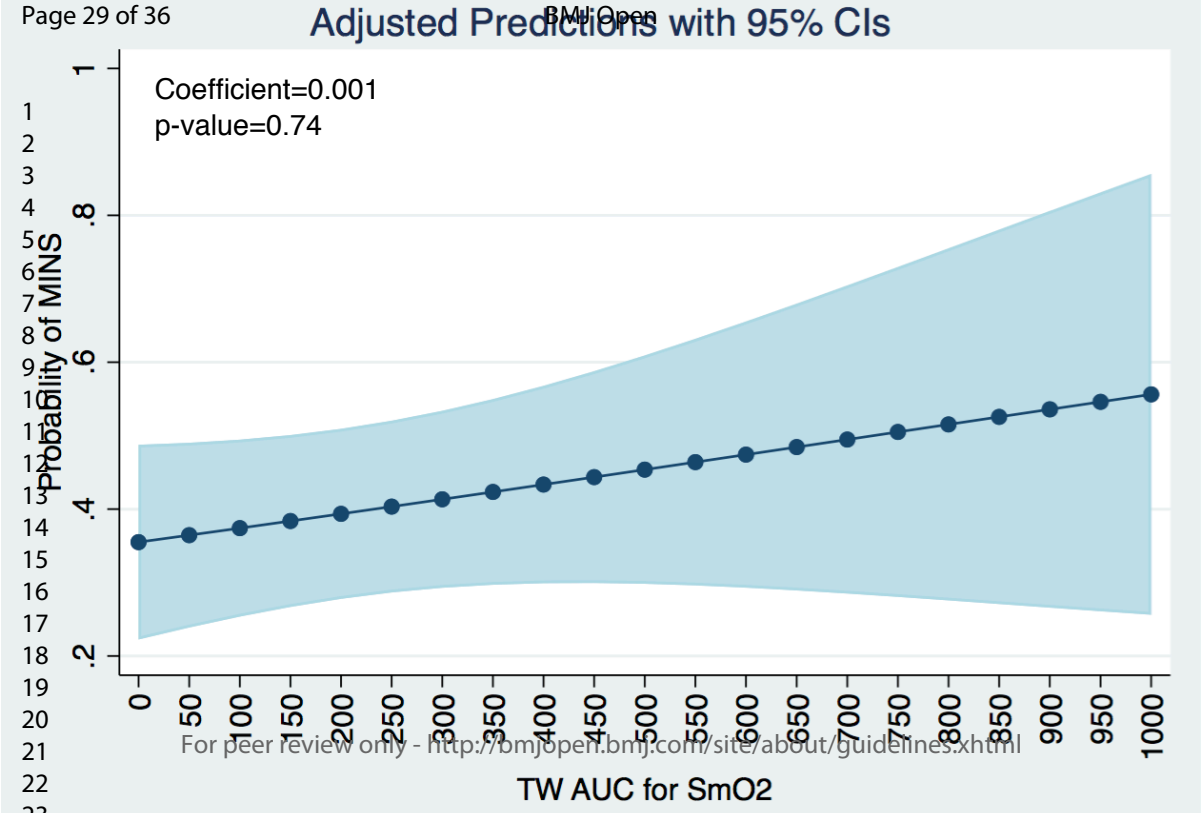
This table shows the odds of having an outcome (high peak hsTnT or MINS, respectively) for every one percent/one unit increase in the specific tissue oxygenation variable. Multivariable analysis is adjusted for age, sex, BMI=body mass index, smoking, diabetes, hypertension, previous stroke, chronic lung disease, arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate. hsTnT=high-sensitivity Troponin T, MINS=myocardial injury after non-cardiac surgery, StO_2=tissue oxygenation, OR=odds ratio, CI=confidence interval, SmO_2=muscle tissue oxygenation, TW AUC=time-weighted area under the curve, ScO_2=cerebral tissue oxygenation.

Figure legends:

Figure 1. Relationship between time-weighted area under the curve (TW AUC) for muscle tissue oxygenation (SmO_2) and peak value of high-sensitivity troponin T (hsTnT) measured within the first two days after surgery.

Figure 2. Adjusted prediction curve for time-weighted area under the curve (TW AUC) for muscle tissue oxygenation (SmO_2) as predictor for myocardial injury after non-cardiac surgery (MINS). CI=confidence interval.





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	"A Prospective Cohort Study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	See abstract
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	"In this prospective cohort study we hypothesized that a decrease in SmO_2 was associated with higher peak postoperative high-sensitivity Troponin T (hsTnT)", "This study was conducted with the aim of examining the association between intraoperative StO2 and myocardial injury in patients undergoing major spine surgery."
Methods				
Study design	4	Present key elements of study design early in the paper	6	"This prospective cohort study was conducted…"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	"This prospective cohort study was conducted at the University of California, San Francisco (UCSF)", "The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018.",

				"Patient characteristics, comorbidities, preoperative physical status and postoperative complications were extracted from the electronical medical record (KFB). Data was collected at two time-points: Prior to surgery and 30 days after surgery. A follow-up phone call to the patient was made 30 days after surgery to verify postoperative outcomes."
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	6	"The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018. The surgeries selected were scheduled to last for more than two hours and included instrumentation. Exclusion criteria were: American Society of Anesthesiologists Physical Status Classification System score (ASA)>IV, surgery for tumor or infection, emergent or urgent surgery.", "…postoperative complications were extracted from the electronical medical record…", "A follow-up phone call to the patient was made 30 days after

				surgery to verify postoperative outcomes."
		(*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		N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 6 9	For outcomes see 'Outcomes' For predictors see 'Tissue Oximetry' "Variables for adjustment in the multivariable analyses were age, sex, body mass index (BMI), smoking, diabetes, hypertension, previous stroke, chronic lung disease, arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate."
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	6, 7	See 'Data Collection', 'Tissue Oximetry' and 'Troponin Measurement'
Bias	9	Describe any efforts to address potential sources of bias	6	See 'Patients' and 'Data Collection'
Study size	10	Explain how the study size was arrived at	9	"Sample size calculations were based on clinical data and previous studies investigating tissue oxygenation as an outcome for postoperative

	complications.[12,13] These studies evaluated all types of complications as primary outcome. Mean (SD) TW AUC for SmO_2 was 1.59 %*min*h^{-1} (2.35).[12] We estimated a minimal clinically relevant difference to be a 36% increase in TW AUC for SmO_2 for participants with high peak hsTnT (with a cut-off of 14 ng/L based on the 99th percentile of a healthy population[15]) compared to participants with low peak hsTnT. Using a power of 80% and a significance level of 0.05, a sample size of 68 participants for this study was needed. We anticipated a low number of drop-outs, as the study design was observational, resulting in a total sample size of 70 participants."

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	9	"Results are presented as mean+/- SD and median (interquartile range, IQR) when appropriate."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	See 'Statistical Analysis'
		(*b*) Describe any methods used to examine subgroups and interactions	9	See 'Statistical Analysis'
		(*c*) Explain how missing data were addressed		N/A
		(*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		N/A
		(*e*) Describe any sensitivity analyses		N/A
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	14	"A total of 70 patients undergoing spine surgery was included in this prospective cohort study"
		(b) Give reasons for non-participation at each stage		N/A
		(c) Consider use of a flow diagram		N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	"Mean age was 65 (33-85) years and 41 (59%) participants were female. The median estimated blood loss was 753 (IQR 400;1400) mL. A summary of patient characteristics, medical history, surgical information and values for tissue oxygenation are found in Table 1."
		(b) Indicate number of participants with missing data for each variable of interest		N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		30 days follow-up described in methods
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11	"The median peak hsTnT was 19 (IQR 10;30) ng/L and based on a

				hsTnT of 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L, 28 (40%) participants had MINS (Table 2). The number of participants with any postoperative complications were 41 (59%) and when MINS was included as a complication, 52 (74%) of participants had one or more postoperative complications (Table 2)."
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		N/A
		Cross-sectional study—Report numbers of outcome events or summary measures		N/A
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	11	See section 'Relationships of tissue oxygenation to MINS and other outcomes' under 'Results'
		(*b*) Report category boundaries when continuous variables were categorized		N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		N/A
Discussion				
Key results	18	Summarise key results with reference to study objectives	13	"In a prospective cohort study of 70 participants, we investigated intraoperative tissue oxygenation as predictor for myocardial injury after spine surgery. We found that muscle and cerebral tissue oxygenation were not independent predictors for elevated high-sensitivity troponin T or MINS. However, in exploratory analyses, some other indices for SmO2 were associated with higher peak hsTnT, whereas ScO2 indices were not."
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	15	See section 'Study limitations' under 'Discussion'
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16	See full discussion section. Concluding remarks: "In summary, tissue oxygenation was not a statistically significant predictor for peak postoperative high-sensitivity troponin but is a potential predictor for other postoperative complications. Future studies should focus on determining a threshold for tissue oxygenation taking inter-individual factors into account. The frequency of MINS was high (40%) and related to blood loss, suggesting supply-demand

				mismatch etiology in spine surgery. Tissue oxygenation did not have the power to predict myocardial injury but other intraoperative indicators for supply-demand mismatch should be considered as potential predictors for MINS in future studies."
Generalisability	21	Discuss the generalisability (external validity) of the study results		Overall described in discussion section.
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	17	"This work was supported by a grant from the Lundbeck Foundation Clinical Research Fellowship 2017-2018 for Katrine Feldballe Bernholm. CAS Medical Systems, Inc. provided the FORE-SIGHT ELITE Tissue Oximeter and probes at no cost."

*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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Association between tissue oxygenation and myocardial injury in patients undergoing major spine surgery: A prospective cohort study

Katrine Feldballe Bernholm, MD[1,2], Christian S. Meyhoff, MD, PhD[2,3,4], Philip Bickler, MD, PhD[1]*

[1]Department of Anesthesia and Perioperative Care, University of California, San Francisco, USA

[2]Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

[3]Copenhagen Center for Translational Research, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark

[4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

* Corresponding author. Email: bernholm3@hotmail.com

Running head: Tissue Oximetry and Myocardial Injury

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Abstract

Objective: To describe the association between intraoperative tissue oxygenation and postoperative troponin elevation in patients undergoing major spine surgery. We hypothesized that a decrease in intraoperative skeletal muscle tissue oxygenation (SmO_2) was associated with the peak postoperative cardiac troponin value.

Design: This is a prospective cohort study.

Setting: Single-center, University of California San Francisco Medical Center.

Participants: Seventy adult patients undergoing major elective spine surgery.

Primary and secondary outcome measures: High-sensitivity troponin T (hsTnT) was measured in plasma pre-operatively and on the first and second day after surgery to assess the primary outcome of peak postoperative hsTnT. Secondary outcomes included MINS and intensive care unit (ICU) admission within 30 days. Cerebral (ScO_2) and skeletal muscle (SmO_2) tissue oxygenation was measured continuously with near-infrared spectroscopy during surgery. The primary exposure variable was time-weighted area under the curve (TW AUC) for SmO_2.

Results: Mean age was 65 (33-85) years and 59% were female. No significant association was found between TW AUC for SmO_2 and peak hsTnT (Spearman's correlation, r_s=0.17, p=0.16). A total of 28 (40%) patients had MINS. ICU admission occurred in 14 (40%) in lower vs. 25 (71%) in upper half of patients based on TW AUC for SmO_2, p=0.008.

Conclusions: Decrease in SmO_2 was not a statistically significant predictor for peak troponin value following major spine surgery but is a potential predictor for other postoperative complications.

Trial registration: Clinicaltrials.gov identifier: NCT03518372.

Article Summary

Strengths and limitations of this study

- Prospective observational study including 70 patients undergoing major spine surgery
- Contributing knowledge to potential predictors for myocardial injury and clinical implications of tissue oxygenation monitoring
- Applying skeletal muscle tissue oxygenation as primary predictor, decreasing risk of cerebral autoregulation modification of outcomes
- There is no clinical consensus of absolute threshold for tissue hypoxemia, thus population median for skeletal muscle tissue oxygenation was used as cut-off in this study.

Introduction

Major non-cardiac surgery is associated with significant risks of postoperative complications which are sometimes asymptomatic such as covert stroke[1] and myocardial infarction and injury.[2] Cardiovascular events are the leading cause of morbidity and mortality[3] with myocardial injury after non-cardiac surgery (MINS) being a major contributor to further postoperative complications.[4–7] MINS is frequently caused by ischemia and can be diagnosed from elevated postoperative high-sensitivity cardiac troponin, in the absence of non-ischemic factors for troponin elevation.[8] The 30-day mortality is increased up to eight-fold in patients with covert stroke compared to matched controls[9] and stroke occurs in 9% of patients with MINS, making it a substantial public health problem.[10] Peak postoperative cardiac troponin has a linear association with 30-day mortality.[7] Each year, 8 million surgical patients worldwide suffer from MINS but there is sparse knowledge about triggering causes and contributing factors to the magnitude of peak postoperative cardiac troponin.[5,11]

Intraoperative tissue oxygen desaturation is common in patients undergoing major spine surgery[12] probably because of the substantial blood loss and hemodynamic changes that occur in this type of operation. Tissue oxygenation (StO_2) can be measured non-invasively with near-infrared spectroscopy (NIRS). Previous studies found that a decrease in intraoperative StO_2 was associated with wound infection, stroke and renal failure,[13] and that decrease in skeletal muscle tissue oxygenation (SmO_2) was a stronger predictor for these complications than cerebral tissue oxygenation (ScO_2) in spine surgery.[12] However, current knowledge of how tissue oxygenation affects other important clinical outcomes, including MINS, is lacking. In this prospective cohort study we hypothesized that a decrease in SmO_2 was associated with higher peak postoperative high-sensitivity Troponin T (hsTnT). The primary exposure variable was time-weighted area under the curve (TW AUC) for SmO_2 and the primary outcome was peak postoperative hsTnT. This study was conducted with the aim

of examining the association between intraoperative tissue oxygenation and postoperative troponin elevation in patients undergoing major spine surgery.

Methods

This prospective cohort study was conducted at the University of California, San Francisco (UCSF) with Clinicaltrials.gov identifier: NCT03518372. The study was approved by the local Institutional Review Board (IRB 14-12996) and both verbal and written consent was obtained from all participants before surgery. This manuscript adheres to the applicable STROBE guidelines.

Patients

The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018. The surgeries selected were scheduled to last for more than two hours and included instrumentation. Exclusion criteria were: American Society of Anesthesiologists Physical Status Classification System score (ASA)>IV, surgery for tumor or infection, emergent or urgent surgery.

Data collection

Patient characteristics, comorbidities, preoperative physical status and postoperative complications were extracted from the electronical medical record (KFB). Data was collected at two time-points: Prior to surgery and 30 days after surgery. A follow-up phone call to the patient was made 30 days after surgery to verify postoperative outcomes. Baseline values were defined as the pre-incision value. Intraoperative values were defined as data from incision to end of procedure when last suture was placed. Study data were managed using the REDCap electronic data capture tools hosted at UCSF.

Tissue oximetry

Tissue oxygenation was monitored using a tissue oximeter based on near-infrared spectroscopy (NIRS) (FORE-SIGHT Elite, CASMED, Inc., Branford, Connecticut, USA). Cerebral and leg skeletal muscle oxygenation was monitored via two cables connected to adhesive probes provided by the manufacturer. Probes were placed after tracheal intubation and a baseline was measured from placing of probe to incision. One probe was placed on the left side on the upper forehead to monitor one-sided frontal cortex ScO_2. The second probe was placed on the left tibialis anterior muscle, four fingers below the tibial tuberosity and two fingers lateral to the anterior edge of the tibial shaft, to monitor the SmO_2 of the lower leg muscle. The oximeter generated a data point every 2 seconds. The anesthesia team was blinded to the oximeter. Data from the oximeter were used for tissue oxygenation indices derivation. Indices were maximum, minimum, median and time-weighted area under the curve (TW AUC) for SmO_2 and ScO_2 respectively. The primary exposure variable was TW AUC for SmO_2. TW AUC was calculated for each participant as the area below the intraoperative median for the study population and divided by length of surgery. This was chosen because there is no international consensus on a universal baseline level or normal range for tissue oxygenation.

Troponin measurements

A total of three blood samples for hsTnT were drawn. First sample was drawn by the anesthesiologist in the operating room after placement of the arterial line prior to surgery. Second and third sample were drawn by a phlebotomist or nurse the first and second day after surgery, respectively. After the blood was drawn, the sample was centrifuged immediately and the plasma was divided into two cryo collecting tubes and placed in a -80 ºCelsius freezer for storage. All plasma samples were sent to a specialized laboratory at Hennepin Medical Center (Minneapolis, MN, USA) to be analyzed for the Roche 5th generation, Elecsys hsTnT

assay after the study was completed. The data collector was blinded to the results of hsTnT and laboratory personnel analyzing the blood samples were blinded to patient data. Medical records and perioperative information (e.g. ECG, laboratory values) were reviewed for patients with troponin elevation, to exclude a non-ischemic etiology.[8]

Outcomes

The primary outcome was defined as postoperative peak high-sensitivity cardiac troponin T (hsTnT). A secondary related outcome was MINS, initially defined as hsTnT ≥14 ng/L[14] with factors for non-ischemic etiology excluded (e.g. sepsis, kidney failure, heart failure). This MINS definition was registered at clinicaltrials.gov, but during the course of the study and prior to hsTnT analysis of the blood samples, new data was published, where MINS was defined as an elevated postoperative hsTnT (i.e. 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L) with factors for non-ischemic etiology excluded (e.g. sepsis, kidney failure, heart failure).[8] We therefore updated the protocol to the latter and current MINS definition. Other secondary outcomes were myocardial infarction, non-fatal cardiac arrest, new-onset arrhythmia (defined as new atrial fibrillation or other treatment requiring arrhythmia), heart failure, transient cerebral ischemia, symptomatic stroke, sepsis, surgical site infection, pulmonary complications (including pulmonary infection, pneumothorax, atelectasis, pulmonary embolus and other pulmonary complication), creatinine elevation (>1.3 mg/dL for men and >1.1 mg/dL for women), intensive care unit (ICU) admission, length of hospital stay and mortality, all within 30 days after surgery. In addition, we analyzed a composite outcome that consisted of all above mentioned postoperative complications.

Sample size

Sample size calculations were based on clinical data and previous studies investigating tissue oxygenation as an outcome for postoperative complications.[12,13] These studies evaluated all types of complications as primary outcome. Mean (SD) TW AUC for SmO_2 was 1.59 %*min*h^{-1} (2.35).[12] We estimated a minimal clinically relevant difference to be a 36% increase in TW AUC for SmO_2 for participants with high peak hsTnT (with a cut-off of 14 ng/L based on the 99th percentile of a healthy population[15]) compared to participants with low peak hsTnT. Using a power of 80% and a significance level of 0.05, a sample size of 68 participants for this study was needed. We anticipated a low number of drop-outs, as the study design was observational, resulting in a total sample size of 70 participants.

Statistical analysis

Results are presented as mean±SD and median (interquartile range, IQR) when appropriate. Postoperative outcomes were compared stratifying the study population in two groups by median TW AUC for SmO_2. Comparison between groups were based on Chi-squared tests for categorical variables, ANOVA and Wilcoxon rank sum test.

The primary analysis of the association between TW AUC for SmO_2 and peak hsTnT was tested by Spearman correlation analysis. Univariable and multivariable logistic regression models were used in secondary analyses to examine the associations of baseline characteristics, intraoperative variables and StO_2 indices with higher peak hsTnT which was dichotomized in high/low categories using median peak hsTnT in the study population as cut-off. Univariable and multivariable logistic regression was used to test the association between StO_2 indices and MINS and the adjusted prediction for TW AUC for SmO_2 and MINS was calculated. Variables for adjustment in the multivariable analyses were age, sex, body mass index (BMI), smoking, diabetes, hypertension, previous stroke, chronic lung disease,

arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate.

Stata Statistical Software (release 15; StataCorp LP, College Station, TX, USA) was used for all analyses.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

Results

A total of 70 patients undergoing spine surgery was included in this prospective cohort study. Mean age was 65 (33-85) years and 41 (59%) participants were female. The median percentage estimated blood loss of estimated blood volume was 17 (IQR 8;31) %. A summary of patient characteristics, medical history, surgical information and values for tissue oxygenation are found in Table 1.

Incidence of MINS and major outcomes

The median peak hsTnT was 19 (IQR 10;30) ng/L and based on a hsTnT of 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L, 28 (40%) participants had MINS (Table 2). The number of participants with any postoperative complications were 41 (59%) and when MINS was included as a complication, 52 (74%) of participants had one or more postoperative complications (Table 2). Estimated blood loss and length of surgery was associated with MINS (odds ratio, OR (95% confidence interval, CI): 1.001 (1.000-1.002), p=0.002 and 1.007 (1.002-1.011), p=0.004, respectively).

Relationships of tissue oxygenation to MINS and other outcomes

In the univariable correlation analysis of TW AUC for SmO_2 and peak hsTnT, no significant association was found (r_s=0.17, p=0.16, Figure 1). There was a statistically significant association between higher TW AUC for SmO_2 and the composite outcome of postoperative complications (participants in lower half: 21 (60%) vs. participants in upper half: 31 (89%), p=0.006, Table 2) but when logistic regression was performed, this association was not significant. Furthermore, a statistically significant association between higher TW AUC for SmO_2 and ICU admission was found (participants in lower half: 14 (40%) vs. participants in upper half: 25 (71%), p=0.008, Table 2). There were no other statistically significant

differences in outcomes between the two groups based on median TW AUC for SmO_2. When testing the StO_2 indices as predictors for higher peak hsTnT by logistic regression, the univariable analysis found that for every one percent increase in median and maximum SmO_2, the odds of having high peak hsTnT decreased (OR (95% CI): 0.93 (0.87-0.996), p-value=0.039 and 0.92 (0.85-0.99), p=0.025, respectively, Table 3). After multivariable adjustment for baseline and clinical variables, median and maximum SmO_2 were not independent predictors for higher peak hsTnT (Table 3). None of the StO_2 indices were found to be significant predictors for MINS (Table 3). Adjusted predicted probability was calculated based on univariable logistic regression and showed increasing probability for MINS with increasing TW AUC for SmO_2 (Figure 2) albeit this was not statistically significant (OR (95% CI): 1.00 (0.99-1.01), p=0.74). Although this was not systematically assessed for the purpose of this study, only one participant presented with ischemic symptoms on the first two postoperative days according to medical records. This patient was not diagnosed with clinical myocardial infarction after examination, although hsTnT was 31 ng/L.

Discussion

In a prospective cohort study of 70 participants, we investigated intraoperative tissue oxygenation as predictor for myocardial injury after spine surgery. We found that skeletal muscle and cerebral tissue oxygenation were not independent predictors for elevated high-sensitivity troponin T or MINS. However, in exploratory analyses, some other indices for SmO_2 were associated with higher peak hsTnT, whereas ScO_2 indices were not.

Tissue oxygenation is a result of the oxygen supply and demand of the specific tissue and is determined by multiple physiological factors including oxygen saturation, hemoglobin concentration and cardiac output.[16] Measurement of tissue oxygenation with NIRS has been investigated in previous studies as predictor for a number of different outcomes. Several studies have examined cerebral oxygenation in patients undergoing cardiac surgery, whereas few studies have investigated skeletal muscle tissue oxygenation as predictor for clinical outcomes. In patients undergoing cardiac surgery, ScO_2 was found to be associated with stroke, cognitive decline, length of hospital stay and mortality.[17,18] One study found that decrease in ScO_2 was not a predictor for delirium in elderly patients.[19] A recent meta-analysis of 10 trials with a total of 1466 patients, found that NIRS-based algorithms for ScO_2 did not reduce mortality or organ injury affecting the heart, brain or kidneys.[20] Despite the lack of evident benefit for ScO_2-guided clinical algorithms, ScO_2 monitoring is routinely used in cardiac surgery.

Cerebral and skeletal muscle tissue have different physiological characteristics. *Meng et al.*[12] found that SmO_2 was a stronger predictor than ScO_2 for composite postoperative outcomes, including myocardial injury, stroke, pulmonary complications and creatinine elevation. Although findings in the current study were statistically insignificant, the exploratory analyses yielded a stronger association between SmO_2 and outcomes as compared to ScO_2.

This aligns with the theory that SmO_2 is a leading indicator for global desaturation due to low autoregulation in skeletal muscle tissue compared with the higher level of autoregulation in cerebral tissue.[21] Of note, skeletal and myocardial autoregulation may not be the same and it is possible that myocardial autoregulation shows similar patterns to cerebral autoregulation in some physiological instances. The importance of preserved cerebral autoregulation is substantial. Brain tissue is more sensitive to hypoxia than skeletal muscle.[16] One study showed that impaired cerebrovascular autoregulation was associated with increased morbidity and mortality within 30 days from surgery in patients undergoing major non-cardiac surgery.[22] A study in healthy subjects suggested SmO_2 to be an early indicator for impending cardiovascular collapse and showed that SmO_2 declined in parallel with stroke volume.[23] Perfusion of skeletal muscle tissue follows the same linearity in decline with decreasing cardiac output whereas cerebral tissue perfusion only decreases approximately one third of cardiac output.[24] This study found TW AUC for SmO_2 to be almost three times larger than TW AUC for ScO_2 (98 vs. 33 %*min*h^{-1}) indicating autoregulation in brain tissue. Of note, spine surgery patients at UCSF almost all receive anesthetics that include very low amounts of inhalational anesthetics, probably preserving brain autoregulation of blood flow. Despite these findings, the clinical implications of SmO_2 monitoring is still yet to be determined.

StO_2 was not statistically significant associated with MINS in the current study but other indicators of supply-demand mismatch, i.e. estimated blood loss and length of surgery, were significantly associated with MINS and peak hsTnT. These are established predictors for MINS[25] and contributes to the understanding of the pathophysiology for elevated troponin.[26] In general, the majority of MINS are undetected (80%) as patients do not have ischemic symptoms.[4,10] In this study only one participant presented with ischemic symptoms. The type of surgery the participants underwent was comprehensive and many participants were treated

with strong analgesics postoperatively which could be a contributing factor to the lack of ischemic symptoms in the participants with MINS. The incidence of MINS among the participants in this study was 40%. In comparison the general incidence of MINS in patients undergoing non-cardiac surgery is 8%[4] but this is not restricted to major surgery only and the incidence depends on the cut-off for troponin elevation used. Other groups found similar high incidence of MINS.[27]

Study limitations

As this was an observational cohort study it was not designed to determine causality between tissue oxygenation and postoperative myocardial injury. The study was not powered for all secondary outcomes, as we based the power calculation on a study with the outcome composite postoperative complications that included less severe complications (constipation, oliguria etc.).[12]

We found a high incidence of MINS in this study but the number of serious outcome events (e.g. death, stroke, non-fatal cardiac, myocardial infarction) were sparse in the 30-day follow-up period. The participants underwent spine surgery which was not emergent, conducted as cancer treatment/tumor resection or indicated by any life-threatening condition. Thus, it is possible that participants were in a better physical condition when scheduled for this type of elective surgery than for other major non-cardiac surgical procedures.

The NIRS method is non-invasive and tracks tissue oxygenation continuously. However, limitations in regards to the technology has been presented and includes bias regarding skin pigmentation, gender and assumed mixture of venous and arterial blood.[28] With the equipment used in this study it was not possible to obtain data on different hemoglobin (Hgb) fractions (total Hgb, oxy-Hgb and deoxy-Hgb), which could potentially have qualified the analysis even further. Inter-individual differences in saturation contributes to the difficulty of

determining an absolute threshold for tissue hypoxia. In the calculation of the primary predictor of TW AUC for SmO_2 we used the population median for intraoperative SmO_2 as cut-off. The choice of cut-off should be considered when interpreting results of studies investigating the impact of tissue oxygenation.

In summary, in this study tissue oxygenation was not a statistically significant predictor for peak postoperative high-sensitivity troponin but is a potential predictor for other postoperative complications. Future studies should focus on determining a threshold for tissue oxygenation taking inter-individual factors into account and apply NIRS technology with the ability of detecting different Hgb fractions. The frequency of MINS was high (40%) and related to blood loss, suggesting supply-demand mismatch etiology in spine surgery. Tissue oxygenation did not have the power to predict myocardial injury but other intraoperative indicators for supply-demand mismatch should be considered as potential predictors for MINS in future studies.

Author contributions

KFB: Conception and design, acquisition, analysis and interpretation of data, drafting, critical revision and final approval of the manuscript. CSM: Conception and design, analysis and interpretation of data, critical revision and final approval of the manuscript. PB: Conception and design, analysis and interpretation of data, critical revision and final approval of the manuscript.

Declaration of interests

Christian S. Meyhoff has received institutional direct and indirect research funding from Boehringer Ingelheim, Ferring Pharmaceuticals, Radiometer and Merch, Sharp & Dohme, as well as lecture fees from Radiometer, all outside submitted work. The remaining authors declare that they have no conflict of interest.

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CAS Medical Systems, Inc. provided the FORE-SIGHT ELITE Tissue Oximeter and probes at no cost.

Data availability statement

Anonymised data will be made available upon reasonable request.

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Table 1. Participant characteristics and intraoperative data.

Variables	*Participants n=70*
Demographics	
Age, years	65 (33-85)
Sex, female	41 (59%)
BMI, kg/m^2	28.8 (24.4;32.9)
ASA	
I	1 (1%)
II	37 (53%)
III	31 (44%)
IV	1 (1%)
Smoking	
Never	37 (53%)
Current	3 (4%)
Former	30 (43%)
Medical history	
Stroke	5 (7%)
TCI	3 (4%)
Hypertension	36 (51%)
Diabetes mellitus	8 (11%)
Chronic lung disease[a]	15 (21%)
Sleep apnea	16 (23%)
Arrhythmia	11 (16%)
Valvular disease	6 (9%)
Coronary artery disease	8 (11%)
Creatinine elevation	2 (3%)
Surgical information	
Length of surgery, minutes	264 (201;405)

2.

Osteotomy performed	35 (50%)
Estimated blood loss, mL	753 (400;1400)
Mean arterial pressure, mmHg	83±9
Heart rate, bpm	69±11
Tissue oximetry	
SmO_2 median, %	75 (70;79)
SmO_2 minimum, %	66 (61;70)
SmO_2 maximum, %	84 (78;88)
TW AUC for SmO_2, %*min*h^{-1}	98 (9;298)
ScO_2 median, %	66 (62;71)
ScO_2 minimum, %	60 (56;65)
ScO_2 maximum, %	77 (72;82)
TW AUC for ScO_2, %*min*h^{-1}	33(0.06;131)

Data are mean (standard deviation) for normally distributed variables and median (interquartile range) for variables with skewed distributions. [a]Includes asthma and chronic obstructive pulmonary disorder (COPD). BMI=body mass index, ASA= American Society of Anesthesiologists Physical Status Classification System score, TCI=transient cerebral ischemia, SmO_2=skeletal muscle tissue oxygenation, TW AUC=time-weighted area under the curve, ScO_2=cerebral tissue oxygenation.

Table 2. Summary of postoperative outcomes within 30 days after spinal surgery.

Postoperative complications	Lower half TW AUC for SmO_2, N=35	Upper half TW AUC for SmO_2, N=35	p-value
TW AUC for SmO2, (%*min*h^{-1})	9 (1;53)	298 (189;586)	<0.001
Peak hsTnT, ng/L	17 (9;26)	24 (10;33)	0.15
MINS	12 (34%)	16 (46%)	0.33
Myocardial infarction	0	0	-
Non-fatal cardiac arrest	0	0	-
New-onset arrhythmia	1 (3%)	2 (6%)	0.56
Heart failure	0	0	-
TCI	0	0	-
Stroke	0	0	-
Sepsis	1 (3%)	1 (3%)	1.00
Surgical site infection	2 (6%)	2 (6%)	1.00
Pulmonary complications	4 (11%)	3 (9%)	0.69
Creatinine elevation	1 (3%)	1 (3%)	1.00
ICU admission	14 (40%)	25 (71%)	0.008
Length of postoperative hospitalization	6 (4;7)	6 (6;8)	0.056
Mortality	0	0	-
Composite outcome	21 (60%)	31 (89%)	0.006

Data are mean (standard deviation) for normally distributed variables and median (interquartile range) for variables with skewed distributions). P-values are based on chi^2-tests, ANOVA and Wilcoxon rank sum tests. TW AUC=time-weighted area under the curve, SmO_2=skeletal muscle tissue oxygenation, hsTnT=high-sensitivity Troponin T, MINS=myocardial injury after non-cardiac surgery, TCI=transient cerebral ischemia, ICU=intensive care unit.

Table 3. Tissue oxygenation measures as predictors for higher peak hsTnT and MINS.

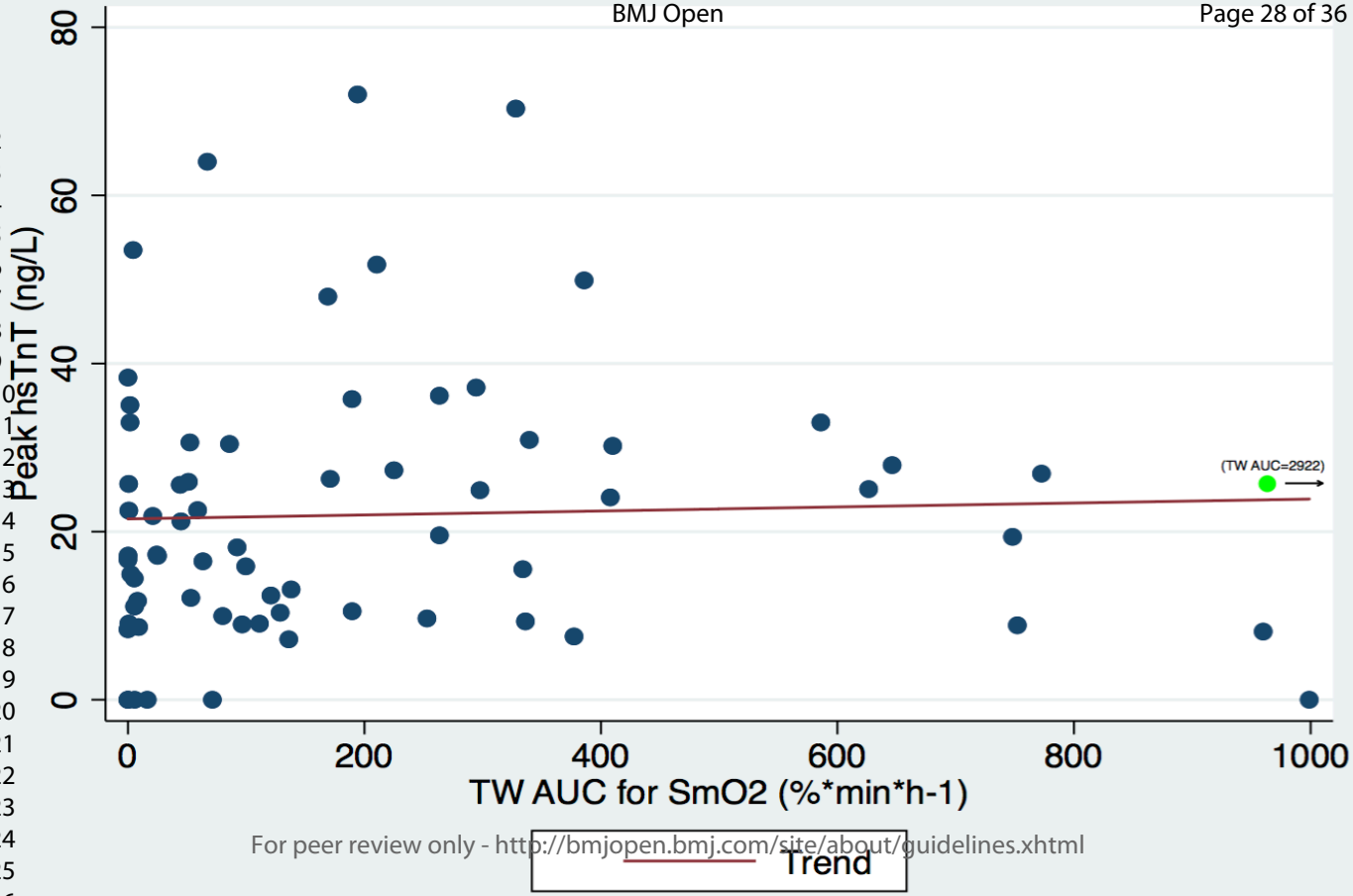
	High peak hsTnT vs. low peak hsTnT				MINS vs. no MINS	
StO_2 indices	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value	Univariable OR (95% CI)	p-value
Median SmO_2, %	0.93 (0.87-0.996)	0.039	0.92 (0.82-1.04)	0.18	0.96 (0.76-1.21)	0.75
Minimum SmO_2, %	0.97 (0.92-1.01)	0.16	0.94 (0.86-1.03)	0.20	0.95 (0.75-1.22)	0.70
Maximum SmO_2, %	0.92 (0.85-0.99)	0.025	0.90 (0.80-1.02)	0.11	0.90 (0.70-1.15)	0.41
TW AUC SmO_2, %*min*h^{-1}	1.00 (1.00-1.00)	0.15	1.00 (1.00-1.01)	0.22	1.00 (0.99-1.01)	0.74
Median ScO_2, %	0.99 (0.91-1.06)	0.70	0.92 (0.79-1.06)	0.24	0.79 (0.59-1.07)	0.13
Minimum ScO_2, %	0.96 (0.91-1.03)	0.26	0.83 (0.69-0.98)	0.030	0.10 (0.00-5.34)	0.26
Maximum ScO_2, %	0.97 (0.90-1.05)	0.47	0.99 (0.94-1.05)	0.82	1.01 (0.96-1.06)	0.76
TW AUC ScO_2, %*min*h^{-1}	1.00 (1.00-1.01)	0.32	1.00 (1.00-1.01)	0.33	1.00 (1.00-1.01)	0.32

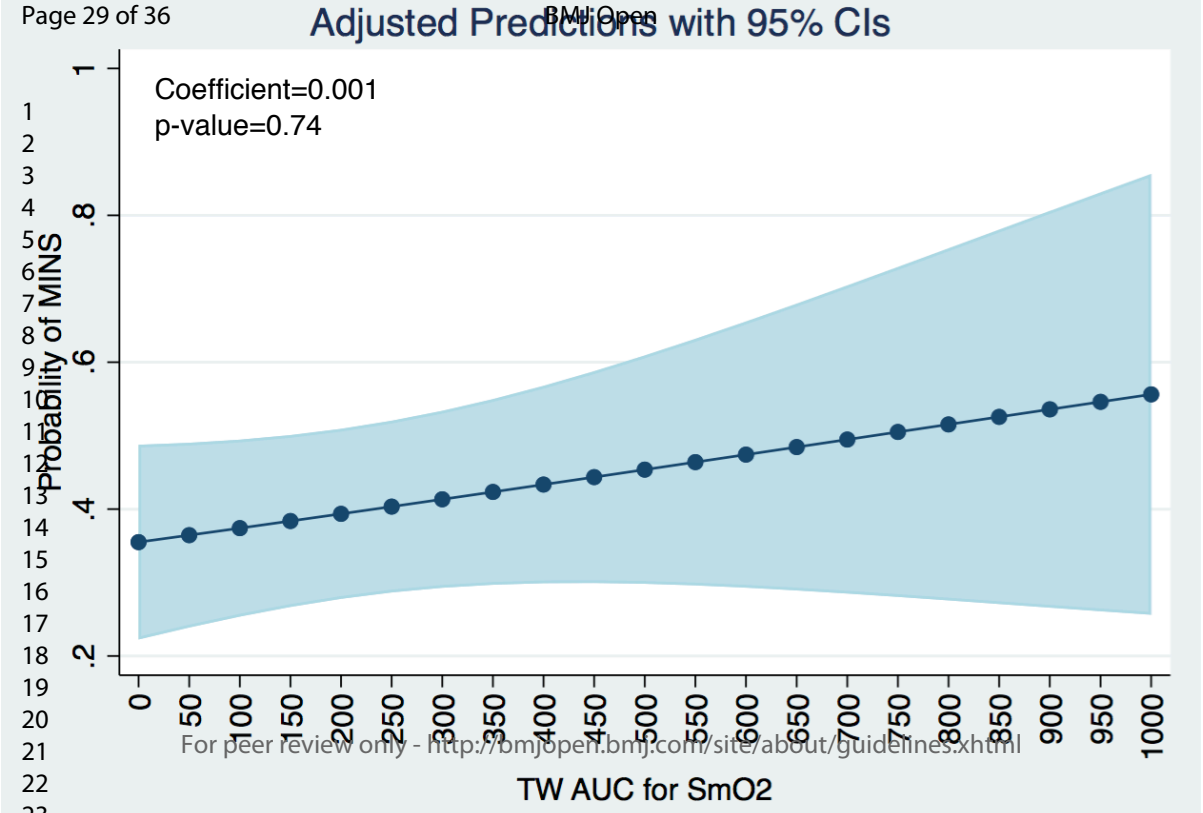
This table shows the odds of having an outcome (high peak hsTnT or MINS, respectively) for every one percent/one unit increase in the specific tissue oxygenation variable. Multivariable analysis is adjusted for age, sex, BMI=body mass index, smoking, diabetes, hypertension, previous stroke, chronic lung disease, arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate. hsTnT=high-sensitivity Troponin T, MINS=myocardial injury after non-cardiac surgery, StO_2=tissue oxygenation, OR=odds ratio, CI=confidence interval, SmO_2=skeletal muscle tissue oxygenation, TW AUC=time-weighted area under the curve, ScO_2=cerebral tissue oxygenation.

Figure legends:

Figure 1. Relationship between time-weighted area under the curve (TW AUC) for skeletal muscle tissue oxygenation (SmO_2) and peak value of high-sensitivity troponin T (hsTnT) measured within the first two days after surgery.

Figure 2. Adjusted prediction curve for time-weighted area under the curve (TW AUC) for skeletal muscle tissue oxygenation (SmO_2) as predictor for myocardial injury after non-cardiac surgery (MINS). CI=confidence interval.





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	"A Prospective Cohort Study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	See abstract
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	"In this prospective cohort study we hypothesized that a decrease in SmO_2 was associated with higher peak postoperative high-sensitivity Troponin T (hsTnT)", "This study was conducted with the aim of examining the association between intraoperative StO2 and myocardial injury in patients undergoing major spine surgery."
Methods				
Study design	4	Present key elements of study design early in the paper	6	"This prospective cohort study was conducted…"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	"This prospective cohort study was conducted at the University of California, San Francisco (UCSF)", "The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018.",

				"Patient characteristics, comorbidities, preoperative physical status and postoperative complications were extracted from the electronical medical record (KFB). Data was collected at two time-points: Prior to surgery and 30 days after surgery. A follow-up phone call to the patient was made 30 days after surgery to verify postoperative outcomes."
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	6	"The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018. The surgeries selected were scheduled to last for more than two hours and included instrumentation. Exclusion criteria were: American Society of Anesthesiologists Physical Status Classification System score (ASA)>IV, surgery for tumor or infection, emergent or urgent surgery.", "…postoperative complications were extracted from the electronical medical record…", "A follow-up phone call to the patient was made 30 days after

				surgery to verify postoperative outcomes."
		(*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		N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 6 9	For outcomes see 'Outcomes' For predictors see 'Tissue Oximetry' "Variables for adjustment in the multivariable analyses were age, sex, body mass index (BMI), smoking, diabetes, hypertension, previous stroke, chronic lung disease, arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate."
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	6, 7	See 'Data Collection', 'Tissue Oximetry' and 'Troponin Measurement'
Bias	9	Describe any efforts to address potential sources of bias	6	See 'Patients' and 'Data Collection'
Study size	10	Explain how the study size was arrived at	9	"Sample size calculations were based on clinical data and previous studies investigating tissue oxygenation as an outcome for postoperative

	complications.[12,13] These studies evaluated all types of complications as primary outcome. Mean (SD) TW AUC for SmO_2 was 1.59 %*min*h^{-1} (2.35).[12] We estimated a minimal clinically relevant difference to be a 36% increase in TW AUC for SmO_2 for participants with high peak hsTnT (with a cut-off of 14 ng/L based on the 99th percentile of a healthy population[15]) compared to participants with low peak hsTnT. Using a power of 80% and a significance level of 0.05, a sample size of 68 participants for this study was needed. We anticipated a low number of drop-outs, as the study design was observational, resulting in a total sample size of 70 participants."

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	9	"Results are presented as mean+/- SD and median (interquartile range, IQR) when appropriate."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	See 'Statistical Analysis'
		(*b*) Describe any methods used to examine subgroups and interactions	9	See 'Statistical Analysis'
		(*c*) Explain how missing data were addressed		N/A
		(*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		N/A
		(*e*) Describe any sensitivity analyses		N/A
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	14	"A total of 70 patients undergoing spine surgery was included in this prospective cohort study"
		(b) Give reasons for non-participation at each stage		N/A
		(c) Consider use of a flow diagram		N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	"Mean age was 65 (33-85) years and 41 (59%) participants were female. The median estimated blood loss was 753 (IQR 400;1400) mL. A summary of patient characteristics, medical history, surgical information and values for tissue oxygenation are found in Table 1."
		(b) Indicate number of participants with missing data for each variable of interest		N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		30 days follow-up described in methods
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11	"The median peak hsTnT was 19 (IQR 10;30) ng/L and based on a

				hsTnT of 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L, 28 (40%) participants had MINS (Table 2). The number of participants with any postoperative complications were 41 (59%) and when MINS was included as a complication, 52 (74%) of participants had one or more postoperative complications (Table 2)."
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		N/A
		Cross-sectional study—Report numbers of outcome events or summary measures		N/A
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	11	See section 'Relationships of tissue oxygenation to MINS and other outcomes' under 'Results'
		(*b*) Report category boundaries when continuous variables were categorized		N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		N/A
Discussion				
Key results	18	Summarise key results with reference to study objectives	13	"In a prospective cohort study of 70 participants, we investigated intraoperative tissue oxygenation as predictor for myocardial injury after spine surgery. We found that muscle and cerebral tissue oxygenation were not independent predictors for elevated high-sensitivity troponin T or MINS. However, in exploratory analyses, some other indices for SmO2 were associated with higher peak hsTnT, whereas ScO2 indices were not."
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	15	See section 'Study limitations' under 'Discussion'
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16	See full discussion section. Concluding remarks: "In summary, tissue oxygenation was not a statistically significant predictor for peak postoperative high-sensitivity troponin but is a potential predictor for other postoperative complications. Future studies should focus on determining a threshold for tissue oxygenation taking inter-individual factors into account. The frequency of MINS was high (40%) and related to blood loss, suggesting supply-demand

				mismatch etiology in spine surgery. Tissue oxygenation did not have the power to predict myocardial injury but other intraoperative indicators for supply-demand mismatch should be considered as potential predictors for MINS in future studies."
Generalisability	21	Discuss the generalisability (external validity) of the study results		Overall described in discussion section.
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	17	"This work was supported by a grant from the Lundbeck Foundation Clinical Research Fellowship 2017-2018 for Katrine Feldballe Bernholm. CAS Medical Systems, Inc. provided the FORE-SIGHT ELITE Tissue Oximeter and probes at no cost."

*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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Association between tissue oxygenation and myocardial injury in patients undergoing major spine surgery: A prospective cohort study

Katrine Feldballe Bernholm, MD[1,2], Christian S. Meyhoff, MD, PhD[2,3,4], Philip Bickler, MD, PhD[1]*

[1]Department of Anesthesia and Perioperative Care, University of California, San Francisco, USA

[2]Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark

[3]Copenhagen Center for Translational Research, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark

[4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

* Corresponding author. Email: bernholm3@hotmail.com

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Abstract

Objective: To describe the association between intraoperative tissue oxygenation and postoperative troponin elevation in patients undergoing major spine surgery. We hypothesized that a decrease in intraoperative skeletal muscle tissue oxygenation (SmO_2) was associated with the peak postoperative cardiac troponin value.

Design: This is a prospective cohort study.

Setting: Single-center, University of California San Francisco Medical Center.

Participants: Seventy adult patients undergoing major elective spine surgery.

Primary and secondary outcome measures: High-sensitivity troponin T (hsTnT) was measured in plasma pre-operatively and on the first and second day after surgery to assess the primary outcome of peak postoperative hsTnT. Secondary outcomes included MINS and intensive care unit (ICU) admission within 30 days. Cerebral (ScO_2) and skeletal muscle (SmO_2) tissue oxygenation was measured continuously with near-infrared spectroscopy during surgery. The primary exposure variable was time-weighted area under the curve (TW AUC) for SmO_2.

Results: Mean age was 65 (33-85) years and 59% were female. No significant association was found between TW AUC for SmO_2 and peak hsTnT (Spearman's correlation, r_s=0.17, p=0.16). A total of 28 (40%) patients had MINS. ICU admission occurred in 14 (40%) in lower vs. 25 (71%) in upper half of patients based on TW AUC for SmO_2, p=0.008.

Conclusions: Decrease in SmO_2 was not a statistically significant predictor for peak troponin value following major spine surgery but is a potential predictor for other postoperative complications.

Trial registration: Clinicaltrials.gov identifier: NCT03518372.

Article Summary

Strengths and limitations of this study

- Prospective observational study including 70 patients undergoing major spine surgery
- Contributing knowledge to potential predictors for myocardial injury and clinical implications of tissue oxygenation monitoring
- Applying skeletal muscle tissue oxygenation as primary predictor, decreasing risk of cerebral autoregulation modification of outcomes
- There is no clinical consensus of absolute threshold for tissue hypoxemia, thus population median for skeletal muscle tissue oxygenation was used as cut-off in this study.

Introduction

Major non-cardiac surgery is associated with significant risks of postoperative complications which are sometimes asymptomatic such as covert stroke[1] and myocardial infarction and injury.[2] Cardiovascular events are the leading cause of morbidity and mortality[3] with myocardial injury after non-cardiac surgery (MINS) being a major contributor to further postoperative complications.[4–7] MINS is frequently caused by ischemia and can be diagnosed from elevated postoperative high-sensitivity cardiac troponin, in the absence of non-ischemic factors for troponin elevation.[8] The 30-day mortality is increased up to eight-fold in patients with covert stroke compared to matched controls[9] and stroke occurs in 9% of patients with MINS, making it a substantial public health problem.[10] Peak postoperative cardiac troponin has a linear association with 30-day mortality.[7] Each year, 8 million surgical patients worldwide suffer from MINS but there is sparse knowledge about triggering causes and contributing factors to the magnitude of peak postoperative cardiac troponin.[5,11]

Intraoperative tissue oxygen desaturation is common in patients undergoing major spine surgery[12] probably because of the substantial blood loss and hemodynamic changes that occur in this type of operation. Tissue oxygenation (StO_2) can be measured non-invasively with near-infrared spectroscopy (NIRS). Previous studies found that a decrease in intraoperative StO_2 was associated with wound infection, stroke and renal failure,[13] and that decrease in skeletal muscle tissue oxygenation (SmO_2) was a stronger predictor for these complications than cerebral tissue oxygenation (ScO_2) in spine surgery.[12] However, current knowledge of how tissue oxygenation affects other important clinical outcomes, including MINS, is lacking. In this prospective cohort study we hypothesized that a decrease in SmO_2 was associated with higher peak postoperative high-sensitivity Troponin T (hsTnT). The primary exposure variable was time-weighted area under the curve (TW AUC) for SmO_2 and the primary outcome was peak postoperative hsTnT. This study was conducted with the aim

of examining the association between intraoperative tissue oxygenation and postoperative troponin elevation in patients undergoing major spine surgery.

Methods

This prospective cohort study was conducted at the University of California, San Francisco (UCSF) with Clinicaltrials.gov identifier: NCT03518372. This manuscript adheres to the applicable STROBE guidelines.

Patients

The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018. The surgeries selected were scheduled to last for more than two hours and included instrumentation. Exclusion criteria were: American Society of Anesthesiologists Physical Status Classification System score (ASA)>IV, surgery for tumor or infection, emergent or urgent surgery.

Data collection

Patient characteristics, comorbidities, preoperative physical status and postoperative complications were extracted from the electronical medical record (KFB). Data was collected at two time-points: Prior to surgery and 30 days after surgery. A follow-up phone call to the patient was made 30 days after surgery to verify postoperative outcomes. Baseline values were defined as the pre-incision value. Intraoperative values were defined as data from incision to end of procedure when last suture was placed. Study data were managed using the REDCap electronic data capture tools hosted at UCSF.

Tissue oximetry

Tissue oxygenation was monitored using a tissue oximeter based on near-infrared spectroscopy (NIRS) (FORE-SIGHT Elite, CASMED, Inc., Branford, Connecticut, USA). Cerebral and leg skeletal muscle oxygenation was monitored via two cables connected to

adhesive probes provided by the manufacturer. Probes were placed after tracheal intubation and a baseline was measured from placing of probe to incision. One probe was placed on the left side on the upper forehead to monitor one-sided frontal cortex ScO_2. The second probe was placed on the left tibialis anterior muscle, four fingers below the tibial tuberosity and two fingers lateral to the anterior edge of the tibial shaft, to monitor the SmO_2 of the lower leg muscle. The oximeter generated a data point every 2 seconds. The anesthesia team was blinded to the oximeter. Data from the oximeter were used for tissue oxygenation indices derivation. Indices were maximum, minimum, median and time-weighted area under the curve (TW AUC) for SmO_2 and ScO_2 respectively. The primary exposure variable was TW AUC for SmO_2. TW AUC was calculated for each participant as the area below the intraoperative median for the study population and divided by length of surgery. This was chosen because there is no international consensus on a universal baseline level or normal range for tissue oxygenation.

Troponin measurements

A total of three blood samples for hsTnT were drawn. First sample was drawn by the anesthesiologist in the operating room after placement of the arterial line prior to surgery. Second and third sample were drawn by a phlebotomist or nurse the first and second day after surgery, respectively. After the blood was drawn, the sample was centrifuged immediately and the plasma was divided into two cryo collecting tubes and placed in a -80 ºCelsius freezer for storage. All plasma samples were sent to a specialized laboratory at Hennepin Medical Center (Minneapolis, MN, USA) to be analyzed for the Roche 5th generation, Elecsys hsTnT assay after the study was completed. The data collector was blinded to the results of hsTnT and laboratory personnel analyzing the blood samples were blinded to patient data. Medical

records and perioperative information (e.g. ECG, laboratory values) were reviewed for patients with troponin elevation, to exclude a non-ischemic etiology.[8]

Outcomes

The primary outcome was defined as postoperative peak high-sensitivity cardiac troponin T (hsTnT). A secondary related outcome was MINS, initially defined as hsTnT ≥14 ng/L[14] with factors for non-ischemic etiology excluded (e.g. sepsis, kidney failure, heart failure). This MINS definition was registered at clinicaltrials.gov, but during the course of the study and prior to hsTnT analysis of the blood samples, new data was published, where MINS was defined as an elevated postoperative hsTnT (i.e. 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L) with factors for non-ischemic etiology excluded (e.g. sepsis, kidney failure, heart failure).[8] We therefore updated the protocol to the latter and current MINS definition. Other secondary outcomes were myocardial infarction, non-fatal cardiac arrest, new-onset arrhythmia (defined as new atrial fibrillation or other treatment requiring arrhythmia), heart failure, transient cerebral ischemia, symptomatic stroke, sepsis, surgical site infection, pulmonary complications (including pulmonary infection, pneumothorax, atelectasis, pulmonary embolus and other pulmonary complication), creatinine elevation (>1.3 mg/dL for men and >1.1 mg/dL for women), intensive care unit (ICU) admission, length of hospital stay and mortality, all within 30 days after surgery. In addition, we analyzed a composite outcome that consisted of all above mentioned postoperative complications.

Sample size

Sample size calculations were based on clinical data and previous studies investigating tissue oxygenation as an outcome for postoperative complications.[12,13] These studies evaluated all

types of complications as primary outcome. Mean (SD) TW AUC for SmO_2 was 1.59 %*min*h^{-1} (2.35).[12] We estimated a minimal clinically relevant difference to be a 36% increase in TW AUC for SmO_2 for participants with high peak hsTnT (with a cut-off of 14 ng/L based on the 99th percentile of a healthy population[15]) compared to participants with low peak hsTnT. Using a power of 80% and a significance level of 0.05, a sample size of 68 participants for this study was needed. We anticipated a low number of drop-outs, as the study design was observational, resulting in a total sample size of 70 participants.

Statistical analysis

Results are presented as mean±SD and median (interquartile range, IQR) when appropriate. Revised Cardiac Risk Index (RCRI) and corresponding risk of cardiac complications at 30 days after surgery were computed according to current criteria[16]. Postoperative outcomes were compared stratifying the study population in two groups by median TW AUC for SmO_2. Comparison between groups were based on Chi-squared tests for categorical variables, ANOVA and Wilcoxon rank sum test.

The primary analysis of the association between TW AUC for SmO_2 and peak hsTnT was tested by Spearman correlation analysis. Univariable and multivariable logistic regression models were used in secondary analyses to examine the associations of baseline characteristics, intraoperative variables and StO_2 indices with higher peak hsTnT which was dichotomized in high/low categories using median peak hsTnT in the study population as cut-off. Univariable and multivariable logistic regression was used to test the association between StO_2 indices and MINS and the adjusted prediction for TW AUC for SmO_2 and MINS was calculated. Variables for adjustment in the multivariable analyses were age, sex, body mass index (BMI), smoking, diabetes, hypertension, previous stroke, chronic lung disease,

arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate.

Stata Statistical Software (release 15; StataCorp LP, College Station, TX, USA) was used for all analyses.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this study.

Results

A total of 70 patients undergoing spine surgery was included in this prospective cohort study. Mean age was 65 (33-85) years and 41 (59%) participants were female. Mean (95% confidence interval, CI) risk of cardiac complications at 30 days after surgery, calculated according to RCRI was 7,7 (7,0-8,3) %. The median percentage estimated blood loss of estimated blood volume was 17 (IQR 8;31) %. A summary of patient characteristics, medical history, surgical information and values for tissue oxygenation are found in Table 1.

Incidence of MINS and major outcomes

The median peak hsTnT was 19 (IQR 10;30) ng/L and based on a hsTnT of 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L, 28 (40%) participants had MINS (Table 2). The number of participants with any postoperative complications were 41 (59%) and when MINS was included as a complication, 52 (74%) of participants had one or more postoperative complications (Table 2). Estimated blood loss and length of surgery was associated with MINS (odds ratio, OR (95% CI): 1.001 (1.000-1.002), p=0.002 and 1.007 (1.002-1.011), p=0.004, respectively).

Relationships of tissue oxygenation to MINS and other outcomes

In the univariable correlation analysis of TW AUC for SmO_2 and peak hsTnT, no significant association was found (r_s=0.17, p=0.16, Figure 1). There was a statistically significant association between higher TW AUC for SmO_2 and the composite outcome of postoperative complications (participants in lower half: 21 (60%) vs. participants in upper half: 31 (89%), p=0.006, Table 2) but when logistic regression was performed, this association was not significant. Furthermore, a statistically significant association between higher TW AUC for SmO_2 and ICU admission was found (participants in lower half: 14 (40%) vs. participants in

upper half: 25 (71%), p=0.008, Table 2). There were no other statistically significant differences in outcomes between the two groups based on median TW AUC for SmO_2. When testing the StO_2 indices as predictors for higher peak hsTnT by logistic regression, the univariable analysis found that for every one percent increase in median and maximum SmO_2, the odds of having high peak hsTnT decreased (OR (95% CI): 0.93 (0.87-0.996), p-value=0.039 and 0.92 (0.85-0.99), p=0.025, respectively, Table 3). After multivariable adjustment for baseline and clinical variables, median and maximum SmO_2 were not independent predictors for higher peak hsTnT (Table 3). None of the StO_2 indices were found to be significant predictors for MINS (Table 3). Adjusted predicted probability was calculated based on univariable logistic regression and showed increasing probability for MINS with increasing TW AUC for SmO_2 (Figure 2) albeit this was not statistically significant (OR (95% CI): 1.00 (0.99-1.01), p=0.74). Although this was not systematically assessed for the purpose of this study, only one participant presented with ischemic symptoms on the first two postoperative days according to medical records. This patient was not diagnosed with clinical myocardial infarction after examination, although hsTnT was 31 ng/L.

Discussion

In a prospective cohort study of 70 participants, we investigated intraoperative tissue oxygenation as predictor for myocardial injury after spine surgery. We found that skeletal muscle and cerebral tissue oxygenation were not independent predictors for elevated high-sensitivity troponin T or MINS. However, in exploratory analyses, some other indices for SmO_2 were associated with higher peak hsTnT, whereas ScO_2 indices were not.

Tissue oxygenation is a result of the oxygen supply and demand of the specific tissue and is determined by multiple physiological factors including oxygen saturation, hemoglobin concentration and cardiac output.[17] Measurement of tissue oxygenation with NIRS has been investigated in previous studies as predictor for a number of different outcomes. Several studies have examined cerebral oxygenation in patients undergoing cardiac surgery, whereas few studies have investigated skeletal muscle tissue oxygenation as predictor for clinical outcomes. In patients undergoing cardiac surgery, ScO_2 was found to be associated with stroke, cognitive decline, length of hospital stay and mortality.[18,19] One study found that decrease in ScO_2 was not a predictor for delirium in elderly patients.[20] A recent meta-analysis of 10 trials with a total of 1466 patients, found that NIRS-based algorithms for ScO_2 did not reduce mortality or organ injury affecting the heart, brain or kidneys.[21] Despite the lack of evident benefit for ScO_2-guided clinical algorithms, ScO_2 monitoring is routinely used in cardiac surgery.

Cerebral and skeletal muscle tissue have different physiological characteristics. *Meng et al.*[12] found that SmO_2 was a stronger predictor than ScO_2 for composite postoperative outcomes, including myocardial injury, stroke, pulmonary complications and creatinine elevation. Although findings in the current study were statistically insignificant, the exploratory analyses yielded a stronger association between SmO_2 and outcomes as compared to ScO_2.

This aligns with the theory that SmO_2 is a leading indicator for global desaturation due to low autoregulation in skeletal muscle tissue compared with the higher level of autoregulation in cerebral tissue.[22] Of note, skeletal and myocardial autoregulation may not be the same and it is possible that myocardial autoregulation shows similar patterns to cerebral autoregulation in some physiological instances. The importance of preserved cerebral autoregulation is substantial. Brain tissue is more sensitive to hypoxia than skeletal muscle.[17] One study showed that impaired cerebrovascular autoregulation was associated with increased morbidity and mortality within 30 days from surgery in patients undergoing major non-cardiac surgery.[23] A study in healthy subjects suggested SmO_2 to be an early indicator for impending cardiovascular collapse and showed that SmO_2 declined in parallel with stroke volume.[24] Perfusion of skeletal muscle tissue follows the same linearity in decline with decreasing cardiac output whereas cerebral tissue perfusion only decreases approximately one third of cardiac output.[25] This study found TW AUC for SmO_2 to be almost three times larger than TW AUC for ScO_2 (98 vs. 33 %*min*h^{-1}) indicating autoregulation in brain tissue. Of note, spine surgery patients at UCSF almost all receive anesthetics that include very low amounts of inhalational anesthetics, probably preserving brain autoregulation of blood flow. Despite these findings, the clinical implications of SmO_2 monitoring is still yet to be determined. TW AUC for SmO_2 was chosen as a predictor in this study as it maximizes sensitivity by including all available data for the specific parameter (magnitude and duration of desaturation as well as covering the entire duration of surgery). Furthermore, it minimizes the effect of potential error measurements on the tissue oxygenation value but because TW AUC for SmO_2 is a calculated value it currently has limitations in regards of clinical utility. StO_2 was not statistically significant associated with MINS in the current study but other indicators of supply-demand mismatch, i.e. estimated blood loss and length of surgery, were

significantly associated with MINS and peak hsTnT. These are established predictors for MINS[26] and contributes to the understanding of the pathophysiology for elevated troponin.[27] In general, the majority of MINS are undetected (80%) as patients do not have ischemic symptoms.[4,10] In this study only one participant presented with ischemic symptoms. The type of surgery the participants underwent was comprehensive and many participants were treated with strong analgesics postoperatively which could be a contributing factor to the lack of ischemic symptoms in the participants with MINS. The incidence of MINS among the participants in this study was 40%. In comparison the general incidence of MINS in patients undergoing non-cardiac surgery is 8%[4] but this is not restricted to major surgery only and the incidence depends on the cut-off for troponin elevation used. Other groups found similar high incidence of MINS.[28]

Study limitations

As this was an observational cohort study it was not designed to determine causality between tissue oxygenation and postoperative myocardial injury. The study was not powered for all secondary outcomes, as we based the power calculation on a study with the outcome composite postoperative complications that included less severe complications (constipation, oliguria etc.).[12]

We found a high incidence of MINS in this study but the number of serious outcome events (e.g. death, stroke, non-fatal cardiac, myocardial infarction) were sparse in the 30-day follow-up period. The participants underwent spine surgery which was not emergent, conducted as cancer treatment/tumor resection or indicated by any life-threatening condition. Thus, it is possible that participants were in a better physical condition when scheduled for this type of elective surgery than for other major non-cardiac surgical procedures. Changes in blood

pressure and heart rate may trigger MINS. Extensive analyses of associations between these parameters an MINS were not possible in this study.

The NIRS method is non-invasive and tracks tissue oxygenation continuously. However, limitations in regards to the technology has been presented and includes bias regarding skin pigmentation, gender and assumed mixture of venous and arterial blood.[29] With the equipment used in this study it was not possible to obtain data on different hemoglobin (Hgb) fractions (total Hgb, oxy-Hgb and deoxy-Hgb), which could potentially have qualified the analysis even further. Total blood loss was included in the predefined model to predict MINS but relative changes in Hgb concentrations, including those caused by transfusions, was not accounted for. Inter-individual differences in saturation contributes to the difficulty of determining an absolute threshold for tissue hypoxia. In the calculation of the primary predictor of TW AUC for SmO_2 we used the population median for intraoperative SmO_2 as cut-off. The choice of cut-off should be considered when interpreting results of studies investigating the impact of tissue oxygenation.

In summary, in this study tissue oxygenation was not a statistically significant predictor for peak postoperative high-sensitivity troponin but is a potential predictor for other postoperative complications. Future studies should focus on determining a threshold for tissue oxygenation taking inter-individual factors into account and apply NIRS technology with the ability of detecting different Hgb fractions. The frequency of MINS was high (40%) and related to blood loss, suggesting supply-demand mismatch etiology in spine surgery. Tissue oxygenation did not have the power to predict myocardial injury but other intraoperative indicators for supply-demand mismatch should be considered as potential predictors for MINS in future studies.

Author contributions

KFB: Conception and design, acquisition, analysis and interpretation of data, drafting, critical revision and final approval of the manuscript. CSM: Conception and design, analysis and interpretation of data, critical revision and final approval of the manuscript. PB: Conception and design, analysis and interpretation of data, critical revision and final approval of the manuscript.

Declaration of interests

Christian S. Meyhoff has received institutional direct and indirect research funding from Boehringer Ingelheim, Ferring Pharmaceuticals, Radiometer and Merch, Sharp & Dohme, as well as lecture fees from Radiometer, all outside submitted work. The remaining authors declare that they have no conflict of interest.

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CAS Medical Systems, Inc. provided the FORE-SIGHT ELITE Tissue Oximeter and probes at no cost.

Data availability statement

Anonymised data will be made available upon reasonable request.

Ethics statements

Patient consent for publication: Not required.

Ethics approval: The study was approved by the University of California San Francisco Institutional Review Board (IRB 14-12996) and both verbal and written consent was obtained from all participants before surgery.

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Table 1. Participant characteristics and intraoperative data.

Variables	*Participants n=70*
Demographics	
Age, years	65 (33-85)
Sex, female	41 (59%)
BMI, kg/m^2	28.8 (24.4;32.9)
ASA	
I	1 (1%)
II	37 (53%)
III	31 (44%)
IV	1 (1%)
Smoking	
Never	37 (53%)
Current	3 (4%)
Former	30 (43%)
Medical history	
Stroke	5 (7%)
TCI	3 (4%)
Hypertension	36 (51%)
Diabetes mellitus	8 (11%)
Chronic lung disease[a]	15 (21%)
Sleep apnea	16 (23%)
Arrhythmia	11 (16%)
Valvular disease	6 (9%)
Coronary artery disease	8 (11%)
Creatinine elevation	2 (3%)
RCRI class	
I	49 (70%)

II	15 (21%)
III	6 (9%)
IV	0
Surgical information	
Length of surgery, minutes	264 (201;405)
Osteotomy performed	35 (50%)
Estimated blood loss, mL	753 (400;1400)
Mean arterial pressure, mmHg	83±9
Heart rate, bpm	69±11
Tissue oximetry	
SmO_2 median, %	75 (70;79)
SmO_2 minimum, %	66 (61;70)
SmO_2 maximum, %	84 (78;88)
TW AUC for SmO_2, %*min*h^{-1}	98 (9;298)
ScO_2 median, %	66 (62;71)
ScO_2 minimum, %	60 (56;65)
ScO_2 maximum, %	77 (72;82)
TW AUC for ScO_2, %*min*h^{-1}	33(0.06;131)

Data are mean (standard deviation) for normally distributed variables and median (interquartile range) for variables with skewed distributions. [a]Includes asthma and chronic obstructive pulmonary disorder (COPD). BMI=body mass index, ASA= American Society of Anesthesiologists Physical Status Classification System score, TCI=transient cerebral ischemia, RCRI=Revised Cardiac Risk Index, SmO_2=skeletal muscle tissue oxygenation, TW AUC=time-weighted area under the curve, ScO_2=cerebral tissue oxygenation.

Table 2. Summary of postoperative outcomes within 30 days after spinal surgery.

Postoperative complications	Lower half TW AUC for SmO_2, N=35	Upper half TW AUC for SmO_2, N=35	p-value
TW AUC for SmO2, (%*min*h^{-1})	9 (1;53)	298 (189;586)	<0.001
Peak hsTnT, ng/L	17 (9;26)	24 (10;33)	0.15
MINS	12 (34%)	16 (46%)	0.33
Myocardial infarction	0	0	-
Non-fatal cardiac arrest	0	0	-
New-onset arrhythmia	1 (3%)	2 (6%)	0.56
Heart failure	0	0	-
TCI	0	0	-
Stroke	0	0	-
Sepsis	1 (3%)	1 (3%)	1.00
Surgical site infection	2 (6%)	2 (6%)	1.00
Pulmonary complications	4 (11%)	3 (9%)	0.69
Creatinine elevation	1 (3%)	1 (3%)	1.00
ICU admission	14 (40%)	25 (71%)	0.008
Length of postoperative hospitalization	6 (4;7)	6 (6;8)	0.056
Mortality	0	0	-
Composite outcome	21 (60%)	31 (89%)	0.006

Data are mean (standard deviation) for normally distributed variables and median (interquartile range) for variables with skewed distributions). P-values are based on chi^2-tests, ANOVA and Wilcoxon rank sum tests. TW AUC=time-weighted area under the curve, SmO_2=skeletal muscle tissue oxygenation, hsTnT=high-sensitivity Troponin T, MINS=myocardial injury after non-cardiac surgery, TCI=transient cerebral ischemia, ICU=intensive care unit.

Table 3. Tissue oxygenation measures as predictors for higher peak hsTnT and MINS.

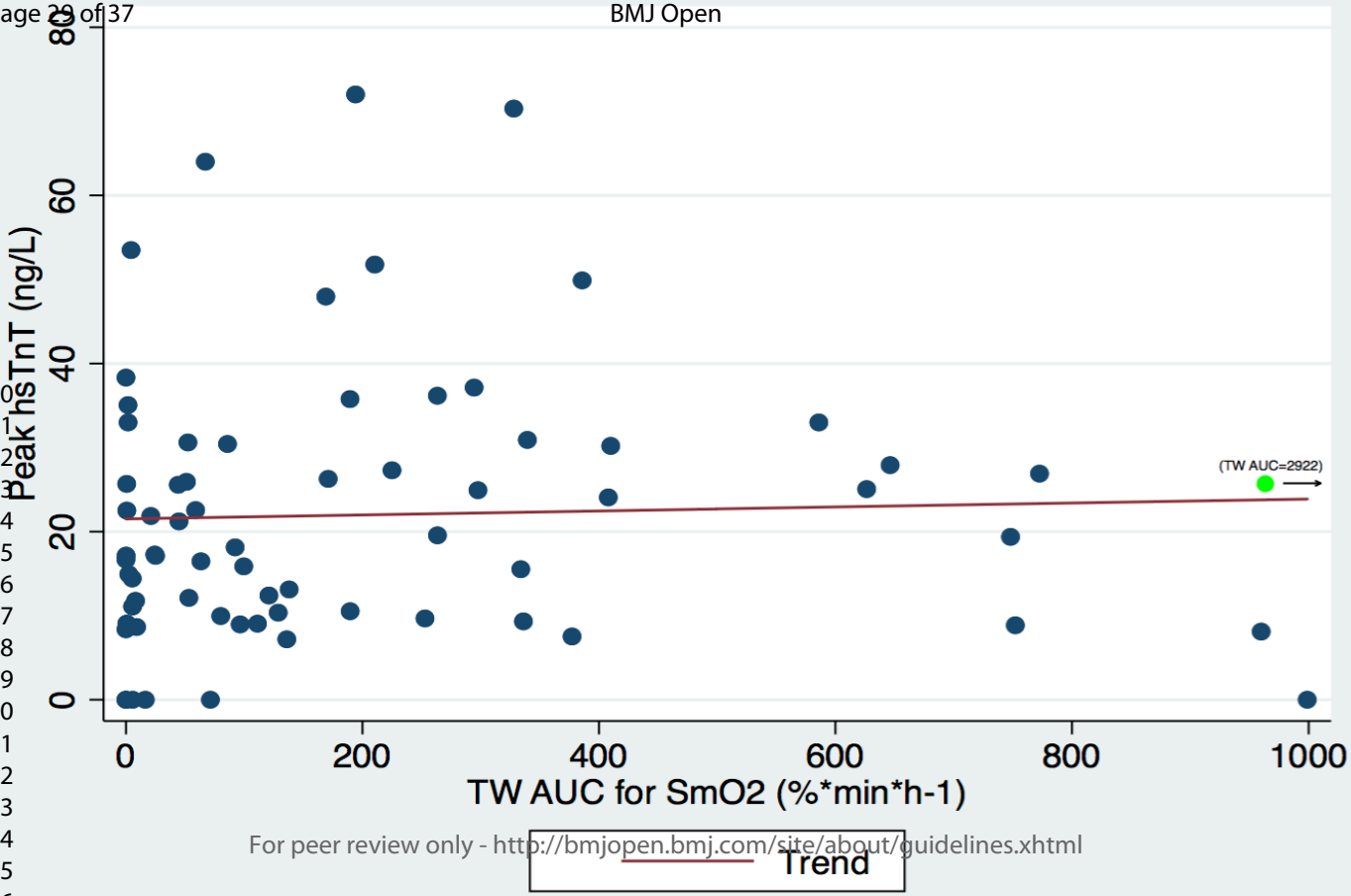
	High peak hsTnT vs. low peak hsTnT				MINS vs. no MINS	
StO_2 indices	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value	Univariable OR (95% CI)	p-value
Median SmO_2, %	0.93 (0.87-0.996)	0.039	0.92 (0.82-1.04)	0.18	0.96 (0.76-1.21)	0.75
Minimum SmO_2, %	0.97 (0.92-1.01)	0.16	0.94 (0.86-1.03)	0.20	0.95 (0.75-1.22)	0.70
Maximum SmO_2, %	0.92 (0.85-0.99)	0.025	0.90 (0.80-1.02)	0.11	0.90 (0.70-1.15)	0.41
TW AUC SmO_2, %*min*h^{-1}	1.00 (1.00-1.00)	0.15	1.00 (1.00-1.01)	0.22	1.00 (0.99-1.01)	0.74
Median ScO_2, %	0.99 (0.91-1.06)	0.70	0.92 (0.79-1.06)	0.24	0.79 (0.59-1.07)	0.13
Minimum ScO_2, %	0.96 (0.91-1.03)	0.26	0.83 (0.69-0.98)	0.030	0.10 (0.00-5.34)	0.26
Maximum ScO_2, %	0.97 (0.90-1.05)	0.47	0.99 (0.94-1.05)	0.82	1.01 (0.96-1.06)	0.76
TW AUC ScO_2, %*min*h^{-1}	1.00 (1.00-1.01)	0.32	1.00 (1.00-1.01)	0.33	1.00 (1.00-1.01)	0.32

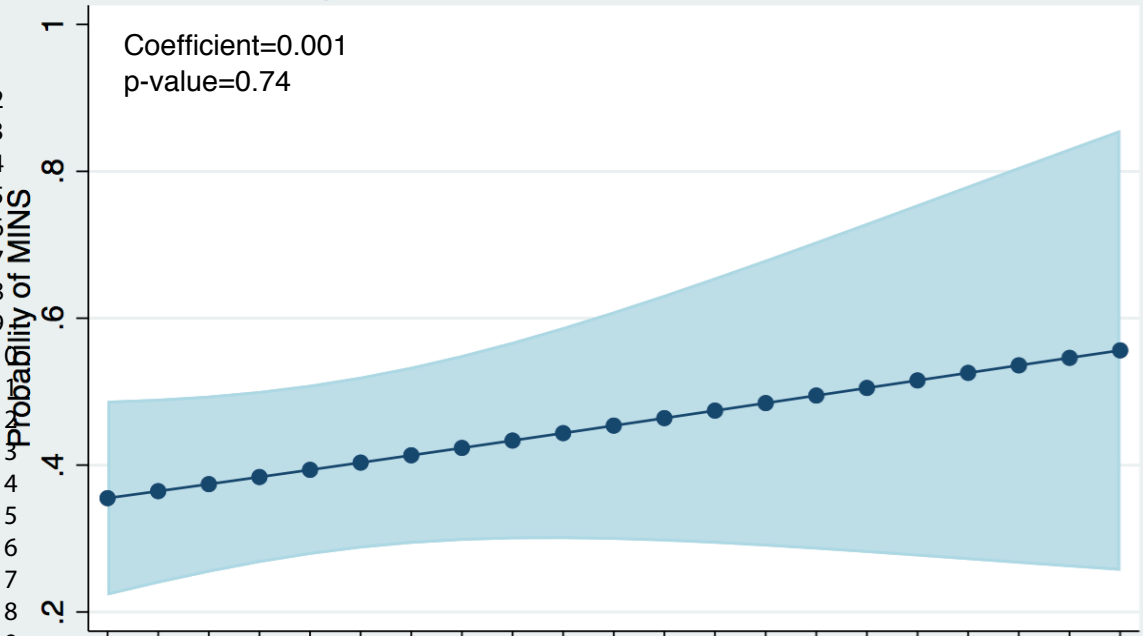
This table shows the odds of having an outcome (high peak hsTnT or MINS, respectively) for every one percent/one unit increase in the specific tissue oxygenation variable. Multivariable analysis is adjusted for age, sex, BMI=body mass index, smoking, diabetes, hypertension, previous stroke, chronic lung disease, arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate. hsTnT=high-sensitivity Troponin T, MINS=myocardial injury after non-cardiac surgery, StO_2=tissue oxygenation, OR=odds ratio, CI=confidence interval, SmO_2=skeletal muscle tissue oxygenation, TW AUC=time-weighted area under the curve, ScO_2=cerebral tissue oxygenation.

Figure legends:

Figure 1. Relationship between time-weighted area under the curve (TW AUC) for skeletal muscle tissue oxygenation (SmO_2) and peak value of high-sensitivity troponin T (hsTnT) measured within the first two days after surgery.

Figure 2. Adjusted prediction curve for time-weighted area under the curve (TW AUC) for skeletal muscle tissue oxygenation (SmO_2) as predictor for myocardial injury after non-cardiac surgery (MINS). CI=confidence interval.





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	"A Prospective Cohort Study"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	See abstract
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	"In this prospective cohort study we hypothesized that a decrease in SmO_2 was associated with higher peak postoperative high-sensitivity Troponin T (hsTnT)", "This study was conducted with the aim of examining the association between intraoperative StO2 and myocardial injury in patients undergoing major spine surgery."
Methods				
Study design	4	Present key elements of study design early in the paper	6	"This prospective cohort study was conducted…"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	"This prospective cohort study was conducted at the University of California, San Francisco (UCSF)", "The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018.",

				"Patient characteristics, comorbidities, preoperative physical status and postoperative complications were extracted from the electronical medical record (KFB). Data was collected at two time-points: Prior to surgery and 30 days after surgery. A follow-up phone call to the patient was made 30 days after surgery to verify postoperative outcomes."
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	6	"The patients were adults (≥18 years) undergoing elective spine surgery at UCSF from January to May 2018. The surgeries selected were scheduled to last for more than two hours and included instrumentation. Exclusion criteria were: American Society of Anesthesiologists Physical Status Classification System score (ASA)>IV, surgery for tumor or infection, emergent or urgent surgery.", "…postoperative complications were extracted from the electronical medical record…", "A follow-up phone call to the patient was made 30 days after

				surgery to verify postoperative outcomes."
		(*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		N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 6 9	For outcomes see 'Outcomes' For predictors see 'Tissue Oximetry' "Variables for adjustment in the multivariable analyses were age, sex, body mass index (BMI), smoking, diabetes, hypertension, previous stroke, chronic lung disease, arrhythmia, valvular disease, chronic kidney disease, length of surgery, osteotomy performed, estimated blood loss, mean arterial blood pressure and mean heart rate."
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	6, 7	See 'Data Collection', 'Tissue Oximetry' and 'Troponin Measurement'
Bias	9	Describe any efforts to address potential sources of bias	6	See 'Patients' and 'Data Collection'
Study size	10	Explain how the study size was arrived at	9	"Sample size calculations were based on clinical data and previous studies investigating tissue oxygenation as an outcome for postoperative

	complications.[12,13] These studies evaluated all types of complications as primary outcome. Mean (SD) TW AUC for SmO_2 was 1.59 %*min*h^{-1} (2.35).[12] We estimated a minimal clinically relevant difference to be a 36% increase in TW AUC for SmO_2 for participants with high peak hsTnT (with a cut-off of 14 ng/L based on the 99th percentile of a healthy population[15]) compared to participants with low peak hsTnT. Using a power of 80% and a significance level of 0.05, a sample size of 68 participants for this study was needed. We anticipated a low number of drop-outs, as the study design was observational, resulting in a total sample size of 70 participants."

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	9	"Results are presented as mean+/- SD and median (interquartile range, IQR) when appropriate."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	See 'Statistical Analysis'
		(*b*) Describe any methods used to examine subgroups and interactions	9	See 'Statistical Analysis'
		(*c*) Explain how missing data were addressed		N/A
		(*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		N/A
		(*e*) Describe any sensitivity analyses		N/A
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	14	"A total of 70 patients undergoing spine surgery was included in this prospective cohort study"
		(b) Give reasons for non-participation at each stage		N/A
		(c) Consider use of a flow diagram		N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	"Mean age was 65 (33-85) years and 41 (59%) participants were female. The median estimated blood loss was 753 (IQR 400;1400) mL. A summary of patient characteristics, medical history, surgical information and values for tissue oxygenation are found in Table 1."
		(b) Indicate number of participants with missing data for each variable of interest		N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		30 days follow-up described in methods
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11	"The median peak hsTnT was 19 (IQR 10;30) ng/L and based on a

				hsTnT of 20 to <65 ng/L with an absolute change ≥5 ng/L or a single hsTnT ≥65 ng/L, 28 (40%) participants had MINS (Table 2). The number of participants with any postoperative complications were 41 (59%) and when MINS was included as a complication, 52 (74%) of participants had one or more postoperative complications (Table 2)."
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		N/A
		Cross-sectional study—Report numbers of outcome events or summary measures		N/A
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	11	See section 'Relationships of tissue oxygenation to MINS and other outcomes' under 'Results'
		(*b*) Report category boundaries when continuous variables were categorized		N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		N/A
Discussion				
Key results	18	Summarise key results with reference to study objectives	13	"In a prospective cohort study of 70 participants, we investigated intraoperative tissue oxygenation as predictor for myocardial injury after spine surgery. We found that muscle and cerebral tissue oxygenation were not independent predictors for elevated high-sensitivity troponin T or MINS. However, in exploratory analyses, some other indices for SmO2 were associated with higher peak hsTnT, whereas ScO2 indices were not."
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	15	See section 'Study limitations' under 'Discussion'
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16	See full discussion section. Concluding remarks: "In summary, tissue oxygenation was not a statistically significant predictor for peak postoperative high-sensitivity troponin but is a potential predictor for other postoperative complications. Future studies should focus on determining a threshold for tissue oxygenation taking inter-individual factors into account. The frequency of MINS was high (40%) and related to blood loss, suggesting supply-demand

				mismatch etiology in spine surgery. Tissue oxygenation did not have the power to predict myocardial injury but other intraoperative indicators for supply-demand mismatch should be considered as potential predictors for MINS in future studies."
Generalisability	21	Discuss the generalisability (external validity) of the study results		Overall described in discussion section.
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	17	"This work was supported by a grant from the Lundbeck Foundation Clinical Research Fellowship 2017-2018 for Katrine Feldballe Bernholm. CAS Medical Systems, Inc. provided the FORE-SIGHT ELITE Tissue Oximeter and probes at no cost."

*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.