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ORIGINAL ARTICLE

The effect of moderate intraoperative blood loss and norepinephrine therapy on sublingual microcirculatory perfusion in patients having open radical prostatectomy

An observational study

Moritz Flick, Luisa Briesenick, Sven Peine, Thomas W.L. Scheeren, Jacques Duranteau* and Bernd Saugel*

BACKGROUND It is not clear whether moderate intraoperative blood loss and norepinephrine used to restore the macrocirculation impair the microcirculation and affect microcirculation/macrocirculation coherence.

OBJECTIVE We sought to investigate the effect of moderate intraoperative blood loss and norepinephrine therapy administered to treat intraoperative hypotension on the sublingual microcirculation.

DESIGN Prospective observational study.

SETTING University Medical Center Hamburg-Eppendorf, Hamburg, Germany, from November 2018 to March 2019.

PATIENTS Thirty patients scheduled for open radical prostatectomy and 29 healthy volunteer blood donors.

INTERVENTION Simultaneous assessment of the macrocirculation using a noninvasive finger-cuff method and the sublingual microcirculation using vital microscopy.

MAIN OUTCOME MEASURES The main outcome measures were changes in the sublingual microcirculation caused by moderate intraoperative blood loss and norepinephrine therapy.

RESULTS General anaesthesia decreased median [IQR] mean arterial pressure from 100 [90 to 104] to 79 [69 to 87] mmHg ($P < 0.001$), median heart rate from 69 [63 to 79] to 53 [44 to 62] beats per minute ($P < 0.001$), median cardiac index from 2.67 [2.42 to 3.17] to 2.09 [1.74 to 2.49] $\text{l min}^{-1} \text{m}^{-2}$ ($P < 0.001$), and median microvascular flow index from 2.75 [2.66 to 2.85] to 2.50 [2.35 to 2.63] ($P = 0.001$). A median blood loss of 600 [438 to 913] ml until the time of prostate removal and norepinephrine therapy to treat intraoperative hypotension had no detrimental effect on the sublingual microcirculation: There were no clinically important changes in the microvascular flow index, the proportion of perfused vessels, the total vessel density, and the perfused vessel density. Blood donation resulted in no clinically important changes in any of the macrocirculatory or microcirculatory variables.

CONCLUSION Moderate intraoperative blood loss and norepinephrine therapy administered to treat intraoperative hypotension have no detrimental effect on the sublingual microcirculation and the coherence between the macrocirculation and microcirculation in patients having open radical prostatectomy.

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Introduction

Intraoperative blood loss is common during major surgery¹ and is associated with adverse postoperative

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outcomes.^{2,3} Intraoperative blood loss clinically presents with hypotension and tachycardia, both clinical symptoms of impaired macrocirculation. These symptoms are

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treated pragmatically with vasopressors and fluids to restore the macrocirculation.

In contrast to the macrocirculation, the microcirculation, that may also be impaired by intraoperative blood loss, is usually not assessed in routine clinical care. It thus remains unknown whether moderate intraoperative blood loss and therapeutic interventions used to restore the macrocirculation impair the microcirculation and affect the coherence between the macrocirculation and microcirculation in patients having surgery with general anaesthesia.⁴ It also remains unknown whether moderate intraoperative blood loss in patients having surgery with general anaesthesia has different effects on the microcirculation compared with moderate blood loss in healthy blood donors.

We, therefore, performed a prospective observational study to investigate the effect of moderate intraoperative blood loss and norepinephrine therapy administered to treat intraoperative hypotension on the sublingual microcirculation measured using vital microscopy in patients having open radical prostatectomy with general anaesthesia. As a control group of patients with moderate blood loss but without general anaesthesia or norepinephrine therapy, we assessed the sublingual microcirculation in healthy blood donors.

Methods

Study design and setting

This single-centre prospective observational study was approved by the ethics committee (Ethikkommission der Ärztekammer Hamburg, Hamburg, Germany; registration number PV5826; Chairperson Prof R. Stahl; 10 August 2018) and all participants provided written informed consent. The study was conducted in the Department of Anaesthesiology, the Martini-Klinik Prostate Cancer Center, and the Blood Donation Center of the Institute for Transfusion Medicine at the University Medical Center Hamburg-Eppendorf (Hamburg, Germany) between November 2018 and March 2019.

Inclusion and exclusion criteria

All patients scheduled for elective open radical prostatectomy were eligible for study inclusion. Exclusion criteria were age less than 45 years or above 75 years, body weight less than 50 kg, arrhythmia, contraindications for monitoring using the finger-cuff method, emergency surgery, and refusal or withdrawal of consent.

As a second group, we included healthy male volunteer blood donors. Exclusion criteria for blood donors were age less than 45 years or above 75 years, body weight less than 50 kg, contraindications for monitoring using the finger-cuff method, or regular intake of blood pressure medication (ACE-inhibitors, angiotensin-1-antagonists, diuretics) that would – in case of surgery – be paused for the perioperative period.

Anaesthesia

Patients had basic anaesthetic monitoring (electrocardiogram, pulse oximetry, upper-arm cuff oscillometry) and three peripheral venous catheters were inserted: one for norepinephrine administration and two for rapid fluid infusion. We induced general anaesthesia with sufentanil, propofol, and rocuronium. The patient's trachea was intubated and mechanical ventilation was performed with a tidal volume of 8 ml kg⁻¹ of predicted body weight, a positive end-expiratory pressure of 5 cmH₂O, and a respiratory rate adjusted to end-expiratory carbon dioxide. We maintained anaesthesia with inhaled sevoflurane and repeated boluses of sufentanil. The vasopressor norepinephrine was the first line treatment to maintain mean arterial pressure according to routine care in our institution. Continuous norepinephrine infusion (via an infusion pump) was started after the administration of anaesthetic induction agents to maintain the mean arterial pressure above 65 mmHg, the routinely used lower mean arterial pressure intervention threshold in our institution. Blood pressure management was at the discretion of the attending anaesthesiologists and mean arterial pressure intervention thresholds higher than 65 mmHg could thus be used in patients with chronic arterial hypertension. A balanced crystalloid fluid (Sterofundin ISO; Braun, Melsungen, Germany) was administered very restrictively until prostate removal. After prostate removal, liberal fluid resuscitation was started with the crystalloid fluid and, if deemed necessary, colloid fluid (Volulyte; Fresenius, Bad Homburg, Germany). We performed frequent venous blood gas analyses. At the end of surgery, the patient's trachea was extubated while in the operating room and subsequently the patients were monitored in the post anaesthesia care unit for at least 2 h before being transferred to the normal ward.

Monitoring of the macrocirculation

In addition to routine anaesthetic monitoring, we measured cardiac index, stroke volume index, pulse pressure variation, and systemic vascular resistance index using a noninvasive finger-cuff method based on the vascular unloading technique (CNAP system; CNSystems Medizintechnik GmbH, Graz, Austria). This finger-cuff method enables blood pressure and advanced haemodynamic variables to be estimated using pulse wave analysis of the continuously recorded pulse pressure waveform.^{5–8} The double finger cuff of the CNAP system was attached to the index and middle finger of the patients' right hand. The CNAP finger sensor-derived arterial blood pressure was calibrated to brachial arterial blood pressure obtained from the system's oscillometric upper arm cuff.

Monitoring of the sublingual microcirculation

We assessed the sublingual microcirculation with a hand-held vital microscope using the incident dark field

imaging technology (CytoCam; Braedius Medical BV, Huizen, The Netherlands). We performed measurements according to current guidelines for the assessment of sublingual microcirculation⁹ before anaesthesia induction, before surgical incision, at the time of prostate removal, and 2 h after surgery. During the measurements, the patients were in supine position and the device was placed on the sublingual mucosa after gentle removal of saliva. At each of the time points, we obtained several 5 s video sequences at different positions under the tongue. Afterwards, all videos were rated according to the 'Microcirculation Image Quality Score'.¹⁰ Videos deemed appropriate for analysis were stabilised and cropped to fit the resolution requirements of the analysis software (Automated Vascular Analysis ver. 3.2; Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands). All videos were processed and analysed by a single investigator (MF), who was also responsible for video acquisition. We analysed the microvascular flow index by quadrant (MFI), the proportion of perfused vessels (PPV), the total vessel density (TVD), and perfused vessel density (PVD).⁹

Measurements in healthy blood donors

Using the same methods and devices as for the patients having prostatectomy, we performed measurements of the macrocirculation (noninvasive finger-cuff method, CNAP system) and the microcirculation (vital microscopy using incident dark field imaging) in the male volunteer blood donors. We performed measurements immediately before and 15 min after a 500 ml blood donation. During the measurements, the participants were placed in supine position and rested for at least 5 min before data acquisition. At both time points, we also performed blood gas analysis.

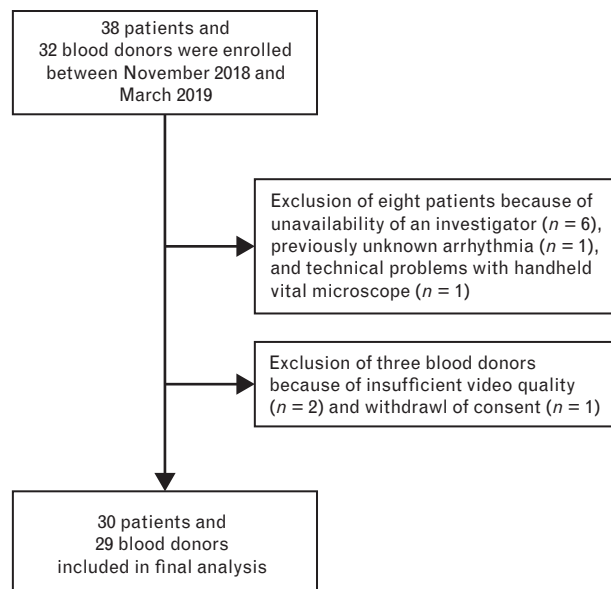
Statistical analysis

Data were analysed with IBM SPSS Statistics 25 (IBM Corp., Armonk, New York, USA). We present descriptive data as medians [IQR] for continuous data and as absolute frequencies (%) for categorical data. We performed Wilcoxon signed rank tests for intra-individual differences in any macrocirculatory or microcirculatory variable between two subsequent time points. The frequency distribution of MFI differences between the different measurement points are shown in histograms. For all statistical tests, a *P* value less than 0.05 was considered statistically significant. Due to the pilot nature of this study, we estimated that complete data from 30 patients would be sufficient to assess the relevant alterations of the macrocirculation and microcirculation.

Results

We enrolled 38 patients scheduled for open radical prostatectomy and eight were excluded: six because the investigator was not available, one because of arrhythmia,

Fig. 1 Flow chart of patients and volunteers.



and one because of technical problems with recording of vital microscope videos. We enrolled 32 blood donors, but one was excluded before the first measurement as he withdrew consent and two were excluded as the video quality of the sublingual microcirculation was rated as 'insufficient'. Thus 30 patients having open radical prostatectomy and 29 blood donors were included in the final analysis (Fig. 1). Patient characteristics are shown in Table 1, and procedural and perioperative data are shown in Table 2.

In the 30 prostatectomy patients, we analysed a total of 386 vital microscope videos (91 videos before induction of anaesthesia, 92 videos before surgical incision, 102 videos at the time of prostate removal, and 101 videos 2 h after surgery). In the 29 blood donors, we analysed a total of 168 vital microscope videos (82 videos before blood donation; 86 videos after blood donation).

General anaesthesia decreased median mean arterial blood pressure, median heart rate, and median cardiac index (Table 3). These differences were clinically important and statistically significant ($P < 0.001$, each). In

Table 1 Characteristics of patients and blood donors

	Prostatectomy patients (n = 30)	Blood donors (n = 29)
Age (years)	66 [57 to 71]	57 [51 to 61]
Male sex	30 (100)	29 (100)
Height (cm)	180 [174 to 182]	182 [178 to 189]
Actual body weight (kg)	81 [78 to 87]	84 [77 to 94]
Diabetes	0 (0)	0 (0)
Arterial hypertension	11 (37)	0 (0)

Data are shown as median [IQR] or absolute number (%).

Table 2 Procedural and perioperative data in patients having prostatectomy

	Before anaesthesia induction	Before surgical incision	Time of prostate removal	2 h after end of surgery
Duration (min)	0 [0 to 0]	25 [20 to 31]	130 [120 to 140]	360 [339 to 390]
Blood loss (ml)	0 [0 to 0]	0 [0 to 0]	600 [438 to 913]	750 [600 to 1113]
Crystalloid fluid (ml)	0 [0 to 0]	200 [188 to 300]	400 [250 to 500]	4000 [3500 to 4500]
Colloid fluid (ml, <i>n</i> = 6)	0 [0 to 0]	0 [0 to 0]	0 [0 to 0]	500 [500 to 500]
Norepinephrine dosage ($\mu\text{g kg}^{-1} \text{min}^{-1}$)	0 [0 to 0]	0.08 [0.06 to 0.10]	0.13 [0.09 to 0.18]	0 [0 to 0]
Norepinephrine cumulative (μg)	0 [0 to 0]	101 [81 to 142]	1005 [702 to 1265]	1758 [1037 to 2648]
Sufentanyl cumulative (μg)	0 [0 to 0]	40 [35 to 40]	75 [70 to 80]	85 [75 to 95]
Propofol cumulative (mg)	0 [0 to 0]	200 [160 to 200]	200 [160 to 200]	200 [178 to 200]
Expired concentration of sevoflurane (Vol %)	0 [0 to 0]	1.4 [1.4 to 1.7]	1.95 [1.9 to 2.0]	0 [0 to 0]
Haemoglobin (mg dl^{-1})	15.3 [14.3 to 16.0]	14.6 [13.5 to 15.1]	14.1 [13 to 15.1]	12.3 [10.8 to 13.0]
Haematocrit (%)	46.8 [43.6 to 49.2]	44.6 [41.1 to 46.6]	42.8 [39.8 to 46.2]	37.8 [33.0 to 39.9]
Lactate (mmol l^{-1})	1.1 [0.9 to 1.5]	0.8 [0.7 to 0.9]	1.0 [0.8 to 1.1]	1.0 [0.7 to 1.3]

Data are shown as median [IQR].

parallel, median MFI decreased from 2.75 [2.66 to 2.85] before anaesthesia induction to 2.50 [2.35 to 2.63] ($P=0.001$) before surgical incision, without clinically important changes in PPV, TVD, and PVD (Table 3).

A median cumulative blood loss of 600 [438 to 913] ml until prostate removal and norepinephrine therapy at a median rate of 0.13 [0.09–0.18] $\mu\text{g kg}^{-1} \text{min}^{-1}$ to treat intraoperative hypotension had no detrimental effect on any of the microcirculatory variables (Table 3). Reflecting the restrictive fluid management strategy, the median cumulative amount of infused crystalloid fluid was 400 [250 to 500] ml until prostate removal. Liberal fluid resuscitation after prostate removal resulted in a total amount of infused crystalloid fluids of 4000 [3500 to 4500] ml until 2 h after surgery (Table 2). Six patients received additional colloid fluid after prostate removal: median 500 [500 to 500] ml. No patient received transfusions of erythrocytes or other blood components. Two hours after surgery, all macrocirculatory variables had returned to levels similar to before induction of anaesthesia.

For individual patients, the changes in mean arterial pressure, heart rate, cardiac index, and pulse pressure

variation are shown in Fig. 2 and the changes in MFI are shown in Fig. 3. Histograms with frequencies of differences in MFI between time points are presented in Fig. 4.

All blood donors donated 500 ml of blood. No fluids or medication were administered during the study period. Blood donation resulted in no clinically important changes in any of the macrocirculatory or microcirculatory variables (Table 4). Haemoglobin, haematocrit, and lactate levels in the blood donors are shown in Supplementary Table S1, <http://links.lww.com/EJA/A485>.

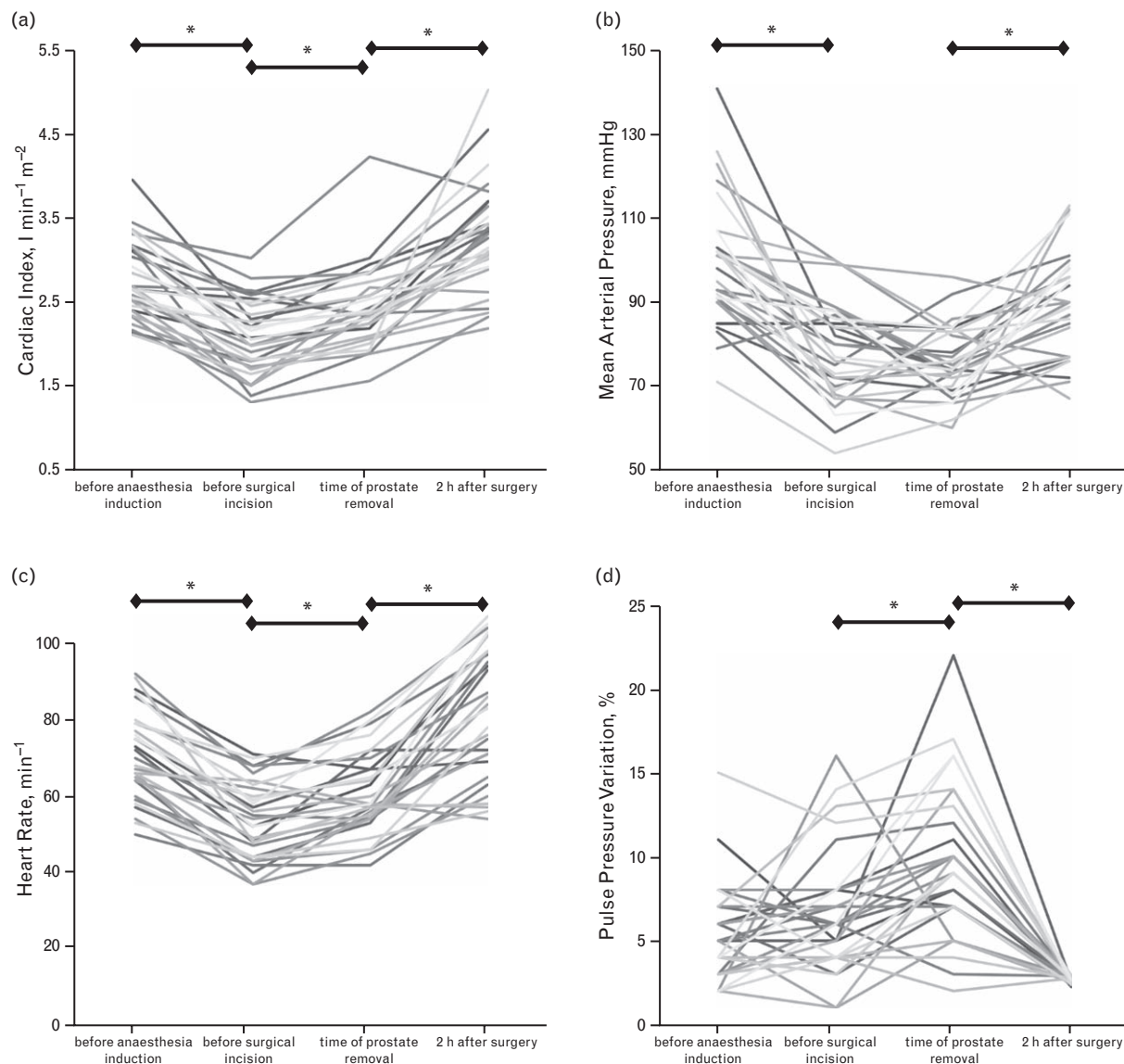
Discussion

In this prospective observational study, moderate intraoperative blood loss and norepinephrine therapy administered to treat intraoperative hypotension had no detrimental effect on the sublingual microcirculation and the coherence between the macrocirculation and microcirculation in patients having open radical prostatectomy. In healthy blood donors, a 500 ml blood donation did not impair any of the measured macrocirculatory or microcirculatory variables.

Table 3 Macrocirculatory and microcirculatory variables in patients having prostatectomy

	Before anaesthesia	Before surgical incision	Time of prostate removal	2 h after surgery
Mean arterial pressure (mmHg)	100 [90 to 104]	79 [69 to 87] [$P<0.001$]	75 [70 to 83] [$P=0.16$]	90 [77 to 98] [$P<0.001$]
Heart rate (min^{-1})	69 [63 to 79]	53 [44 to 62] [$P<0.001$]	58 [54 to 68] [$P<0.001$]	84 [68 to 98] [$P<0.001$]
Cardiac index ($\text{l min}^{-1} \text{m}^{-2}$)	2.67 [2.42 to 3.17]	2.09 [1.74 to 2.49] [$P<0.001$]	2.38 [2.18 to 2.71] [$P<0.001$]	3.30 [2.93 to 3.67] [$P<0.001$]
Stroke volume index (ml m^{-2})	39.1 [34.3 to 43.6]	39.0 [34.1 to 42.8] [$P=0.99$]	40.5 [35.5 to 44.3] [$P=0.63$]	38.4 [35.9 to 47.4] [$P=0.60$]
Pulse pressure variation (%)	5 [3 to 7]	6 [4 to 8] [$P=0.15$]	9 [7 to 12] [$P=0.001$]	6 [4 to 8] [$P=0.001$]
Systemic vascular resistance index ($\text{dyn s m}^{-2} \text{cm}^{-5}$)	2670 [2418 to 3041]	2496 [2305 to 3228] [$P=0.99$]	2364 [1938 to 2620] [$P<0.001$]	1956 [1725 to 2492] [$P=0.026$]
MFI (au)	2.75 [2.66 to 2.85]	2.50 [2.35 to 2.63] [$P=0.001$]	2.56 [2.33 to 2.75] [$P=0.45$]	2.67 [2.50 to 2.75] [$P=0.006$]
PPV (%)	98.4 [97.5 to 99.0]	96.9 [95.6 to 98.0] [$P=0.003$]	96.5 [94.4 to 97.9] [$P=0.17$]	97.3 [95.9 to 98.8] [$P=0.06$]
TVD (mm mm^{-2})	21.7 [20.0 to 22.8]	22.6 [20.1 to 24.4] [$P=0.22$]	22.5 [19.3 to 23.8] [$P=0.63$]	21.0 [19.4 to 23.0] [$P=0.21$]
PVD (mm mm^{-2})	21.0 [19.6 to 22.5]	21.3 [19.2 to 23.9] [$P=0.57$]	21.3 [18.0 to 23.1] [$P=0.60$]	20.7 [18.8 to 22.2] [$P=0.43$]
Number of microcirculation videos per patient	3 [3 to 3]	3 [2 to 4]	3 [3 to 4]	3 [3 to 4]

Data are shown as median [IQR]. *P* values refer to the comparison between a variable and the same variable measured at the previous time point. au, arbitrary unit; MFI, microvascular flow index; PPV, proportion of perfused vessels; PVD, perfused vessel density; TVD, total vessel density.

Fig. 2 Macrocirculatory variables in individual patients having prostatectomy

Spaghetti plots showing individual changes in cardiac index (a), mean arterial pressure (b), heart rate (c), and pulse pressure variation (d) during the study period in individual patients. An asterisk indicates a P value less than 0.05 between the connected measurement points.

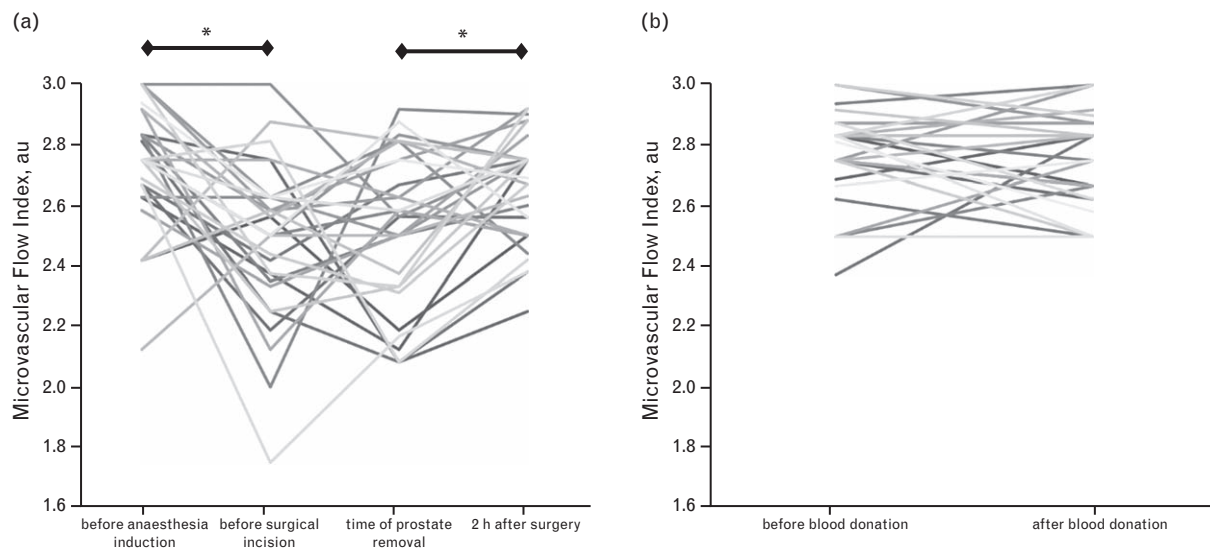
The setting of open radical prostatectomy seems to be ideal to study the effect of moderate intraoperative blood loss and norepinephrine therapy on the sublingual microcirculation in a clinical study. In these patients, fluids are given restrictively and intraoperative hypotension is treated primarily with vasopressors (e.g. continuous norepinephrine infusion) until prostate removal to reduce blood loss and create good surgical conditions.^{11,12} After prostate removal, liberal fluid resuscitation is started to increase intravascular volume and induce urine production.

Vital microscopy using handheld cameras allows visualisation and quantitative analysis of the sublingual

microcirculation. It thus provides information on capillary function and microcirculatory blood flow. However, there are sparse data on sublingual microcirculation in patients having noncardiac surgery as only few clinical studies have been performed in this setting.^{13–15}

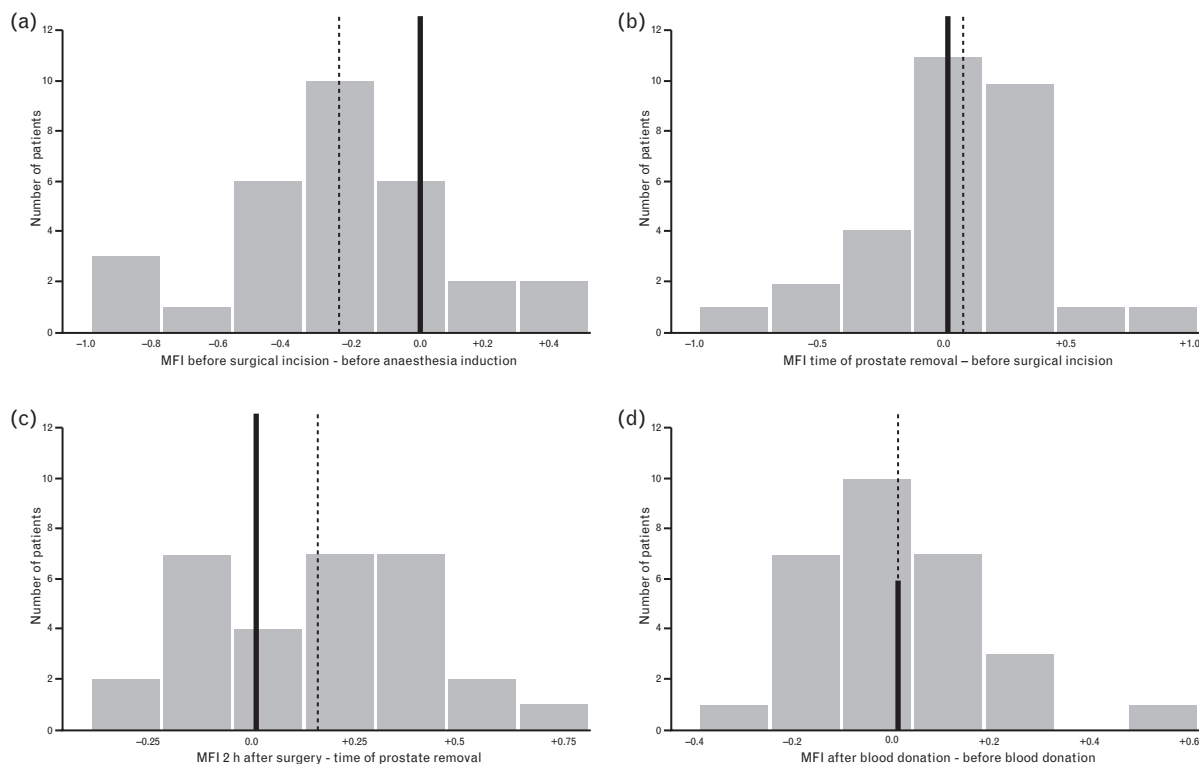
We accounted for the effect of general anaesthesia on the sublingual microcirculation by performing vital microscopy before anaesthesia induction and before surgical incision. The distinct effects of general anaesthesia on the microcirculation remain unclear as previous studies are heterogeneous regarding investigated variables and the technologies used.^{13,16,17} In our study, general

Fig. 3 Microvascular flow index in individual patients having prostatectomy and blood donors



Spaghetti plots showing individual changes in the microvascular flow index during study period in patients having open radical prostatectomy (a) and blood donors (b). An asterisk indicates a *P* value less than 0.05 between the connected measurement points. au, arbitrary unit.

Fig. 4 Histograms with frequencies of differences in microvascular flow index



Histograms showing the frequency of the differences in microvascular flow index (MFI) between measurement points before anaesthesia induction and before surgical incision (a; median difference: -0.25), before surgical incision and time of prostate removal (b; median difference: 0.06), time of prostate removal and 2 h after surgery (c; median difference: 0.15), and before and after 500 ml blood donation (d; median difference: 0.00). The black vertical line indicates the zero point. The dotted vertical line represents the median difference.

Table 4 Macrocirculatory and microcirculatory variables in blood donors

	Before blood donation	After blood donation	P
Mean arterial pressure (mmHg)	95 [90 to 107]	96 [89 to 99]	0.44
Heart rate (min ⁻¹)	66 [61 to 75]	64 [59 to 71]	0.025
Cardiac index (l min ⁻¹ m ⁻²)	2.9 [2.5 to 3.1]	2.9 [2.5 to 3.2]	0.93
Stroke volume index (ml m ⁻²)	40.6 [37.2 to 48.1]	42.8 [39.2 to 47.9]	0.37
Pulse pressure variation (%)	7 [4 to 9]	7 [4 to 9]	0.81
Systemic vascular resistance index (dyn s m ² cm ⁻⁵)	2564 [2345 to 2938]	2437 [2188 to 2784]	0.20
MFI (au)	2.81 [2.68 to 2.86]	2.81 [2.65 to 2.88]	0.88
PPV (%)	98.1 [96.9 to 99.0]	98.4 [97.0 to 99.0]	0.43
TVD (mm mm ⁻²)	20.5 [18.8 to 21.9]	20.0 [18.7 to 21.4]	0.29
PVD (mm mm ⁻²)	19.7 [18.4 to 21.6]	19.7 [18.1 to 20.9]	0.37
Number of microcirculation videos per patient	3 [3 to 4]	3 [3 to 3]	

Data are shown as median [IQR]. P values refer to the comparison between variables before and after blood donation. au, arbitrary unit; MFI, microvascular flow index; PPV, proportion of perfused vessels; PVD, perfused vessel density; TVD, total vessel density.

anaesthesia decreased median MFI. Median MFI had returned to the median baseline value 2 h after surgery. General anaesthesia did not result in clinically important changes in PPV, TVD, or PVD. This shows that overall, despite a slight reduction in microcirculatory flow, there was no clinically important anaesthesia-induced impairment of sublingual microcirculation.

In our study, moderate blood loss did not impair sublingual microcirculation either in patients having prostatectomy under general anaesthesia or in awake blood donors. In contrast to moderate blood loss, severe blood loss can result in haemorrhagic circulatory shock with impaired microcirculation and subsequent organ dysfunction.^{18,19} Several experimental studies have shown that severe acute blood loss markedly impairs the sublingual and intestinal microcirculation.^{20,21}

We infused norepinephrine continuously to treat intraoperative hypotension. Norepinephrine is widely used for this indication. Previous clinical studies showed that norepinephrine has beneficial effects on blood loss as well as on gastrointestinal and cardiac complications in patients having open radical prostatectomy.^{11,12} We observed no detrimental effect of continuous norepinephrine infusion on sublingual microcirculation. This is in line with a previous small clinical study, which found that the sublingual microcirculation was not altered by continuous norepinephrine infusion in 20 women having breast cancer surgery under general anaesthesia.²² These clinical findings are backed up by the results of experimental studies. Norepinephrine administration to treat hypotension did not have adverse effects on the intestinal microcirculation in a pig model of abdominal surgery²³ and in a mouse model of uncontrolled haemorrhagic shock.²⁴

There is still an ongoing debate about the coherence or decoupling of the macrocirculation and microcirculation.²⁵ In our study, the changes in median MFI were coherent with changes in median mean arterial pressure, median heart rate, and median cardiac index. Global haemodynamic variables and MFI simultaneously

decreased with general anaesthesia, remained stable during surgery, and had recovered by 2 h after surgery. This indicates that the coherence between the macrocirculation and the microcirculation was preserved throughout the study period. In contrast, a loss of haemodynamic coherence (i.e. decoupling) has been repeatedly reported in patients having cardiac surgery^{16,26,27} and in critically ill patients with sepsis.²⁸ Our results support the conclusion that we can assume the haemodynamic coherence of the macrocirculation and microcirculation is intact in otherwise healthy patients presenting for elective non-cardiac surgery. In addition, haemodynamic coherence seems to persist even during prostatectomy with moderate blood loss. Prostatectomy is considered moderate risk surgery and is representative for surgical procedures with a significant risk of blood loss.^{29,30} Nonetheless, more severe surgical trauma causing systemic inflammation may lead to an impairment of microcirculatory perfusion and result in a loss of haemodynamic coherence as seen in patients with septic shock.²⁸ Future research needs to investigate if a loss of coherence occurs in the course of major surgery.

We are not able to distinguish between the effects of moderate intraoperative blood loss and norepinephrine infusion on sublingual microcirculation. This is also true for the effects of liberal fluid resuscitation and emergence of anaesthesia. However, our findings in blood donors also suggest that moderate blood loss can be compensated without macrocirculatory and microcirculatory alterations. As we only studied patients having open radical prostatectomy, our cohort consisted of male patients. The generalisation of the results should, therefore, be considered carefully. The measurement performance of the CNAP system for blood pressure and cardiac output monitoring has been investigated in method comparison studies in surgical and critically ill patients with inconsistent results compared with invasive reference methods, and noninvasive finger-cuff methods may not be interchangeable with invasive reference methods.³¹ However, their use allowed us to derive advanced haemodynamic variables without using more invasive techniques such as indicator dilution

methods, which are not used routinely in prostatectomy patients. Data acquisition and video analyses were performed by a single investigator. The investigator was consequently not blinded during the analysis of the microcirculation videos, which could have affected the results. On the other hand, the use of a single investigator prevented the risk of inter-observer bias for video acquisition and video analysis. More research is necessary to establish whether regional sublingual microcirculation reflects microcirculation in other organ systems under various clinical conditions.

In conclusion, moderate intraoperative blood loss and norepinephrine therapy administered to treat intraoperative hypotension have no detrimental effect on the sublingual microcirculation and the coherence between the macrocirculation and microcirculation in patients having open radical prostatectomy. Our findings support the use of norepinephrine to treat intraoperative hypotension during moderate intraoperative blood loss in patients having noncardiac surgery under general anaesthesia.

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References

- Kozek-Langenecker SA, Ahmed AB, Afshari A, *et al.* Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: first update 2016. *Eur J Anaesthesiol* 2017; **34**:332–395.
- Glance LG, Dick AW, Mukamel DB, *et al.* Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. *Anesthesiology* 2011; **114**:283–292.
- Ball CG, Pitt HA, Kilbane ME, *et al.* Peri-operative blood transfusion and operative time are quality indicators for pancreatoduodenectomy. *HPB (Oxford)* 2010; **12**:465–471.
- Ince C. Hemodynamic coherence and the rationale for monitoring the microcirculation. *Crit Care* 2015; **19** (Suppl 3):S8.
- Saugel B, Cecconi M, Wagner JY, *et al.* Noninvasive continuous cardiac output monitoring in perioperative and intensive care medicine. *Br J Anaesth* 2015; **114**:562–575.
- Teboul JL, Saugel B, Cecconi M, *et al.* Less invasive hemodynamic monitoring in critically ill patients. *Intensive Care Med* 2016; **42**:1350–1359.
- De Backer D, Bakker J, Cecconi M, *et al.* Alternatives to the Swan-Ganz catheter. *Intensive Care Med* 2018; **44**:730–741.
- Kouz K, Scheeren TWL, de Backer D, *et al.* Pulse wave analysis to estimate cardiac output. *Anesthesiology* 2020; **134**:119–126.
- Ince C, Boerma EC, Cecconi M, *et al.* Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2018; **44**:281–299.
- Massey MJ, Larochelle E, Najarro G, *et al.* The microcirculation image quality score: development and preliminary evaluation of a proposed approach to grading quality of image acquisition for bedside videomicroscopy. *J Crit Care* 2013; **28**:913–917.
- Wuethrich PY, Studer UE, Thalmann GN, Burkhard FC. Intraoperative continuous norepinephrine infusion combined with restrictive deferred hydration significantly reduces the need for blood transfusion in patients undergoing open radical cystectomy: results of a prospective randomised trial. *Eur Urol* 2014; **66**:352–360.
- Wuethrich PY, Burkhard FC, Thalmann GN, *et al.* Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: a randomized clinical trial. *Anesthesiology* 2014; **120**:365–377.
- Bansch P, Flisberg P, Bentzer P. Changes in the sublingual microcirculation during major abdominal surgery and postoperative morbidity. *Acta Anaesthesiol Scand* 2014; **58**:89–97.
- Stens J, de Wolf SP, van der Zwan RJ, *et al.* Microcirculatory perfusion during different perioperative hemodynamic strategies. *Microcirculation* 2015; **22**:267–275.
- Bouattour K, Teboul JL, Varin L, *et al.* Preload dependence is associated with reduced sublingual microcirculation during major abdominal surgery. *Anesthesiology* 2019; **130**:541–549.
- De Backer D, Dubois MJ, Schmartz D, *et al.* Microcirculatory alterations in cardiac surgery: effects of cardiopulmonary bypass and anesthesia. *Ann Thorac Surg* 2009; **88**:1396–1403.
- Koch M, De Backer D, Vincent JL, *et al.* Effects of propofol on human microcirculation. *Br J Anaesth* 2008; **101**:473–478.
- Tachon G, Harrois A, Tanaka S, *et al.* Microcirculatory alterations in traumatic hemorrhagic shock. *Crit Care Med* 2014; **42**:1433–1441.
- Hutchings SD, Naumann DN, Hopkins P, *et al.* Microcirculatory impairment is associated with multiple organ dysfunction following traumatic hemorrhagic shock: the MICROSHOCK Study. *Crit Care Med* 2018; **46**:e889–e896.
- Ferrara G, Edul VSK, Canales HS, *et al.* Systemic and microcirculatory effects of blood transfusion in experimental hemorrhagic shock. *Intensive Care Med Exp* 2017; **5**:24.
- Dubin A, Pozo MO, Ferrara G, *et al.* Systemic and microcirculatory responses to progressive hemorrhage. *Intensive Care Med* 2009; **35**:556–564.
- Chiarandini P, Pompei L, Costa MG, *et al.* Effects of catecholamines on microcirculation during general inhalation anesthesia. *J Cardiothorac Vasc Anesth* 2013; **27**:1239–1245.
- Hiltebrand LB, Koepfli E, Kimberger O, *et al.* Hypotension during fluid-restricted abdominal surgery: effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. *Anesthesiology* 2011; **114**:557–564.
- Harrois A, Baudry N, Huet O, *et al.* Norepinephrine decreases fluid requirements and blood loss while preserving intestinal villi microcirculation during fluid resuscitation of uncontrolled hemorrhagic shock in mice. *Anesthesiology* 2015; **122**:1093–1102.
- Libert N, Harrois A, Duranteau J. Haemodynamic coherence in hemorrhagic shock. *Best Pract Res Clin Anaesthesiol* 2016; **30**:429–435.
- Koning NJ, Vonk AB, Meesters MI, *et al.* Microcirculatory perfusion is preserved during off-pump but not on-pump cardiac surgery. *J Cardiothorac Vasc Anesth* 2014; **28**:336–341.

- 27 Flick M, Duranteau J, Scheeren TWL, *et al.* Monitoring of the sublingual microcirculation during cardiac surgery: current knowledge and future directions. *J Cardiothorac Vasc Anesth* 2020; **34**:2754–2765.
- 28 De Backer D, Donadello K, Sakr Y, *et al.* Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. *Crit Care Med* 2013; **41**:791–799.
- 29 Freeman WK, Gibbons RJ. Perioperative cardiovascular assessment of patients undergoing noncardiac surgery. *Mayo Clin Proc* 2009; **84**:79–90.
- 30 Carvalhal GF, Griffin CR, Kan D, *et al.* Reducing blood loss in open radical retropubic prostatectomy with prophylactic periprostatic sutures. *BJU Int* 2010; **105**:1650–1653.
- 31 Saugel B, Hoppe P, Nicklas JY, *et al.* Continuous noninvasive pulse wave analysis using finger cuff technologies for arterial blood pressure and cardiac output monitoring in perioperative and intensive care medicine: a systematic review and meta-analysis. *Br J Anaesth* 2020; **125**: 25–37.