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## Microvascular flow and tissue oxygenation after major abdominal surgery: association with post-operative complications

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### Electronic supplementary material

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**Abstract Objective:** To evaluate the relationship between global oxygen delivery (DO<sub>2</sub>I), microvascular flow and tissue oxygenation in patients who did and did not develop complications following major abdominal surgery. **Design:** Prospective observational study. **Setting:** Post-operative critical care unit. **Participants:** Twenty-five patients receiving standard peri-operative care following major abdominal surgery. **Measurements and main results:** Data were collected before, and for 8 h after surgery. DO<sub>2</sub>I was measured by lithium dilution and arterial waveform analysis. Cutaneous PtO<sub>2</sub> was measured at two sites on the abdominal wall using a Clark electrode. The sublingual microcirculation was visualised using sidestream darkfield imaging. Cutaneous red cell flux was measured using laser Doppler flowmetry. Fourteen patients (56%) developed complications with two deaths. Small

vessel (<20 µm) microvascular flow index in those patients who developed complications was lower before ( $P < 0.05$ ) and after surgery ( $P < 0.0001$ ) compared to patients who did not develop complications. Both the proportion and density of perfused small vessels were also lower in patients who developed complications after surgery ( $P < 0.01$ ) but not before surgery. DO<sub>2</sub>I was low in all patients but did not differ between patients who did and did not develop complications. Similarly, there were no associated differences in cutaneous red cell flux or PtO<sub>2</sub>. **Conclusion:** In a group of patients with low DO<sub>2</sub>I following major abdominal surgery, microvascular flow abnormalities were more frequent in patients who developed complications. However, there were no differences in DO<sub>2</sub>I, cutaneous PtO<sub>2</sub> or red cell flux between the two groups. Impaired microvascular flow may be associated with the development of post-operative complications.

**Keywords** Peri-operative care · Oxygen consumption and delivery · Cardiovascular monitoring

## Introduction

It is estimated that 234 million major surgical procedures are performed worldwide each year [1]. Complications following major surgery are a leading cause of morbidity and mortality [2, 3]. High-risk surgical patients account for over 80% of deaths but only 12.5% of in-patient surgical procedures [4, 5]. In the UK, around 170,000 patients undergo high-risk surgical procedures each year, of whom 25,000 patients die and as many as 100,000 develop complications. Data from mainland Europe and North America suggest that this problem is not unique to the UK [6, 7]. Even for those patients who survive to leave hospital, post-operative complications remain an important determinant of long-term survival [6]. It is essential, therefore, that we improve outcomes following major surgery.

The aetiology of post-operative complications is complex. Risk factors include advanced age, co-morbid disease and major and urgent surgery [4, 5]. A number of reports describe an association between derangements in global oxygen delivery ( $DO_2I$ ) or related parameters and poor outcome following major surgery [8–10]. In several small studies, the use of fluid and inotropic therapy to enhance global oxygen delivery has led to a reduction in post-operative complications [11–14]. It has been suggested that the benefits of this approach are a result of improved tissue perfusion and oxygenation. Whilst unconfirmed, this hypothesis is consistent with the findings of a number of previous investigations. Surgical wound infections are associated with reductions in tissue  $PO_2$  [15], and may be prevented by the early use of supplemental inspired oxygen [16, 17]. The use of warming blankets to prevent peri-operative hypothermia may also reduce the incidence of wound infection, suggesting a pathophysiological process related to tissue perfusion [18, 19]. The findings of several studies suggest that reductions in microvascular blood flow during gastro-intestinal surgery may be associated with impaired anastomotic healing [20–22]. However, a more detailed knowledge of the relationship between changes in global determinants of oxygen delivery and regional measures of tissue perfusion and oxygenation is required. The objective of this study was to describe the relationship between global oxygen delivery, tissue microvascular flow and oxygenation in high-risk patients who did and did not develop complications following major abdominal surgery.

## Patients and methods

The study was approved by the Local Research Ethics Committee. Written informed consent was obtained prior to surgery. Patients admitted to a critical care unit following major elective abdominal surgery were eligible for recruitment. Exclusion criteria were refusal of consent, concurrent lithium therapy, acute myocardial ischaemia,

acute arrhythmias, pregnancy, patients receiving palliative treatment only and weight less than 40 kg. Patients were enrolled when a member of the research team was available. General anaesthesia was standardised to include intravenous fentanyl, propofol and atracurium for induction of anaesthesia and maintenance with inhaled isoflurane in oxygen-enriched air alongside epidural analgesia. Clinical staff administered intravenous fluids, blood products and, if required, vasoactive drugs in order to maintain pulse rate, arterial pressure, central venous pressure, urine output, haematological and biochemical parameters within the normal range. Appropriate measures were taken to maintain  $SpO_2 \geq 94\%$ , haemoglobin above  $8 \text{ g dl}^{-1}$  and temperature at  $37^\circ\text{C}$ . Following surgery, all patients were managed in a critical care unit. Additional fluid challenges and inotropic therapy were prescribed by clinical staff. Cardiac output data were made available when specifically requested by clinical staff. Patients did not, however, receive specific flow guided haemodynamic therapy in order to attain pre-determined values for stroke volume, cardiac index or global oxygen delivery.

## Measurements

In addition to heart rate, mean arterial pressure and central venous pressure, cardiac output and  $DO_2I$  were measured by lithium indicator dilution and arterial waveform analysis (LiDCOplus, LiDCO Ltd, Cambridge, UK) [23]. Arterial and central venous blood samples were taken for analysis of blood gases, lactate and haemoglobin concentration (ABL 600 and OSM3, Radiometer, Copenhagen, Denmark). Cutaneous tissue  $PtO_2$  was measured at two sites on the abdominal wall using a Clark electrode (TCM400, Radiometer, Copenhagen, Denmark). These probes are designed to warm the skin to  $44^\circ\text{C}$  in order to minimise artefact due to local vasoconstriction. Cutaneous red blood cell flux was measured at two sites on the abdominal wall by laser Doppler flowmetry (Moorlab, Moor Instruments, Axminster, UK). Sublingual microvascular flow was evaluated using sidestream darkfield imaging with a  $5\times$  objective lens (Microscan, Microvision Medical, Amsterdam, Netherlands) [24]. Microvascular and tissue oxygenation data were obtained on the ward prior to surgery and all data were collected at 2-h intervals after surgery for 8 h. Hour 0 refers to the time of admission to the critical care unit. Image acquisition and subsequent analysis was performed according to published consensus criteria [25]. In brief, SDF images were obtained from at least three sublingual areas at each time point. Microvascular flow index (MFI) was calculated after dividing each image into four equal quadrants. Quantification of flow was determined using an ordinal scale (0: no flow, 1: intermittent flow, 2: sluggish flow, 3: normal flow) for small ( $<20 \mu\text{m}$ ) and large ( $>20 \mu\text{m}$ ) vessels. MFI is the average score of all quadrants for a given category of

**Table 1** Demographical characteristics of patients who did and did not develop complications after surgery

	No complications ( <i>n</i> = 11)	Complications ( <i>n</i> = 14)
Age (years)	66 (63–72)	69 (64–73)
Gender	5 males (45%)	6 males (43%)
P-POSSUM score	35 (31–37)	37.5 (33–43)
Upper gastrointestinal surgery	4 (36%)	4 (29%)
Pancreatic surgery	3 (27%)	5 (36%)
Lower gastrointestinal surgery	3 (27%)	5 (36%)
Open abdominal aneurysm repair	1 (9%)	0 (0%)

Data presented as median (IQR) or absolute values (%).  
*P-POSSUM* Physiological and operative severity score for the enumeration of mortality score

vessel size at a given time point. Images were recorded at three sites at each time point giving 12 quadrants for analysis. Vessel density is calculated by inserting a grid of three equidistant horizontal and three equidistant vertical lines over the image. Vessel density is equal to the number of vessels crossing these lines divided by their total length. Flow is then categorised as present, intermittent or absent to calculate the proportion of perfused vessels and thus the perfused vessel density. Analysis of the videos was performed by two observers (SJ and CL). Patients were followed up for 28-day in-hospital post-operative complications (supplementary file), mortality and duration of hospital stay. The major categories of complications were infectious, respiratory, cardiovascular, renal, neurological and gastrointestinal.

#### Statistical analysis

For evaluating changes over time between groups, two-way repeated measures analysis of variance (ANOVA) was used. Post hoc *t* tests were performed at the different time points using the Bonferroni correction for multiple testing. Analysis was performed using GraphPad Prism version 4.0 (GraphPad Software, San Diego, USA). Significance was set at  $P < 0.05$ . Data are presented as mean (SD) where normally distributed or median (IQR) where

not normally distributed. Inter-observer variability for analysis of the SDF images was assessed by calculating the Kappa coefficient ( $\kappa$ ) [26]. We did not perform a sample size calculation based on any single variable and instead elected prospectively to recruit 25 patients.

## Results

Twenty-five patients were recruited with a median age of 69 (63–72) years. Demographical patient characteristics, peri-operative haemodynamic management and outcome data are summarised in Tables 1 and 2. Two patients were mechanically ventilated after surgery. All other patients were extubated prior to critical care admission. Two patients died (8%) and 14 patients (56%) developed post-operative complications. The median time to first complication was 3 (2–6) days. Ten patients (40%) developed infectious complications (Table 3). Critical care ( $P < 0.01$ ) and hospital stay ( $P < 0.001$ ) were significantly longer in those patients who developed complications. There were no differences in  $PtO_2$ ,  $DO_2I$ ,  $ScvO_2$ , cardiac index, heart rate, mean arterial pressure, serum lactate or cutaneous red cell flux between patients who did and did not develop complications. There was a significant difference in base deficit (Fig. 1; Tables 4, 5). The inspired fractional concentration of oxygen after surgery at all time points was 0.4 (0.4–0.4).

There was a significant difference in sublingual MFI in small vessels ( $<20 \mu\text{m}$ ) after surgery between those patients who subsequently developed complications and those who did not (Fig. 2). The MFI of the large vessels ( $>20 \mu\text{m}$ ) remained normal in all patients throughout the study period. Neither the total vessel density nor the small vessel ( $<20 \mu\text{m}$ ) density was significantly different between these groups. The proportion of perfused small vessels ( $<20 \mu\text{m}$ ) was significantly lower after surgery in those patients who developed complications. Perfused vessel density, a measure of functional capillary density, was also lower after surgery in patients who developed complications (Table 5). The density and proportion of

**Table 2** Data describing intra-venous fluid and vasoactive agent use and outcome data for patients who did and did not develop complications after surgery

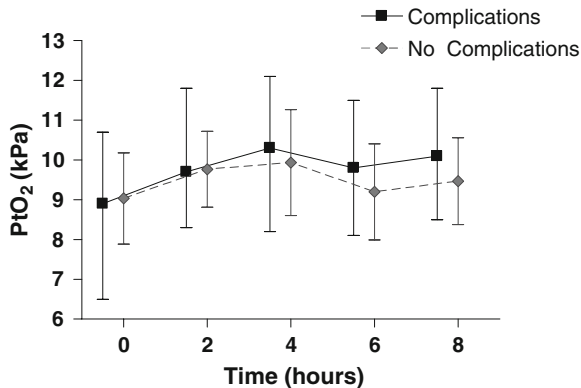
	No complications ( <i>n</i> = 11)	Complications ( <i>n</i> = 14)
Intra-venous fluid during surgery (ml)	4,500 (3,250–5,000)	5,375 (3,500–6,500)
Intra-venous fluid during study period (ml)	1,250 (1,000–1,650)	1,250 (1,100–2,200)
Number of patients receiving vasopressor therapy	2 (18%)	4 (29%)
Critical care free days within 28 days of surgery	27 (26–27)	24 (22–26)*
Duration of hospital stay (days)	8 (8–9.5)	20 (14–26)**
Mortality	0 (0%)	2 (14%)

Data presented as median (IQR) or absolute values (%). \* $P < 0.01$ , \*\* $P < 0.001$

**Table 3** Frequency of complications following surgery

Primary complication	Number of patients
Infectious	10
Cardiovascular	1
Respiratory	1
Gastrointestinal	2
Neurological	0

Fourteen patients developed complications in total



**Fig. 1** Cutaneous tissue oxygenation after abdominal surgery in patients who did and did not develop complications. Data presented as median (IQR)

perfused large vessels ( $>20\ \mu\text{m}$ ) were not significantly different between groups. We were only able to collect sublingual microvascular images prior to surgery in 14 patients. Despite this, MFI for small vessels ( $<20\ \mu\text{m}$ ) was reduced in those patients who subsequently developed complications compared to those who did not (2.6 [2.5–2.9] vs. 3.0 [3.0–3.0];  $P < 0.05$ ). Large vessel MFI ( $>20\ \mu\text{m}$ ) was 3.0 (3.0–3.0) in both groups. The kappa coefficient for inter-observer reliability was 0.81 (95%CI 0.72–0.89). In one patient, it was not possible to obtain any SDF images due to painful oral mucositis related to chemotherapy.

## Discussion

The principle finding of this study is that, in a group of patients with low global oxygen delivery following major abdominal surgery, impairment of microvascular flow was more marked in those patients who developed complications. Importantly, this difference in microvascular flow was present even before surgery. Although the incidence of complications was high, there were no associated differences in global oxygen delivery, cutaneous red cell flux or tissue oxygenation between patients who did and did not develop complications. These data suggest that

impairment of microvascular flow may play an important role in the evolution of complications after abdominal surgery. Further research is required to confirm these findings and to investigate this area in more detail.

A number of investigators have described abnormalities in gastro-intestinal total red blood cell flux (laser Doppler flowmetry) in patients who develop post-operative complications [20–22]. This reduction in mucosal blood flow has been associated with an increased incidence of anastomotic breakdown following both oesophagectomy [21] and colorectal surgery [22]. Although oesophageal anastomotic flow improved following the topical application of nitroglycerin [27], this effect was not observed with intravenous infusions of either prostaglandin E<sub>1</sub> or nitroglycerin [21, 28]. We are not, however, aware of any previous reports of cutaneous red cell flux following gastro-intestinal surgery. In a recent investigation, Boerma et al. [29] did not identify any heterogeneity of microvascular flow in colonic stoma within 24 h of elective colo-rectal surgery. Sublingual microvascular flow was not reported, although it seems likely that the findings would have been similar. There are several reasons why these previous findings in non-septic patients contrast with those of the current study. We identified abnormalities of microvascular flow that were most evident in the early post-operative phase and appeared to be returning to normal by 8 h. In the previous study, stomal microvascular flow was evaluated only once in the first 24 h after surgery and possibly at variable time points. Early changes in microvascular flow may have therefore been missed. Perhaps more importantly, we specifically recruited a high-risk group of patients undergoing complex surgery who were deemed to require post-operative critical care admission whilst patients in the previous study were all admitted to a standard surgical ward. The finding of impaired sublingual microvascular flow prior to surgery in those patients who subsequently developed complications was unexpected. This observation may have related to mild hypovolaemia or to the underlying diagnosis (cancer in almost all cases) but does not appear to have resulted from diabetes or other co-morbid disease. Importantly, microvascular indices continued to deteriorate during and after surgery and appeared to be returning to normal by 8 h after surgery. Further work in a larger group of patients is required to confirm these findings and to explore the underlying explanation in more detail.

Decreased PtO<sub>2</sub> has previously been associated with an increased incidence of post-operative wound infection [15]. Furthermore, peri-operative supplemental inspired oxygen [16, 17] and therapies to increase global oxygen delivery [11, 12] seem to decrease the incidence of wound infections. Supplemental oxygen may also improve colonic anastomotic PtO<sub>2</sub> in pigs [30]. It is not clear why we did not identify any differences, in either cutaneous tissue oxygenation or DO<sub>2</sub>I between patients who did and did not develop complications. In the

**Table 4** Cardiovascular physiology during 8 h study period

	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8
Heart rate (bpm)					
Complications	70 (15)	75 (19)	73 (15)	73 (15)	66 (5)
No complications	78 (17)	76 (17)	73 (16)	74 (15)	75 (15)
MAP (mmHg)					
Complications	77 (13)	79 (13)	76 (17)	74 (10)	75 (12)
No complications	89 (15)	78 (14)	79 (17)	78 (17)	75 (16)
CVP (mmHg)					
Complications	7 (4)	7 (4)	6 (2)	8 (7)	9 (6)
No complications	7 (3)	6 (4)	7 (5)	6 (4)	6 (3)
Cardiac index ( $l \text{ min}^{-1} \text{ m}^{-2}$ )					
Complications	2.9 (0.9)	3.0 (0.9)	2.9 (0.9)	2.9 (0.8)	2.7 (0.7)
No complications	2.8 (0.7)	2.9 (0.8)	2.8 (0.8)	2.7 (0.9)	2.8 (0.9)
$DO_2I$ ( $ml \text{ min}^{-1} \text{ m}^{-2}$ )					
Complications	373 (102)	394 (103)	379 (98)	384 (124)	345 (87)
No complications	361 (55)	379 (106)	361 (104)	356 (115)	369 (111)
$ScvO_2$ (%)					
Complications	71 (11)	73 (9)	73 (9)	72 (9)	68 (7)
No complications	68 (9)	70 (8)	68 (6)	69 (8)	72 (7)
Serum lactate ( $mmol \text{ l}^{-1}$ )					
Complications	1.2 (0.9–2.0)	1.2 (0.9–2.0)	1.2 (0.8–2.1)	1.3 (0.9–2.5)	1.3 (0.8–1.4)
No complications	1.4 (1.2–1.7)	1.0 (0.9–1.2)	1.1 (0.9–1.2)	1.0 (0.8–1.6)	1.1 (1.0–1.7)
Base deficit ( $mmol \text{ l}^{-1}$ )					
Complications*	2.6 (2.6)	3.3 (3.1)	3.0 (3.3)	3.8 (4.6)	2.3 (1.5)
No complications	2.1 (2.7)	1.6 (1.9)	1.0 (2.1)	1.1 (2.1)	0.9 (2.3)

Data presented as mean (SD) or median (IQR)

MAP mean arterial pressure, CVP central venous pressure,  $DO_2I$  oxygen delivery index,  $ScvO_2$  central venous oxygen saturation\* $P < 0.01$  between groups over time (two-way repeated measures ANOVA)**Table 5** Sublingual small (<20  $\mu\text{m}$ ) vessel density and red cell flux

	Pre-op	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8
Microvascular flow index						
Complications**	2.6 (2.5–2.9)	2.5 (1.9–2.8)	2.0 (1.8–2.4)†	2.5 (2.3–2.9)	2.3 (2.0–2.7)	2.7 (1.9–2.9)
No complications	3.0 (3.0–3.0)	2.5 (2.4–2.8)	2.8 (2.6–3.0)	2.8 (2.3–3.0)	2.8 (2.6–3.0)	2.6 (2.3–2.9)
Small vessel density $mm^{-1}$						
Complications	6.8 (5.5–7.8)	6.5 (5.8–7.4)	6.1 (4.6–7.3)	6.9 (6.2–7.4)	6.3 (4.6–7.0)	6.8 (5.1–7.5)
No complications	5.9 (5.7–6.5)	6.3 (5.3–8.2)	6.7 (6.0–7.4)	6.2 (5.3–8.0)	6.6 (5.9–7.6)	7.0 (6.5–7.5)
Proportion of perfused small vessels (%)						
Complications*	79 (73–92)	74 (61–90)	64 (45–80)	67 (58–85)	75 (60–83)	87 (78–100)
No complications	89 (83–95)	80 (61–93)	86 (72–99)	86 (57–93)	90 (78–97)	95 (83–97)
Perfused small vessel density $mm^{-1}$						
Complications*	5.7 (4.1–6.9)	4.5 (3.8–6.2)	3.8 (3.0–4.4)	4.9 (4.0–5.5)	4.1 (3.1–6.2)	6.3 (3.7–6.8)
No complications	5.6 (4.8–5.8)	4.9 (3.6–6.3)	5.8 (4.3–6.6)	5.1 (3.5–6.3)	5.7 (5.1–7.2)	6.6 (5.2–7.3)
Heterogeneity index						
Complications	0.09 (0.0–0.50)	0.13 (0.0–0.3)	0.25 (0.07–0.47)	0.21 (0.0–0.44)	0.10 (0.0–0.54)	0.32 (0.09–0.35)
No complications	0.0 (0.0–0.0)	0.25 (0.09–0.25)	0.11 (0.0–0.28)	0.18 (0.0–0.32)	0.18 (0.04–0.25)	0.09 (0.0–0.26)
Red cell flux (arbitrary units)						
Complications	30 (19–40)	38 (28–43)	28 (21–38)	37 (26–44)	34 (25–46)	31 (24–55)
No complications	33 (22–41)	34 (26–64)	32 (19–55)	35 (30–60)	31 (19–40)	41 (27–66)

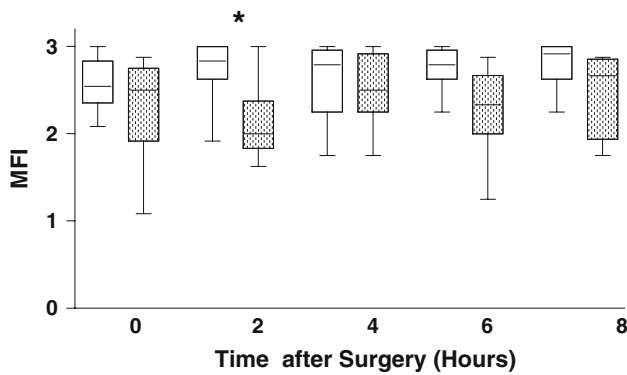
Data presented as mean (SD) or median (IQR)

\*\* $P < 0.001$  and \* $P < 0.01$  between groups over time (two-way repeated measures ANOVA)† $P < 0.01$  between groups at this time point (post-hoc t-test with Bonferroni correction)

current study, cutaneous  $PtO_2$  was considerably greater than previously reported ( $10 \pm 3$  kPa vs.  $6.5 \pm 1.5$  kPa) [15], perhaps reflecting the routine use of supplemental oxygen in the current investigation whereas in the previous study patients only received supplemental oxygen if  $SpO_2$  decreased to less than 90%. In addition, in the

current study, every patient received epidural analgesia, which may also improve abdominal wall cutaneous oxygenation [31, 32]. These differences may also relate to the use of a cutaneous Clark electrode, which warms the skin in order to minimise artefact due to local vasoconstriction as opposed to a subcutaneous catheter.





**Fig. 2** Sublingual microvascular flow index (MFI) of small vessels (<20  $\mu\text{m}$ ) in patients who did and did not develop complications. Shaded boxes complications, open boxes no complications. Data presented as median (IQR).  $P < 0.0001$  between groups over time (two-way repeated measures ANOVA). \*  $P < 0.01$  between groups at this timepoint (post hoc  $t$  test with Bonferroni correction)

However,  $\text{PtO}_2$  values in the current study were similar to those previously measured using a subcutaneous catheter in patients receiving 40% oxygen after abdominal surgery [33].

Sublingual sidestream darkfield imaging is a valuable technique, which allows real time imaging of the intact microcirculation in the clinical environment. Whilst not as versatile as laser Doppler flowmetry, the capacity to explore heterogeneity of flow in vessels of different sizes has allowed important advances of our understanding of the microcirculation in critical illness [24, 34]. However, this technique remains semi-quantitative and data reliability may be affected by technical expertise and inter-observer bias. It is uncertain to what extent sublingual

microvascular flow correlates with that in other vascular beds [29, 35]. We used the two-way repeated measures ANOVA test to evaluate changes over the entire course of the study rather than at individual time points. Whilst significant differences were identified in three measures of microvascular flow (MFI, proportion of perfused vessels and perfused vessel density), more stringent post-hoc testing identified a difference at only one time point. It seems likely that this relates to the small sample size. A larger study is therefore required to confirm these important preliminary findings and to evaluate this area in more detail.

In summary, we have identified an impairment of sublingual microvascular flow in patients who developed complications both prior to and following major abdominal surgery. However, there were no related differences in cutaneous red cell flux,  $\text{PtO}_2$  or global oxygen delivery. The findings of previous studies suggest that vasoactive agents may improve sublingual microvascular flow in septic patients [35–37]. Further investigations are indicated to confirm our findings and to evaluate the effects of haemodynamic interventions and vasoactive agents on tissue microvascular flow and oxygenation following major surgery.

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