

Intraoperative tissue oxygenation and postoperative outcomes after major non-cardiac surgery: an observational study†

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Editor's key points

- It is important to identify perioperative factors that contribute to mortality and major morbidity.
- Low levels of tissue oxygenation may be an important determining factor in outcome.
- Minimum perioperative peripheral tissue oxygenation was found to relate to subsequent major postoperative problems.
- The relationship between tissue oxygenation and outcome is complex and needs further study.

Background. The relationship between tissue oxygen saturation (StO₂) and serious postoperative complications remains unclear. We tested the hypothesis that perioperative StO₂ in patients undergoing major non-cardiac surgery is inversely related to serious surgical outcomes.

Methods. We enrolled 124 patients, ASA physical status ≤IV, having elective major non-cardiac surgeries with general anaesthesia. An InSpectra Model 650 StO₂ monitor (Hutchinson Technology, Hutchinson, MN, USA) was used to measure StO₂ at the thenar eminence throughout surgery and for two postoperative hours. Our primary outcome was a composite of 30 day mortality and serious in-hospital complications. The secondary outcome was an *a priori* subset of the primary composite outcome representing infectious and wound-healing complications. Multivariable logistic regression was used to evaluate the associations between our primary and secondary outcomes and time-weighted average (TWA) and minimum StO₂.

Results. Patients were 61 (12), mean (SD) yr old. The minimum StO₂ was inversely associated with our primary composite outcome ($P=0.02$). The estimated odds ratio (97.5% CI) of having any major postoperative morbidity was 0.82 (0.67, 1.00) for a 5% increase in the minimum StO₂. In contrast, TWA StO₂ was not significantly associated with major postoperative morbidity ($P=0.35$). Furthermore, neither TWA ($P=0.65$) nor minimum ($P=0.70$) StO₂ was significantly associated with wound complications.

Conclusions. Minimum perioperative peripheral tissue oxygenation predicted a composite of major complications and mortality from major non-cardiac surgery. This is an observational association and whether clinical interventions to augment tissue oxygenation will improve outcomes remains to be determined.

Keywords: hypoxia; oxygen; postoperative complications; postoperative period; tissues

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Tissue oxygenation reflects the balance between supply and utilization of oxygen, with hypoxia being defined by inadequate cellular oxygen. Tissue oxygenation is always considerably lower than arterial oxygenation because a gradient is needed to drive oxygen molecules from capillaries to the surrounding cells.^{1,2} Depending on regional perfusion and other

factors, the relationship between arterial and tissue partial pressures can differ considerably.³

Copious previous work links tissue oxygenation—as distinct from arterial partial pressure—to surgical site infection (SSI) and wound-related complications,⁴ presumably because oxidative killing of bacteria by neutrophils is one of the primary

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defences against SSI⁵ and because killing efficacy depends on the partial pressure of oxygen over the entire physiological range of tissue values.^{6, 7} For example, patients with low tissue oxygen partial pressure³ or saturation⁸ are more susceptible to wound infection and bowel anastomotic leaks after colorectal surgery.⁹ Consistent with these observational data, supplemental inspired oxygen (which roughly doubles peripheral tissue oxygen partial pressure) reduces the risk of SSI in some,^{10, 11} but not all,¹² randomized trials.

Tissue oxygenation correlates with outcomes in non-surgical settings such as heart failure.¹³ Low or inadequate tissue oxygenation is also associated with specific perioperative complications including acute postoperative kidney injury,¹⁴ septic shock, and acute systemic inflammatory conditions.¹⁵ Because adequate tissue oxygenation is fundamental to cellular function, tissue hypoxia may be a root cause of many serious perioperative complications.

The relationship of tissue oxygen saturation (StO₂) to immediate postoperative serious morbidity and mortality has not been fully characterized. We therefore tested the primary hypothesis that intraoperative and immediate postoperative tissue oxygen saturation in patients undergoing major non-cardiac surgery, as measured at the thenar eminence with near-infrared spectroscopy (NIRS), is inversely related to a composite of serious postoperative complications and 30 day mortality. Our secondary hypothesis was that there is an inverse relationship between StO₂ and a composite outcome of SSI and wound-healing complications.

Methods

We report the results of a substudy of the DeLiT trial (ClinicalTrials.gov Identifier: NCT00433251),¹⁶ a factorial randomized single-centre study designed to test the primary hypotheses that major postoperative morbidity is reduced by: (i) low-dose dexamethasone; (ii) intensive intraoperative glucose control; and (iii) lighter anaesthesia. Patients ≥ 40 yr of age, ASA \leq IV, undergoing elective major non-cardiac surgeries (open major vascular, major abdominal, major urological surgery) were enrolled. Exclusion criteria included: recent i.v. or oral steroid therapy (within 30 days); any contraindications to the proposed interventions; ASA physical status $>$ IV; and procedures done under regional anaesthesia. The trial was conducted with Institutional Review Board approval and written informed consent was obtained from each participant.

All patients were given general anaesthesia, and tracheal intubation, with sevoflurane in air and oxygen mixture and i.v. fentanyl infusion after a standardized anaesthetic protocol consistent with the randomization to light or deep anaesthesia. Patients were also randomized to blood glucose concentrations of 80–110 mg dl⁻¹ (intensive control) or $<$ 200 mg dl⁻¹ (conventional control) and simultaneously randomized to receive i.v. dexamethasone (8 mg immediately before operation, 4 and 2 mg on postoperative days 1 and 2, respectively) or placebo as part of the underlying factorial study. The lungs were mechanically ventilated at the discretion of the anaesthesiologist who was blinded to the StO₂

reading to maintain end-tidal P_{CO₂} near 35 mm Hg. Typically, patients are ventilated with a tidal volume of \sim 8 ml kg⁻¹ with PEEP of 5 cm H₂O. Normothermia was maintained with forced-air warming.

There are many methods of measuring tissue oxygenation, including optodes,¹⁷ polarographic (Clark) electrodes,^{18, 19} injectable tissue markers, electron spin resonance, fluorine tuned MRI,²⁰ and tissue blood saturation monitors. All have drawbacks. For example, the Clark-type electrode, while it is only minimally invasive, it is expensive and technically tricky. We thus chose an alternative non-invasive rapidly responsive approach, near-infrared spectrometry, which estimates tissue oxygen saturation from absorption of light by tissue chromophores in the 700–1000 nm spectrum.^{21, 22}

Specifically, we used an InSpectra StO₂ Tissue Oxygenation Monitor, Model 650 (Hutchinson Technology, Hutchinson, MN, USA). This FDA-approved device continuously measures tissue oxygen saturation at a depth of \approx 15 mm under the surface from a sensor adhered to the skin. The sensor was attached to the patient's thenar eminence after anaesthetic induction, and maintained throughout surgery and for two postoperative hours. StO₂ values were recorded at 2 s intervals and downloaded into a computer for subsequent analysis; the values were not available to clinicians and therefore could not provoke changes in patient management.

Intraoperative arterial pressure was controlled to within a range of +20% to –30% of the preoperative baseline value. Heart rate was controlled to within a range of 40–90 beats min⁻¹. This was achieved through standardized protocol with consideration to the depth of anaesthesia, blood volume status assessment, and vasoactive drugs if required. These included nitroglycerine and/or esmolol for treating hypertension and/or tachycardia. Phenylephrine, ephedrine, and/or glycopyrrolate were used to treat hypotension and/or bradycardia.

The primary i.v. fluid was lactated Ringer's solution unless contraindicated. Up to 500 ml were given with induction of anaesthesia at the anaesthesiologist's discretion. Subsequently, lactated Ringer's solution was given as the maintenance crystalloid. Blood loss was replaced with lactated Ringer's solution at a 3:1 ratio, colloid at a 1–2:1 ratio, or red cells at a 1:1 ratio at the anaesthesiologist's discretion.

Red cell transfusions were controlled by protocol as well. Target minimum haematocrits (HCTs) were determined before operation based on the patient's cardiovascular status. The HCT was maintained at 25–28% in patients without substantial cardiac disease, but maintained at 30% in those with significant cardiac disease (defined as previous myocardial infarction, angina, congestive heart failure, or cardiomyopathy).

Our primary outcome was a composite of 30 day mortality and serious in-hospital complications. The secondary outcome was a subset of the primary outcome composite and included deep or organ-space SSI; sepsis; internal or external fistula formation; and bowel and surgical anastomosis stricture/obstruction or anastomotic leak (Table 1).

We assessed the associations between the collapsed composite of any major complication and time-weighted average (TWA) of all StO_2 values, and also the minimum StO_2 [defined as the minimum value sustained ($\pm 1\%$) over at least 5 min], using multivariable logistic regressions with the backward model selection (significance-to-stay criteria was 0.20). Few patients had an oscillometric arterial pressure cuff on the same arm as the tissue oxygen probe. Because the activation of an oscillometric arterial pressure cuff may produce a very brief period of low flow in distal tissues, followed by a brief hyperaemic period, we used 5 min as the duration over which the lowest StO_2 was sustained as a criteria to define the analysed minimum StO_2 (while it was recorded every 2 s) to eliminate any potential artifactual effect the oscillometric cuff might have had on StO_2 readings. We considered the following pre-specified potential confounders: age, gender, smoking status, type of surgery, BMI, history of coronary artery disease, congestive heart failure, stroke, chronic obstructive pulmonary disease, and transient ischaemic attacks, insulin therapy, preoperative creatinine >2.0 mg dl^{-1} , and HCT, and the three randomized interventions of the DeLiT trial. To account for testing two predictors of interest, we used a significance criterion of $P < 0.025$ for each assessment (Bonferroni's adjustment to control the overall significance level at 0.05). Since this relationship may or may not be linear, we first visually assessed it by plotting the estimated probability (on the logit scale) of having the outcome as a function of StO_2 , using a univariable logistic regression incorporating a smooth (thin-plate regression spline) term for StO_2 (smoothing parameter obtained via cross-validation). We assessed the associations between the secondary outcome and the TWA of StO_2 and the minimum of StO_2 , using the same method. The fit of each model was assessed by the Hosmer–Lemeshow goodness-of-fit test.²³

In addition, intraoperative usage of vasoactive drugs and fluids management were summarized using standard summary statistics, and were compared among patients who had the primary outcome and those who did not using the standardized difference and by standard statistical tests. Standardized difference was defined as the difference in means or proportions divided by the pooled standard deviation. A standardized difference of ≤ 0.20 in the absolute value suggests that the compared two groups are descriptively similar.

Sample size calculations are based on the primary outcome. We assumed a standard deviation of 10% for the TWA of StO_2 and 20% for the proportion having at least one major complication from clinical experience. In order to have 85% power at the 0.025 significance level (Bonferroni's adjustment for two predictors, overall 0.05 type I error) to detect at least a 30% relative reduction in the primary outcome (i.e. an odds ratio of 0.65 or lower) per 5% increase in the TWA of StO_2 , a calculated sample size of 113 was obtained. Thus, a total sample size of 124 patients, allowing for 10% drop-out was selected to ensure an adequately powered study.

For our main analysis, we used the logistic procedure in SAS software version 9.2 for Windows (SAS Institute, Cary,

NC, USA) and the gam function available in the mgcv library for R software version 2.8.1 for Windows (The R Foundation for Statistical Computing, Vienna, Austria). R was used for graphics.

Results

Table 2 provides a summary of patient characteristic, baseline, and intraoperative characteristics of the 124 patients who were enrolled. The incidence of the primary composite postoperative morbidity was 19% (Table 1). For individual morbidity, the incidence observed ranged from 0% to 13%, with deep- or organ-space SSI being the single most common serious complication.

The observed median TWA StO_2 from incision to 2 h after arrival in recovery was 85% [79–90% (1st–3rd quartile)] and the median minimum StO_2 was 78% [70–85%]. We also observed 17 (14%) patients with a TWA of $\text{StO}_2 < 75\%$ and 3 (2%) patients with a TWA of StO_2 exceeding 95%. The median analysed StO_2 time period was 6.2 [5.2–7.9] h.

The minimum of StO_2 was inversely associated with the primary outcome—collapsed composite of 30 day mortality and serious in-hospital complications ($P=0.02$); the estimated odds ratio was 0.82 (97.5% CI: 0.67, 1.00) for a 5% increase in the minimum of StO_2 . Unlike minimum StO_2 , TWA StO_2 was not significantly associated with our primary outcome ($P=0.35$) with an odds ratio of 0.89 (97.5% CI: 0.66, 1.19) for a 5% increase in the TWA. Both analyses were adjusted for BMI, the only covariable which entered the multivariable model out of the 16 pre-specified potential confounders (detailed in the Methods section). The assumption of linearity was reasonable for both predictors of interest (Fig. 1); the Hosmer–Lemeshow goodness-of-fit test results do not suggest lack of fit in any of the models.

Neither TWA StO_2 ($P=0.65$) nor minimum StO_2 ($P=0.70$) was significantly associated with our secondary outcome, collapsed composite of major infections, and wound-healing complications, after adjusting for BMI. The estimated odds ratios (95% CI) were 1.08 (0.78, 1.50) and 0.96 (0.79, 1.18) for a 5% increase in TWA StO_2 and in minimum StO_2 , respectively.

We also observed that patients who had a primary outcome and those who did not were descriptively similar (absolute standardized difference ≤ 0.20) on amount of ephedrine, epinephrine, esmolol, metoprolol, and cell saver transfusion during surgery (Table 3). Although patients who had a primary outcome, on average, were more likely to receive more phenylephrine, labetalol, colloid, and red blood cell, and received less nitroglycerine, norepinephrine, and crystalloid (absolute standardized difference >0.20). The differences were not statistically different (except for colloid), but none of the differences were clinically significant (Table 3).

Discussion

NIRS, based on the Beer–Lambert law, evaluates the amount of haemoglobin in tissues crossed by the near-infrared light.²⁴ It primarily measures the per cent haemoglobin oxygen saturation in the capillaries, venules, and arterioles

Table 1 Incidence of primary outcomes ($n=124$). *Variables included in the secondary outcome analysis

Major complications	Requirements for acceptance	%
Deep or organ/space SSI*	Deep incisional SSI: clinical signs of infection in the deep soft tissue and one of the following: Purulent drainage from the deep incision Spontaneous dehiscence or the wound is deliberately opened by the surgeon, a positive culture, and one of the following: fever $>38^{\circ}\text{C}$, or localized pain and tenderness Abscess or other evidence of infection involving the deep incision Diagnosis of deep SSI by attending surgeon Organ/space infection: infection involving any part of the anatomy other than the incision, opened or manipulated during the operative procedure operative and one of the following: Purulent drainage from a drain. Positive culture from fluid or tissue in the organ/space An abscess or other evidence of infection Diagnosis of an organ/space SSI site by attending surgeon	12.9
Pneumonia	New infiltrate on CXR combined with two of the following: temperature $>38^{\circ}\text{C}$, leukocytosis, and positive sputum or bronchial culture	3.2
Bowel and surgical anastomosis stricture/obstruction or anastomotic leak*	Requiring surgical intervention	3.2
Bleeding	Requiring transfusion >4 units of RBCs within the first 72 h after surgery	2.4
Sepsis*	Positive blood culture and at least two of the following: hypo or hyperthermia, tachycardia, tachypnoea, leucopaenia/leukocytosis \pm DIC or multiorgan dysfunction	1.6
Pulmonary oedema and congestive heart failure	Shortness of breath, crepitation, peripheral oedema, and third heart sound and radiological signs (cardiomegaly, interstitial oedema, alveolar oedema), medical treatment with diuretics	1.6
Ventricular arrhythmias	ECG changes requiring medical treatment and/or electro-conversion	1.6
Renal failure	Requiring dialysis	1.6
Respiratory failure	Requiring intubation for more than 3 days	1.6
Mortality	All-cause death within 30 postoperative days	0.8
Myocardial infarction	ECG changes and/or elevated myocardial enzymes (cTn-T ≥ 0.2 ng ml $^{-1}$ and /or CK ≥ 170 IU and MB $\geq 5\%$)	0.8
Internal or external fistula formation*	Requiring intervention	0.8
Vascular graft thrombosis	Requiring surgical intervention	0
Large peritoneal/pleural effusion	Diagnosed by X-ray, ultrasound, and/or aspiration, and requiring chest tube, surgery, or ICU admission	0
Stroke	New focal neurological deficit of presumed vascular aetiology persisted more than 24 h with a neurological study that did not indicate a different aetiology	0
Pulmonary emboli	Sudden death or confirmation by V-Q scan showing high probability for PE, spiral CT scan or pulmonary arteriogram	0

of the microcirculation of peripheral tissue with a diameter <1 mm because the high concentration of blood in arteries and veins makes photon emergence unlikely.²⁵ That said, the monitored tissue segment is somewhat poorly defined and for simplicity is referred to as ‘tissue oxygenation’.

In healthy volunteers, normal tissue oxygen saturation is 87 (69%) [mean (SD)] obtained by NIRS at the thenar eminence.²⁶ This is similar to that of our cohort of non-cardiac surgery patients in whom the median [1st, 3rd quartile] was 85% [79%, 90%] during the intraoperative and immediate postoperative period.

Temporary hypoxia in acute wounds serves as a signal that stimulates many aspects of the wound-healing process. In contrast, prolonged or chronic hypoxia delays wound healing.^{6, 27} For example, an StO_2 threshold of 75% provides a good positive predictive value and positive likelihood ratio for predicting low central venous oxygen saturation—values

which reflect overall state of systemic oxygenation.²⁸ Similar findings were reported in non-surgical settings where peripherally measured StO_2 in heart failure patients correlated with hospitalization for heart failure and mortality.¹³ We nonetheless found that minimum StO_2 , rather than TWA StO_2 , was associated with poor postoperative composite outcome—a result suggesting that episodes of extreme tissue hypoxia contribute more to adverse outcomes than periods of relative tissue hypoxia and hypoperfusion.

We observed a significant and potentially clinically important association between minimum (mostly intraoperative) StO_2 and a composite of serious outcomes. StO_2 —measure of systemic oxygenation²⁴—is associated with a composite of systemic complications which is perhaps unsurprising. But curiously, there was no independent association between StO_2 and infectious complications. This result thus differs somewhat from those reported by Govinda and

Table 2 Patient baseline and intraoperative characteristics (n=124). AAA, abdominal aortic aneurysm; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; STD, standardized difference; StO₂, tissue oxygen saturation; TIA, transient ischaemic attack; and TWA, time-weighted average. Summary statistics presented as mean (SD), median (Q1, Q3), or percentage of patients. *Morbidity was defined as a composite of 30 day mortality and 15 serious in-hospital complications (Table 1). †Standardized difference, which is the difference in means or proportions divided by the pooled standard deviation

Variables	Overall (n=124)	Morbidity* (n=24)	No morbidity* (n=100)	STD†
Age (yr)	61 (40–95)	62 (40–93)	61 (40–95)	0.06
Gender, female (%)	41	42	41	0.01
Body mass index (kg m ⁻²)	28 (25, 32)	31 (9)	28 (5)	0.35
Smoking status (%)	36	45	34	0.28
Medical history (%)				
COPD	6	4	6	-0.08
CAD	25	25	25	0.00
CHF	7	8	6	0.09
Ischaemic stroke	4	4	4	0.01
TIA	2	0	2	-0.20
Serum creatinine (mg dl ⁻¹)	0.8 (0.7, 1.0)	0.8 (0.8, 1.0)	0.8 (0.7, 1.1)	-0.03
Haematocrit (%)	41 (5)	41 (5)	40 (5)	0.09
Type of surgery (%)				0.49
Colorectal	44	42	44	
Whipples/pancreas	22	33	19	
Cystectomy	15	8	17	
Peripheral revascularization	11	12	11	
AAA	5	4	5	
Others	3	0	4	
Glucose control, intensive (%)	50	46	51	-0.10
Depth of anaesthesia, light (%)	51	46	52	-0.12
Anti-inflammatory, steroid (%)	51	50	51	-0.02
Tissue oxygen saturation (%)				
TWA StO ₂	85 (79, 90)	84 (76, 88)	85 (80, 91)	-0.26
Minimum StO ₂	78 (70, 85)	74 (60, 83)	79 (72, 86)	-0.42
TWA StO ₂ <75%, yes	14	25	11	0.37
TWA StO ₂ >95%, yes	2	0	3	-0.25

colleagues⁸ who measured postoperative StO₂ at the surgical wound, upper arm, and thenar eminence—but only observed a significant association between StO₂ measured at the upper arm and SSI. Thus, timing of measurements and the measurement site may both prove to be important. We measured StO₂ continuously during surgery and for the first 2 h of the immediate postoperative period. In contrast, Govinda and colleagues measured StO₂ 75 min after surgery and 1 day after the operation. By virtue of our continuous measurements, our measurements might better represent the perioperative period. This is especially the case since the time frame we evaluated represents the surgical insult and the time when patients' care is anaesthesiologist-driven. If it were shown to be helpful, anaesthesiologists could implement a myriad of interventional strategies to improve tissue oxygenation such as supplemental oxygen, vascular volume repletion, treatment of pain, etc. An additional difference between our current study and Govinda and colleagues is that we studied patients undergoing a range of major non-cardiac surgeries and evaluated the impact of StO₂ on a

composite of systemic outcomes and wound-healing complications, whereas the previous study was restricted to colon resection and evaluated only wound-related infectious complications. We also note that both studies were relatively small and spurious associations remain a risk—although our analysis was based on an *a priori* plan and included statistical compensations for various analyses.

Tissue oxygen partial pressure is probably the best single predictor of wound infection risk.³ As might thus be expected, low StO₂ at the distal colon anastomosis is a risk factor for anastomotic dehiscence after operation.⁹ Furthermore, several randomized trials conclude that supplemental perioperative oxygen (80% vs 30%), which normally roughly doubles tissue oxygenation,¹⁰ halves the risk of surgical wound infection.^{10 11} Others, although, have found that infection rates are similar with and without supplemental oxygen, including the PROXI trial in which 1400 patients were randomized to receive 80% or 30% of supplemental oxygen intraoperatively and 2 h after operation.²⁹ The divergent results are difficult to explain, but a variety of factors besides inspired

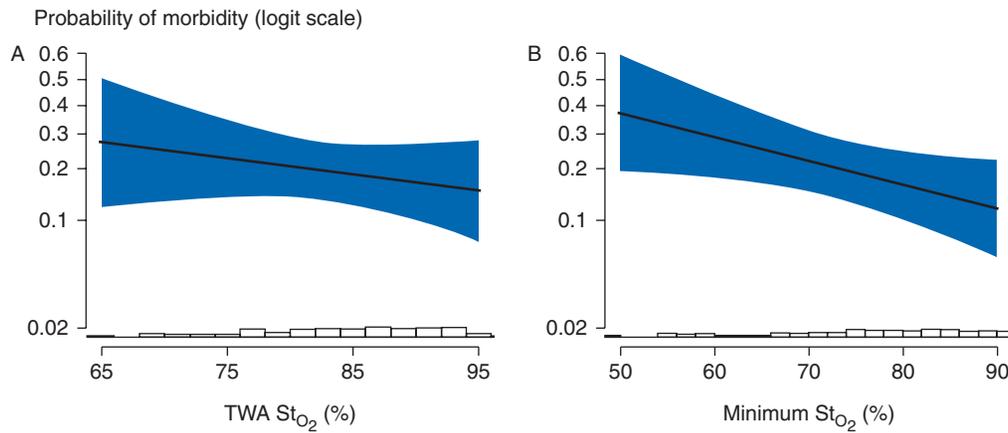


Fig 1 Probability of the any postoperative morbidity (on the logit scale) vs (A) TWA and (B) minimum StO_2 . Histograms of (A) TWA StO_2 and (B) minimum StO_2 were plotted along the x-axes. Probabilities were estimated using univariable logistic regressions with a smooth term for StO_2 . All patients ($n=124$) were used for the estimation; however, the x-axes were truncated due to sparse data at the ends (seven patients for the TWA and 14 patients for the minimum).

Table 3 Summary of intraoperative usage of vasoactive drugs and fluids management. Summary statistics presented as mean (sd) or median (Q1, Q3). *A composite of 30 day mortality and 15 serious in-hospital complications (Table 1). [†]Wilcoxon rank-sum test or Pearson χ^2 test, as appropriate. [‡]Standardized difference, which is the difference in means or proportions divided by the pooled standard deviation; >0.2 in absolute value suggests a small difference between the two compared groups

Variable	Morbidity* (n=24)	No morbidity* (n=100)	P-value [†]	D [‡]
Phenylephrine, yes [no. (%)]	17 (71)	59 (59)	0.29	0.25
Phenylephrine (μ g)	100 (0, 812)	100 (0, 450)	0.21	0.28
Ephedrine, yes [no. (%)]	14 (58)	52 (52)	0.58	0.13
Ephedrine (mg)	5 (0, 15)	5 (0, 10)	0.58	0.13
Nitroglycerine, yes [no. (%)]	3 (12)	23 (23)	0.26	-0.28
Nitroglycerine (μ g)	0 (0, 0)	0 (0, 0)	0.28	-0.26
Epinephrine, yes [no. (%)]	2 (8)	4 (4)	0.37	0.18
Epinephrine (μ g)	0 (0, 0)	0 (0, 0)	0.36	0.18
Norepinephrine, yes [no. (%)]	0 (0)	3 (3)	0.39	-0.25
Norepinephrine (μ g)	0 (0, 0)	0 (0, 0)	0.39	-0.25
Esmolol, yes [no. (%)]	7 (29)	21 (21)	0.39	0.19
Esmolol (mg)	0 (0, 21)	0 (0, 0)	0.36	0.20
Metoprolol, yes [no. (%)]	4 (17)	12 (12)	0.54	0.13
Metoprolol (mg)	0 (0, 0)	0 (0, 0)	0.63	0.11
Labetalol, yes [no. (%)]	6 (25)	15 (15)	0.24	0.25
Labetalol (mg)	0 (0, 1)	0 (0, 0)	0.25	0.24
Crystalloid (litre)	3.6 (1.7)	4.0 (1.7)	0.27	-0.25
Colloid (litre)	1.0 (0.5, 1.5)	0.5 (0.3, 1.0)	0.01	0.60
RBC transfusion (litre)	0 (0, 0.7)	0 (0, 0.3)	0.11	0.34
Cell saver (litre)	0 (0, 0)	0 (0, 0)	0.83	-0.05

oxygen fraction F_{IO_2} determine oxygenation of surgical tissues. For example, tissue oxygenation is modulated by anaesthetic management,³⁰ cardiac output,³¹ vasomotor status,^{31 32} suture tension,³¹ surgical tissue oedema,³³ and local and core temperature.³⁴ To the extent that other factors—such as hypovolaemia—limit oxygen delivery to

peripheral tissues, supplemental oxygen alone may be insufficient in some patients. In our study, patients were receiving a mixture of air and oxygen (1:1) resulting in an F_{IO_2} of ~55%.

The intriguing aspect of non-invasively measuring tissue oxygenation is that it opens the possibility of intervening to improve oxygenation in individual patients. For example,

supplemental oxygen could be followed—if necessary—with vascular volume repletion, measures to increase cardiac output, vasodilators, or local and/or system warming.³⁵ Such progressive interventions may be more effective than simply providing supplemental oxygen to all patients. But whether this approach will actually reduce wound-related complications remains to be determined in randomized intervention trials. Promising results have been shown already in studying similar concepts. Intraoperative fluid replacement based on the measurement of subcutaneous oxygen tension (PscO₂) vs clinical judgement has been shown to correlate favourably with the collagen deposits, indicative of better wound healing.³⁶

Red blood cell transfusions have shown an improvement in global measures of oxygen delivery but not in oxygen consumption.³⁷ However, whether an improvement in oxygen delivery and consumption translate into an actual increase in regional tissue oxygenation is still controversial. Several recent studies using NIRS technology has suggested that blood transfusion may improve tissue oxygenation,^{38–40} although others have not.^{41–42} Furthermore, the added impact of stored red cell age while being explored in a variety of clinical settings did not show any effect on tissue oxygenation.⁴¹ In our study, red blood cell transfusion was controlled per protocol, and our blood bank that was blinded to the study used the same unit allocation strategy for all patients who needed transfusion. Therefore, we had no reason to believe that red blood cell age or transfusion had any significant impact on our results.

The use of vasopressors may also impact tissue perfusion; however, the clinical significance of such a very small impact on tissue oxygenation is questionable.⁴³ In our study, there was no difference between the patients who had a primary outcome and those who did not in the use of vasopressors.

We chose the thenar eminence as our measurement site partially because it has been used in previous studies, because the site resists oedema, and because it is an area that rarely accumulates substantial adiposity.⁴⁴ We nonetheless adjusted our analysis for BMI. All our patients had major surgery and thus usually had i.v. catheters inserted in both arms. Generally, fluid was warmed to body temperature when given rapidly, and slow infusions have little effect on tissue temperature, even near the infusion site. The InSpec-tra StO₂ monitor used reports an accurate value for StO₂ regardless of body temperature.⁴⁵

Our study is limited by its observational cohort design; we are thus unable to determine causality from our results. Oxygenation in various tissues can obviously diverge depending on local perfusion. For example, supplemental perioperative fluid improves subcutaneous oxygen partial pressure in the upper arm,⁴⁶ but does not appear to reduce the risk of SSI in colectomy patients⁴⁷—perhaps because interstitial oedema actually reduces oxygenation in the tissue of interest.³³ However, the aforementioned study by Kabon and colleagues was stopped early. If the difference in infection rates (11.3 vs 8.5%) had held up with a sufficient sample size, the 25% absolute reduction in infection rate could have been

clinically important. It should be noted that a recent preclinical study in pigs indicated that gut tissue oxygenation was not affected by low-, moderate-, or high-volume resuscitation techniques.⁴⁸ The same group of authors demonstrated that goal-directed fluid therapy with colloids improved gut oxygenation that was not affected by goal-directed fluid therapy with crystalloids or restrictive fluid administration.⁴⁹ Whether these results translate into similar findings in other non-mesenteric tissues is largely unknown. In support of this concern, oesophageal Doppler goal-directed fluid management has resulted in inconsistent results in terms of StO₂.⁵⁰

A second limitation is that we measured StO₂ at the thenar eminence without simultaneous measurements at or near the surgical site which might better reflect saturation in wounds and other tissues of interest. However, intraoperative measurements near the surgical sites are rarely practical. Any study evaluating the effect of various StO₂ interventions on outcomes would thus have to be based on measurements at some site remote to the surgical incision.

In summary, minimum perioperative peripheral tissue oxygenation predicted a composite of major complications and mortality in patients having major non-cardiac surgery. However, this is an observational association. Whether clinical interventions to augment tissue oxygenation will improve outcomes remains to be determined.

Declaration of interest

None declared.

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