Microcirculatory tissue perfusion during general anaesthesia and noncardiac surgery
An observational study using incident dark field imaging with automated video analysis

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BACKGROUND Handheld vital microscopy allows direct observation of red blood cells within the sublingual microcirculation. Automated analysis allows quantifying microcirculatory tissue perfusion variables – including tissue red blood cell perfusion (tRBCp), a functional variable integrating microcirculatory convection and diffusion capacities.

OBJECTIVE We aimed to describe baseline microcirculatory tissue perfusion in patients presenting for elective noncardiac surgery and test that microcirculatory tissue perfusion is preserved during elective general anaesthesia for noncardiac surgery.

DESIGN Prospective observational study.

SETTING University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

PATIENTS 120 elective noncardiac surgery patients (major abdominal, orthopaedic or trauma and minor urologic surgery) and 40 young healthy volunteers.

MAIN OUTCOME MEASURES We measured sublingual microcirculation using incident dark field imaging with automated analysis at baseline before induction of general anaesthesia, under general anaesthesia before surgical incision and every 30 min during surgery. We used incident the dark field imaging technology with a validated automated analysis software.

RESULTS A total of 3687 microcirculation video sequences were analysed. Microcirculatory tissue perfusion variables varied substantially between individuals – but ranges were similar between patients and volunteers. Under general anaesthesia before surgical incision, there were no important changes in tRBCp, functional capillary density and capillary haematocrit compared with preinduction baseline. However, total vessel density was higher and red blood cell velocity and the proportion of perfused vessels were lower under general anaesthesia. There were no important changes in any microcirculatory tissue perfusion variables during surgery.

CONCLUSION In patients presenting for elective noncardiac surgery, baseline microcirculatory tissue perfusion variables vary substantially between individuals – but ranges are similar to those in young healthy volunteers. Microcirculatory tissue perfusion is preserved during general anaesthesia and noncardiac surgery – when macrocirculatory haemodynamics are maintained.

Published online 16 June 2022

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DOI:10.1097/EJA.0000000000001699
Introduction

The ultimate goal of intraoperative haemodynamic management is maintaining adequate microcirculatory tissue perfusion and oxygenation, or simply, perfusing the tissues with oxygen-carrying red blood cells. However, it is macrocirculatory haemodynamics, mainly blood pressure and cardiac output, and not microcirculatory tissue perfusion, that are routinely monitored and therapeutically targeted during surgery. Current intraoperative haemodynamic management strategies thus aim at maintaining blood pressure and cardiac output, assuming that this also ensures adequate microcirculatory tissue perfusion with oxygen-carrying red blood cells. This assumption is based on the concept of coupling between macrocirculatory haemodynamics and microcirculatory tissue perfusion.

Handheld vital microscopy using the incident dark field imaging technology allows direct observation of red blood cells within the sublingual microcirculation. Total vessel density (TVD) and functional capillary density (FCD) reflect the microcirculatory diffusion capacity of oxygen transport from red blood cells to tissue cells. Red blood cell velocity (RBCv) and the proportion of perfused vessels (PPV) reflect microcirculatory convection capacity. Additionally, tissue red blood cell perfusion (tRBCp) was recently proposed as an innovative functional variable to assess microcirculatory tissue perfusion and oxygen delivery. tRBCp integrates individual RBCv, capillary haematocrit (cHct) and capillary density reflecting both microcirculatory diffusion and convection capacity.

In the past, vital microscopy required cumbersome manual or semi-automated offline analysis and could thus not be used at the bedside, but now the validated software MicroTools (Active Medicals BV, Leiden, the Netherlands) allows automated analysis of microcirculatory tissue perfusion, potentially in real-time at the bedside. This could allow targeting microcirculatory tissue perfusion during intraoperative haemodynamic management. However, developing specific intraoperative haemodynamic management strategies requires a better understanding of baseline microcirculatory tissue perfusion and how it is affected by general anaesthesia and surgery.

Thus we performed an observational study using incident dark field imaging with automated analysis to describe baseline microcirculatory tissue perfusion in patients presenting for elective noncardiac surgery and to test the hypothesis that microcirculatory tissue perfusion is preserved during general anaesthesia and noncardiac surgery.

Methods

Study design and setting

This single centre prospective observational study was performed at the University Medical Center Hamburg-Eppendorf (Hamburg, Germany) between April 2018 and April 2019. The study was approved by the ethics committee (Ethikkomission der Ärztekammer Hamburg, Hamburg, Germany; registration number PV565; Chairperson Prof M. Carstensen) on 22 September 2017 and all patients and volunteers provided written informed consent.

Study participants

We included adult patients (≥18 years) scheduled for three types of elective noncardiac surgery with general anaesthesia: major abdominal surgery expected to last at least 120 min, orthopaedic or trauma surgery expected to last at least 60 min and minor urologic surgery expected to last 60 min or less. Pregnant patients and patients having surgery in positions other than supine position were not included. We also included 20 to 30-year-old healthy volunteers to observe any changes in the absence of surgery and anaesthesia.

Clinical management

General anaesthesia was performed per institutional routine. Patients received no premedication. If clinically indicated, an epidural catheter was inserted before the induction of general anaesthesia and a mixture of 0.25% bupivacaine and sufentanil (0.75 µg ml⁻¹) was administered repetitively during surgery in addition to general anaesthesia. After pre-oxygenation, general anaesthesia was induced using an opioid (either sufentanil bolus or continuous remifentanil infusion), propofol and if tracheal intubation was to be performed, a neuromuscular blocking agent. After tracheal intubation or placement of a supraglottic airway device, patients were mechanically ventilated with a tidal volume of 6 to 8 ml kg⁻¹ predicted body weight and a target end-tidal carbon dioxide of 35 to 45 mmHg. General anaesthesia was maintained with either repeated sufentanil boluses or continuous remifentanil infusion and either inhaled sevoflurane or continuous propofol infusion. Haemodynamic management aimed at maintaining mean arterial pressure above

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65 mmHg using a balanced crystalloid fluid (Sterofundin Iso, Braun, Melsungen, Germany), and if necessary, additional crystalloid or colloid fluids and norepinephrine at the discretion of the attending anaesthesiologists.

**Study measurements**

In surgical patients, we simultaneously assessed variables reflecting both the sublingual microcirculation and the macrocirculatory haemodynamics at baseline before induction of general anaesthesia (pre-induction baseline), under general anaesthesia before surgical incision (pre-incision) and every 30 min during surgery (up to a maximum of 120 min after surgical incision). In resting young healthy volunteers, we performed three measurements within 30 min: at baseline, at 15 min and at 30 min.

Sublingual microcirculatory tissue perfusion was assessed using a handheld vital microscope with incident dark field imaging technology\(^\text{11}\) (Cytocam, Braedius, Huizen, the Netherlands) in accordance with the guidelines on the assessment of the sublingual microcirculation set forth by an international task force of the European Society of Intensive Care Medicine.\(^\text{10}\) After gentle removal of saliva, the handheld vital microscope was carefully placed under the tongue and several 5 s video sequences were recorded at different spots. The quality of all video sequences was systematically evaluated and objectively scored considering six quality criteria (as previously recommended).\(^\text{10,15}\) Only video sequences with appropriate quality (defined as a Microcirculation Image Quality Score <10) were analysed further.\(^\text{15}\) Video sequences were stabilised using Analysis Manager (v2; Braedius) and automatically analysed using MicroTools.\(^\text{12}\) We assessed tRBCp, FCD, TVD, RBCv, PPV and cHct.\(^\text{10,13}\)

We averaged the available measurements for each patient at each time point for statistical analysis.

Macrocirculatory haemodynamics were assessed using a noninvasive finger-cuff device (CNAP system, CNSystems Medizintechnik, Graz, Austria) allowing for continuous blood pressure and advanced haemodynamic monitoring.\(^\text{16,17}\) We recorded heart rate, mean arterial pressure, cardiac index, systemic vascular resistance index and stroke volume variation.

**Statistical analysis**

Data are presented as median [IQR and/or range], mean ± SD, or as number (%). We show baseline values of microcirculatory tissue perfusion variables of surgical patients and of young healthy volunteers as one dimensional scatter plots with overlying boxplots. We compared baseline values of microcirculatory tissue perfusion variables between men and women (patients and volunteers) using Welch’s two-sample \(t\)-test. We assessed the correlation between baseline microcirculatory tissue perfusion variables and age and BMI using Pearson’s product-moment correlation.

Values of microcirculatory tissue perfusion and macrocirculatory haemodynamic variables of individual patients and volunteers are shown in spaghetti plots. We used mixed effects models to estimate changes over time in microcirculatory tissue perfusion and macrocirculatory haemodynamic variables. In the mixed effects models, values of microcirculatory tissue perfusion and macrocirculatory haemodynamic variables were the response; each time point was modelled as a fixed effect, and the patients were modelled as random effects to account for the repeated measures design. To illustrate changes in microcirculatory tissue perfusion and macrocirculatory haemodynamic variables over time, expected marginal means and corresponding 95% confidence intervals (95% CI) of the fixed effects were estimated and are shown overlying the spaghetti plots. We estimated pairwise contrasts (and corresponding 95% CI) between expected marginal means to compare values of microcirculatory tissue perfusion and macrocirculatory haemodynamic variables between time points. As a sensitivity analysis for the results on microcirculatory tissue perfusion, age was included in the mixed effects models as a covariate to obtain age-adjusted effect estimates. Statistical analysis was performed using R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

At the time of study conception, there were no data on microcirculatory tissue perfusion assessed using the automated analysis software MicroTools in patients having noncardiac surgery. Therefore, we did not perform a formal sample size calculation. On the basis of previous studies investigating sublingual microcirculatory tissue perfusion in surgical patients,\(^\text{18–21}\) we estimated that a total number of 120 patients (40 patients per group) would be sufficient to identify clinically meaningful changes in microcirculatory tissue perfusion. A sample size of 40 patients per group achieves 87% power to detect a medium effect size of 0.5 with a significance level of 5% using a two-sided paired \(t\)-test (calculated using PASS 2008; NCSS, Kaysville, Utah, USA). As the data is analysed using a mixed effects model, which includes all time points at the same time, the true power is expected to be even higher.

**Results**

We included 40 young healthy volunteers and 120 surgical patients: 40 having major abdominal surgery, 40 having orthopaedic or trauma surgery and 40 having minor urologic surgery (Table 1). A total of 3687 sublingual microcirculation video sequences were automatically analysed.

The baseline microcirculatory tissue perfusion in the patients and volunteers is shown in Fig. 1 and Table 2. In both patients and volunteers, microcirculatory tissue perfusion variables varied substantially between individuals. Age was weakly positively correlated with tRBCp \((r = 0.35; 95\% \text{ CI}, 0.20 \text{ to } 0.48; P < 0.001)\), TVD \((r = 0.36,\)
95% CI, 0.21 to 0.49; $P < 0.001$), FCD ($r = 0.36$, 95% CI, 0.21 to 0.49; $P < 0.001$) and cHct ($r = 0.29$, 95% CI, 0.13 to 0.42; $P < 0.001$) (Supplementary Figure 1, http://links.lww.com/EJA/A709). Sex and BMI were not statistically associated with microcirculatory tissue perfusion variables.

Compared with pre-induction baseline, there were no important changes in tRBCp under general anaesthesia before surgical incision. There were also no important changes in FCD and cHct. However, TVD was higher and RBCv and PPV were lower under general anaesthesia before surgical incision compared with pre-induction baseline.

**Fig. 1** Baseline microcirculatory tissue perfusion

![Graphs showing baseline microcirculatory tissue perfusion variables](image-url)

One-dimensional scatter plots with overlying boxplots showing baseline values of microcirculatory tissue perfusion variables of surgical patients and healthy volunteers. cHct, capillary haematocrit; FCD, functional capillary density; PPV, proportion of perfused vessels; RBCv, red blood cell velocity; tRBCp, tissue red blood cell perfusion; TVD, total vessel density.
In this prospective observational study, we assessed sublingual microcirculatory tissue perfusion using incident dark field imaging with automated analysis to describe baseline microcirculatory tissue perfusion in healthy young volunteers (Supplementary Fig. 2, http://links.lww.com/EJA/A710).

During all three types of surgery, there were no important changes in tRBCp. FCD, TVD, RBCv, PPV and cHct also remained at similar levels observed under general anaesthesia before surgical incision (Fig. 2, Supplementary Table 1, http://links.lww.com/EJA/A711, and Supplementary Table 2, http://links.lww.com/EJA/A712). These findings also persisted when adjusting for age (Supplementary Table 3, http://links.lww.com/EJA/A713). These results were consistent in patients presenting for elective noncardiac surgery and to test the hypothesis that microcirculatory tissue perfusion is preserved during general anaesthesia and noncardiac surgery when macrocirculatory haemodynamics are maintained.

We first assessed baseline microcirculatory tissue perfusion in patients presenting for elective noncardiac surgery. Baseline microcirculatory tissue perfusion variables varied substantially between individuals. This substantial inter-individual variability makes it difficult to interpret single intraoperative measurements and to determine individual harm thresholds without considering pre-induction baseline measurements. Despite the substantial inter-individual variability, microcirculatory tissue perfusion generally seems to be intact when patients present for elective surgery. Ranges of baseline microcirculatory tissue perfusion variables in surgical patients were similar to those in young healthy volunteers. Volunteers were markedly younger than surgical patients – which may explain subtle differences in tRBCp, FCD, TVD, and cHct.

We then investigated the effect of general anaesthesia on sublingual microcirculatory tissue perfusion. There were no important changes in tRBCp, FCD and cHct under general anaesthesia before surgical incision compared with pre-induction baseline values. This indicates that microcirculatory tissue perfusion was overall preserved during general anaesthesia. However, TVD was higher and RBCv and PPV were lower under general anaesthesia compared with baseline. The cause of TVD, RBCv and PPV changes remains elusive. One may speculate that anaesthetic agents promote opening of precapillary arterioles and capillary recruitment, and thus, an increase in

**Table 2** Baseline microcirculatory tissue perfusion and macrocirculatory haemodynamics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Major abdominal surgery (n = 40)</th>
<th>Trauma/orthopaedic surgery (n = 38)</th>
<th>Minor urologic surgery (n = 39)</th>
<th>Healthy volunteers (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tRBCp (µm/min⁻¹)</td>
<td>50.4 [42.0 to 54.9; 24.1 to 79.9]</td>
<td>45.2 [41.3 to 50.4; 29.6 to 65.0]</td>
<td>46.1 [41.6 to 52.4; 22.4 to 59.0]</td>
<td>45.3 [39.5 to 52.0; 22.4 to 70.9]</td>
</tr>
<tr>
<td>TVD (mm/mm²)</td>
<td>21.5 [18.9 to 23.1; 11.4 to 27.7]</td>
<td>20.1 [18.3 to 21.8; 15.4 to 28.2]</td>
<td>21.0 [18.8 to 22.0; 13.3 to 24.7]</td>
<td>18.2 [17.2 to 20.1; 14.0 to 25.4]</td>
</tr>
<tr>
<td>FCD (mm/mm²)</td>
<td>20.9 [18.7 to 22.0; 15.6 to 26.8]</td>
<td>19.3 [17.9 to 20.9; 14.9 to 27.5]</td>
<td>20.5 [18.2 to 21.3; 9.0 to 24.3]</td>
<td>20.5 [18.2 to 21.3; 9.0 to 24.3]</td>
</tr>
<tr>
<td>RBCv (µm/s⁻¹)</td>
<td>334 [327 to 359; 273 to 427]</td>
<td>331 [305 to 353; 248 to 410]</td>
<td>335 [317 to 356; 265 to 471]</td>
<td>340 [302 to 357; 260 to 431]</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>96.9 [96.3 to 98.2; 87.2 to 99.4]</td>
<td>97.3 [95.7 to 98.3; 85.0 to 99.1]</td>
<td>97.1 [95.1 to 98.1; 88.3 to 100.0]</td>
<td>97.6 [94.3 to 98.4; 85.0 to 100.0]</td>
</tr>
<tr>
<td>cHct (%)</td>
<td>5.2 [4.8 to 5.7; 3.8 to 6.8]</td>
<td>5.2 [4.8 to 5.7; 3.8 to 6.8]</td>
<td>5.1 [4.7 to 5.5; 3.6 to 6.2]</td>
<td>5.1 [4.7 to 5.5; 3.6 to 6.2]</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>76 [66 to 84; 50 to 106]</td>
<td>72 [65 to 81; 49 to 108]</td>
<td>69 [50 to 78; 49 to 100]</td>
<td>74 [64 to 80; 45 to 102]</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>89 [80 to 101; 60 to 122]</td>
<td>88 [84 to 102; 50 to 116]</td>
<td>89 [83 to 104; 61 to 136]</td>
<td>88 [81 to 103; 71 to 107]</td>
</tr>
<tr>
<td>Cardiac index (l/min⁻¹m⁻²)</td>
<td>3.0 [2.6 to 3.7; 2.0 to 5.4]</td>
<td>3.4 [3.0 to 3.9; 2.3 to 5.6]</td>
<td>3.2 [2.8 to 3.8; 1.3 to 4.7]</td>
<td>3.6 [3.0 to 4.0; 2.6 to 5.1]</td>
</tr>
<tr>
<td>SVRI (dyns cm⁻⁵m²)</td>
<td>2204 [1879 to 2838; 1241 to 3637]</td>
<td>1912 [1518 to 2343; 652 to 3258]</td>
<td>2197 [1891 to 2706; 1431 to 3488]</td>
<td>1715 [1572 to 1969; 1135 to 2476]</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>11 [9 to 17; 4 to 25]</td>
<td>11 [9 to 15; 4 to 30]</td>
<td>11 [7 to 15; 3 to 34]</td>
<td>12 [10, 16; 6 to 23]</td>
</tr>
</tbody>
</table>

Values are presented as median [IQR; range]. MAP, mean arterial pressure; SVRI, systemic vascular resistance index; SVV, stroke volume variation.

**Discussion**

In this prospective observational study, we assessed sublingual microcirculatory tissue perfusion using incident dark field imaging with automated analysis to describe baseline microcirculatory tissue perfusion in healthy young volunteers (Figs. 2 and 3, and Supplementary Table 5, http://links.lww.com/EJA/A715).
Changes in microcirculatory tissue perfusion variables over time are shown as spaghetti plots for individual patients (grey) and as expected marginal means (black dot) and corresponding 95% confidence intervals (black vertical lines) of the fixed effects. cHct, capillary haematocrit; FCD, functional capillary density; PPV, proportion of perfused vessels; RBCv, red blood cell velocity; tRBCp, tissue red blood cell perfusion; TVD, total vessel density.
Changes in macrocirculatory haemodynamic variables over time are shown as spaghetti plots for individual patients (grey) and as expected marginal means (black dot) and corresponding 95% confidence intervals (black vertical lines) of the fixed effects.
TVD. The decreases in RBCv and PPV may be explained by the anaesthesia-induced macrohaemodynamic changes such as a reduction in blood pressure and cardiac output.

Previous studies investigating the effects of general anaesthesia on sublingual microcirculatory tissue perfusion showed inconsistent results. Some studies found reduced 18,21 and others preserved 19,20 FCD under general anaesthesia compared with pre-induction baseline. These contradictory observations may, in part, result from using different camera technologies and analysis methods. Further, studies reporting preserved FCD found either increased 20 or decreased 19 microvascular blood flow. In our study, preserved tRBCp and FCD indicate that microcirculatory tissue perfusion was not impaired under general anaesthesia before surgical incision – despite reduced microcirculatory flow (RBCv and PPV) and clinically important decreases in blood pressure and cardiac output.

Furthermore we investigated the effect of noncardiac surgery on microcirculatory tissue perfusion. During the intraoperative period, there were no clinically important changes in tRBCp or other microcirculatory tissue perfusion variables, indicating that microcirculatory tissue perfusion was preserved during surgery. These findings were consistent in all patient groups, that is, patients having major abdominal surgery, orthopaedic or trauma surgery and minor urologic surgery.

Previous studies also observed that sublingual microcirculatory tissue perfusion was maintained during noncardiac surgery, even during major abdominal surgery. 19,20,22 This may be surprising as one could assume that surgical trauma causes systemic inflammation, and thus, impairs microcirculatory tissue perfusion. However, microcirculatory tissue perfusion seems to be preserved during surgery – at least when macrocirculatory haemodynamics are maintained.

The idea that maintaining macrocirculatory haemodynamics also ensures adequate microcirculatory tissue perfusion is based on the concept of haemodynamic coupling. 9 This concept assumes that microcirculatory tissue perfusion is preserved when macrocirculatory haemodynamics are maintained above a certain critical level but would be impaired when the macrocirculation is impaired. 23 In contrast, haemodynamic decoupling, 9 an impairment of microcirculatory tissue perfusion independent of macrocirculatory haemodynamics, has been described in patients having cardiac surgery 21,24 and in patients with septic 25 or haemorrhagic shock. 26 During states of haemodynamic decoupling, maintaining blood pressure and cardiac output may not ensure adequate microcirculatory tissue perfusion. In our study, microcirculatory tissue perfusion was not impaired, neither under general anaesthesia nor during noncardiac surgery. This indicates that macrocirculatory haemodynamics and microcirculatory tissue perfusion are indeed coupled in patients presenting for elective noncardiac surgery, and remain coupled under general anaesthesia and throughout surgery.

We recorded sublingual microcirculation video sequences using an incident dark field imaging camera and automatically analysed the sequences using the software MicroTools. 11,12 This software, in addition to established variables, analyses tRBCp, a functional microcirculation variable that integrates microcirculatory convection and diffusion capacities. 13 Automated analysis of vital microscopy, with potentially real-time quantification of microcirculatory tissue perfusion variables at the bedside, is a crucial step towards implementing microcirculation monitoring into clinical practice and specifically optimising microcirculatory tissue perfusion. 27 Further research is necessary to investigate peri-operative applications of handheld vital microscopes and identify possible microcirculatory treatment targets, especially in high-risk settings. 27,28

Our study has limitations. We performed the study in a single university medical centre where previous studies on peri-operative cardiovascular dynamics may have increased clinicians’ awareness for haemodynamic management. Intra-operative management may thus not be representative for other centres. We did not investigate the relationship between microcirculatory tissue perfusion and patient outcome. In a recent multicentre cohort study, reduced microcirculatory tissue perfusion, as reflected by a low peripheral perfusion index, was associated with poor outcome in high risk noncardiac surgery patients. 29 Whether there is a relationship between impaired sublingual microcirculatory tissue perfusion and patient outcome in noncardiac surgery will need further elucidation. Future research is necessary to investigate tissue red blood cell perfusion in different settings. We performed baseline measurements before the induction of general anaesthesia but only observed the first 120 min of surgery. Also, we did not perform any postoperative measurements. 30 Further, sublingual microcirculatory perfusion may not always reflect perfusion of other organ systems. However, correlation between sublingual microcirculatory tissue perfusion and that of vital organs has been shown in several experimental 31–33 and clinical studies during abdominal surgery. 34

Conclusion
In conclusion, in patients presenting for elective noncardiac surgery, baseline microcirculatory tissue perfusion variables vary substantially between individuals but ranges are similar to those in young healthy volunteers. Microcirculatory tissue perfusion is preserved during general anaesthesia and noncardiac surgery – when macrocirculatory haemodynamics are maintained.

Acknowledgements relating to this article
Assistance with the study: none.
Financial support and sponsorship: the Cytocam camera was provided through a collaboration with Fresenius Kabi (Bad Homburg, Germany). Fresenius Kabi was not involved in the development of the study design, data acquisition or analysis, writing of the article or the decision to submit for publication.

Eur J Anaesthesiol 2022; 39:582–590
manuscript, or the decision to submit the manuscript for publication. Analysis of the microcirculatory data using MicroTools was carried out by Active Medical BV (Leiden, the Netherlands).

Conflicts of interest: MF has received honoraria for consulting and giving lectures from CNSystems Medizintechnik (Graz, Austria). THS, JMK, LAK have no conflicts of interest to declare. KK is a consultant for Edwards Lifesciences Inc. (Irvine, California, USA) and Vygon (Aachen, Germany). HDdB has received honoraria for giving lectures and travel grants from Merck (Darmstadt, Germany). TWLS has received research grants and honoraria from Edwards Lifesciences (Irvine, California, USA) and Masimo (Irvine, California, USA) for consulting and lecturing (payments made to institution). CIL and MH are shareholders of Active Medicals BV (Leiden, the Netherlands) a company that offers services, hardware, software (MicroTools) and education (microcirculationacademy.org) related to clinical microcirculation. CI has received educational grants from Fresenius Kabi (Bad Homburg, Germany), Cytoremedien (Germany), Multimedica (Monmouth Junction, New Jersey, USA) and La Jolla Pharmaceuticals (San Diego, California, USA) in the past. BS is a consultant for and has received honoraria for giving lectures from Edwards Lifesciences (Irvine, California, USA). BS is a consultant for and has received institutional restricted research grants and honoraria for giving lectures from Philips Medizin Systeme BmbH (Böblingen, Germany). BS is a consultant for and has received honoraria for giving lectures from GE Healthcare (Chicago, Illinois, USA). BS is a consultant for and has received honoraria for giving lectures from Pulsion Medical Systems (Feldkirchen, Germany). BS has received institutional restricted research grants for giving lectures from Pulsion Medical Systems (Feldkirchen, Germany). BS has received institutional restricted research grants and honoraria for giving lectures from Edwards Lifesciences (Irvine, California, USA). BS is a consultant for and has received honoraria for giving lectures from Philips Medizin Systeme BmbH (Böblingen, Germany). BS is a consultant for and has received honoraria for giving lectures from GE Healthcare (Chicago, Illinois, USA). BS is a consultant for and has received honoraria for giving lectures from Pulsion Medical Systems (Feldkirchen, Germany). BS has received institutional restricted research grants and honoraria for giving lectures from Franck et al. (2021). BS has received institutional restricted research grants and honoraria for giving lectures from Franck et al. (2021). BS has received institutional restricted research grants and honoraria for giving lectures from Franck et al. (2021). BS has received institutional restricted research grants and honoraria for giving lectures from Franck et al. (2021). BS has received institutional restricted research grants and honoraria for giving lectures from Franck et al. (2021).

Presentation: This study was - in part - presented at the 41st International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium.

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Eur J Anaesthesiol 2022; 39:582–590