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Original Article

Association between serosal intestinal microcirculation and blood pressure during major abdominal surgery

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ABSTRACT

Background: In clinical practice, blood pressure is used as a resuscitation goal on a daily basis, with the aim of maintaining adequate perfusion and oxygen delivery to target organs. Compromised perfusion is often indicated as a key factor in the pathophysiology of anastomotic leakage. This study was aimed at assessing the extent to which the microcirculation of the bowel coheres with blood pressure during abdominal surgery.

Methods: We performed a prospective and observational cohort study. In patients undergoing abdominal surgery, the serosal microcirculation of either the small intestine or the colon was visualized using handheld vital microscopy (HVM). From the acquired HVM image sequences, red blood cell velocity (RBCv) and total vessel density (TVD) were calculated using MicroTools and AVA software, respectively. The association between microcirculatory parameters and blood pressure was assessed using Pearson's correlation analysis. We considered a two-sided *P*-value of <0.050 to be significant.

Results: In 28 patients undergoing abdominal surgery, a total of 76 HVM images were analyzed. The RBCv was 335 ± 96 μm/s and the TVD was 13.7 ± 3.4 mm/mm^2. Mean arterial pressure (MAP) was 71 ± 12 mm Hg during microcirculatory imaging. MAP was not correlated with RBCv (Pearson's $r = -0.049$, $P = 0.800$) or TVD (Pearson's $r = 0.310$, $P = 0.110$).

Conclusion: In 28 patients undergoing abdominal surgery, we found no association between serosal intestinal microcirculatory parameters and blood pressure.

Introduction

The perioperative optimization of hemodynamics reduces surgical mortality and morbidity [1]. Additionally, inadequate blood flow is often indicated as an important factor that determines the occurrence of anastomotic leakage, and there exist instances in the literature that associate perioperative disturbances in perfusion with anastomotic leakage that arises pursuant to abdominal surgery [2]. In clinical practice, systemic parameters, such as blood pressure, are used as resuscitation goals for maintenance of tissue oxygenation in target organs. However, the extent to which blood pressure adequately represents the microcirculatory perfusion of the intestine during surgery remains to be elucidated. Hemodynamic coherence between macrocirculation and microcirculation can be lost during states of shock [3]. A reduced sublingual microcirculation was associated with postoperative complications following cases of major abdominal surgery, although no differences in blood pressure were found [4]. Additionally, in septic patients, no correlation was identified between systemic hemodynamic variables and intestinal microcirculation [5]. Handheld vital microscopy (HVM) is a technique that allows for the direct visualization of erythrocytes and, therefore, microcirculation. HVM uses a noninvasive device that images a region of interest upon di-

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rect contact with a tissue surface and has been shown to be feasible for imaging the serosa of the intestine during surgery [6]. The association between blood pressure and sublingual microcirculation has been previously studied [3]. However, there is a scarcity of studies that examine the association between blood pressure and intestinal microcirculation during abdominal surgery. Therefore, our goal was to study the coherence between intestinal microcirculation, as visualized using HVM, and blood pressure during abdominal surgery. We hypothesized that during abdominal surgery, the intestinal microcirculation, as assessed with HVM, would show a positive correlation with mean arterial pressure (MAP).

Methods

Study design

A prospective and observational cohort study (clintrials.gov identifier: NCT02688946) was performed at the St. Antonius Hospital, Nieuwegein, the Netherlands. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by all relevant local and institutional ethics committees. Patients older than 18 years, who were scheduled to have open gastrointestinal surgery or laparoscopic surgery with externalization of the bowel, were eligible for inclusion. All patients included in the study gave written informed consent. Data from subgroups of this cohort have been previously published [6–10]. In the present study, all patients for whom intestinal serosal microcirculation was visualized with incident dark-field imaging were included. The primary endpoint of this study was the correlation between microcirculatory parameters and blood pressure. Secondary endpoints were the correlation between microcirculatory parameters and the cardiac index (CI), central venous pressure (CVP), and the use of crystalloids and vasoactive agents.

Surgery and anesthesia

Surgery and anesthesia were conducted in accordance with standard clinical practice. To facilitate induction of general anesthesia, fentanyl (3 μg/kg), propofol (2 mg/kg), and atracurium (0.4 mg/kg) were used; this was followed by continuous infusion with propofol or sevoflurane. The heart rate was registered once every minute from the electrocardiogram. In patients for whom continuous invasive blood pressure monitoring was performed, CI and stroke volume variation (SVV) were automatically recorded each minute using the Flo-trac/Vigileo® system (Edwards Lifesciences, USA). In other patients, systolic blood pressure (SBP) and MAP were monitored non-invasively. CVP was recorded in patients using an internal jugular central venous catheter. The targets for macrohemodynamics and the therapeutic interventions applied to achieve those targets were determined according to the insight of the attending anesthesiologist.

Image acquisition and study procedure

HVM is a technique that applies light at a wavelength that is absorbed by hemoglobin in erythrocytes. HVM directly visualizes erythrocytes as dark globules moving in the microcirculation. HVM is performed with a handheld device that can be used non-invasively through contact with a tissue surface. In this study, the Cytocam®-incident dark field imaging device (Braedius, Huizen, the Netherlands) was used. Figure 1 displays HVM imaging during surgery. The imaging procedure has previously been described and was performed in accordance with international consensus.[7,8,10,11] HVM was performed by two trained researchers, with one researcher handling the microscope under sterile conditions and the other researcher operating the computer. Images were included after the assessment of stability, focus, illumination, and pressure artifacts, which can be identified by a lack of flow in venules and veins. Additionally, all images were re-assessed during offline analysis. In all patients, one bowel site was imaged. For each bowel site, three unique image sequences, lasting at least 5 s each (25 frames/s), were recorded. During the open procedure, images were acquired at the commencement of surgery. After the induction of anesthesia and completion of laparotomy, a period of at least 15 min of hemodynamic monitoring and stabilization was allowed before HVM imaging was performed. During laparoscopic surgery, imaging is possible exclusively by externalizing the bowel through a Pfannenstiel incision, since direct bowel access is required for HVM imaging. Images were acquired after the surgeon macroscopically assessed the bowel perfusion of this colonic limb.

Data collection

Patient characteristics, including age, sex, body mass index (BMI), and comorbidities, were retrieved from the patients' medical records. The parameters recorded during surgery were retrieved from operative reports and included the type of surgery, SBP, MAP, heart rate, CI, SVV, CVP, the use of vasopressor agents, and the volume of crystalloids administered. Hemodynamic parameters were recorded simultaneously with HVM imaging.

Data analysis

The analysis of acquired HVM images was performed in accordance with guidelines, while blinded for patient and measurement characteristics, and the images were analyzed in a random order [11,12]. Images of inadequate quality were excluded from the analysis. Images were analyzed and stabilized using AVA 3.2 software. After manually identifying vessels, the total vessel density (TVD) was calculated as the total length of vessels per surface area (mm/mm^2). Absolute red blood cell velocity (RBCv) was automatically calculated using MicroTools (Active Medical BV, Leiden, the Netherlands) [13,14]. RBCv provides information regarding the convective capacity of microcirculation, and TVD provides information about the diffusion of microcirculation. For microcirculatory parameters, the average of all videos per measurement was calculated. For each patient, one measurement was included in the analysis. All values presented for microcirculatory parameters were obtained for small vessels (diameter <20 μm).

Statistical analysis

IBM SPSS 23.0 was used for statistical analysis. To test correlations, Pearson's correlation analysis was used for normally distributed parameters, and Spearman's rank analysis was used for

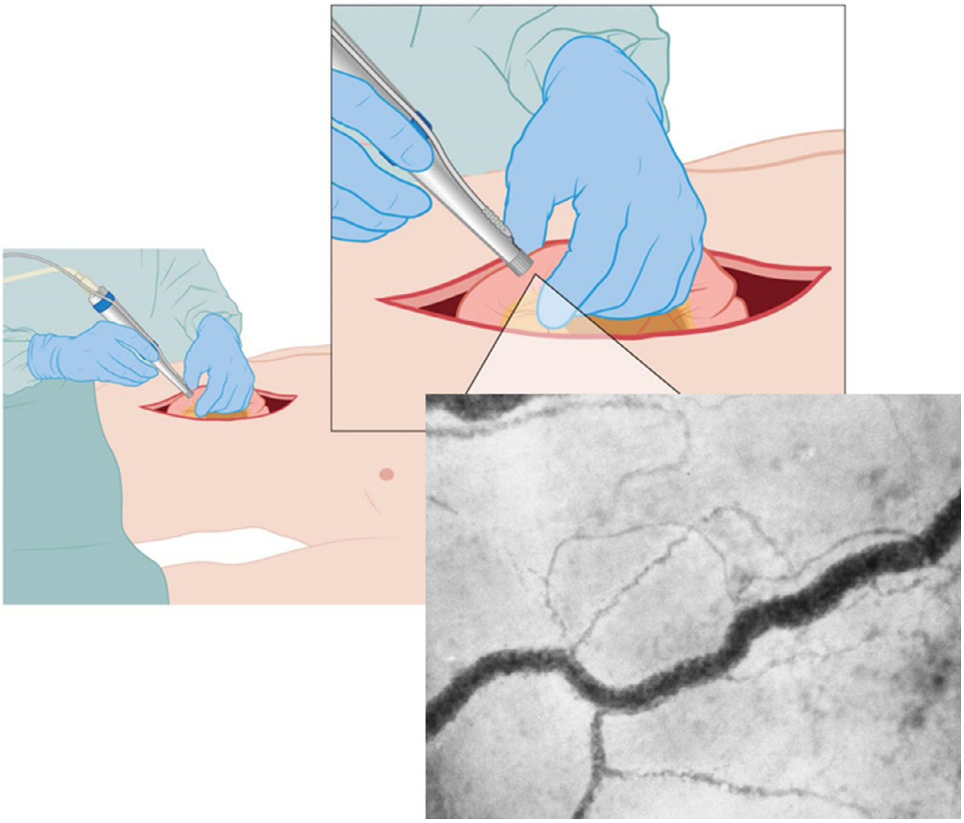

Fig. 1. The use of Handheld vital microscopy during surgery. Figure 1 is an adaptation of a previously published figure and is reprinted with permission from Springer © 2018.[8]

parameters that are not normally distributed. The normal distribution of parameters was visually assessed. Values are presented as either the median (IQR) or as the mean ± standard deviation, based on the normality of distribution. In a subgroup analysis, patients were grouped according to the use of noradrenaline. To examine differences between groups, a Student's t-test was performed. We considered a two-sided P-value <0.050 to be significant.

Results

Study population

A total of 31 patients were enrolled in the study, of which 28 were included in the final analysis. In one patient, no images were acquired because the surgery was discontinued due to peritoneal metastasis. Two other patients were excluded because only measurements of a primary anastomosis were performed and baseline values were not recorded. A total of 84 unique HVM imaging sequences were acquired during surgery. After the offline assessment of image illumination, focus, duration, stability, and the absence of pressure artifacts, 8 images were excluded, resulting in the inclusion of 76 unique HVM imaging sequences. In 21 patients, the small intestine was visualized, whereas in 7 patients the colon was visualized. Patient characteristics are presented in Table 1. Table 2 shows intraoperative factors during HVM.

Table 1
The characteristics of the analyzed patients ($n = 28$).

Item	Data
Age (years)	63 ± 12
Women	13 (46%)
BMI (kg/m^2)	26 ± 3.4
Diabetes mellitus type 2	6 (21%)
Hypertension	5 (18%)
COPD	3 (11%)
History of myocardial infarct	2 (7%)
Smoker	7 (25%)
Preoperative hemoglobin (mmol/L)	8.3 ± 1.0
Type of surgery	
Pancreatic	9 (32%)
HIPEC	9 (32%)
Colorectal	7 (25%)
Other	3 (11%)
Open surgery	22 (79%)

Data are expressed as n (%) or mean ± standard deviation.
BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; HIPEC: Hyperthermic intraperitoneal chemotherapy.

Primary endpoint

The MAP during HVM was 71 ± 12 mm Hg, ranging from 55 mm Hg to 106 mm Hg. The RBCv was 335 ± 96 μm/s, ranging from 176 μm/s to 596 μm/s, and the TVD was 13.7 ± 3.4 mm/mm^2, ranging from 7.6 mm/mm^2 to 21.0 mm/mm^2. Figure 2 displays the correlation between blood pressure and microcirculatory parameters. Neither the RBCv nor the TVD of the intestinal microcirculation was significantly correlated with blood pressure. For the correlation between RBCv and MAP, we found a Pearson's r-value of −0.049 ($P = 0.800$). For TVD and MAP, the Pearson's r was 0.310 ($P = 0.110$).

Secondary endpoints

The CVP was available in 15 patients, and the CI was calculated in 18 patients. The values of these parameters are pre-

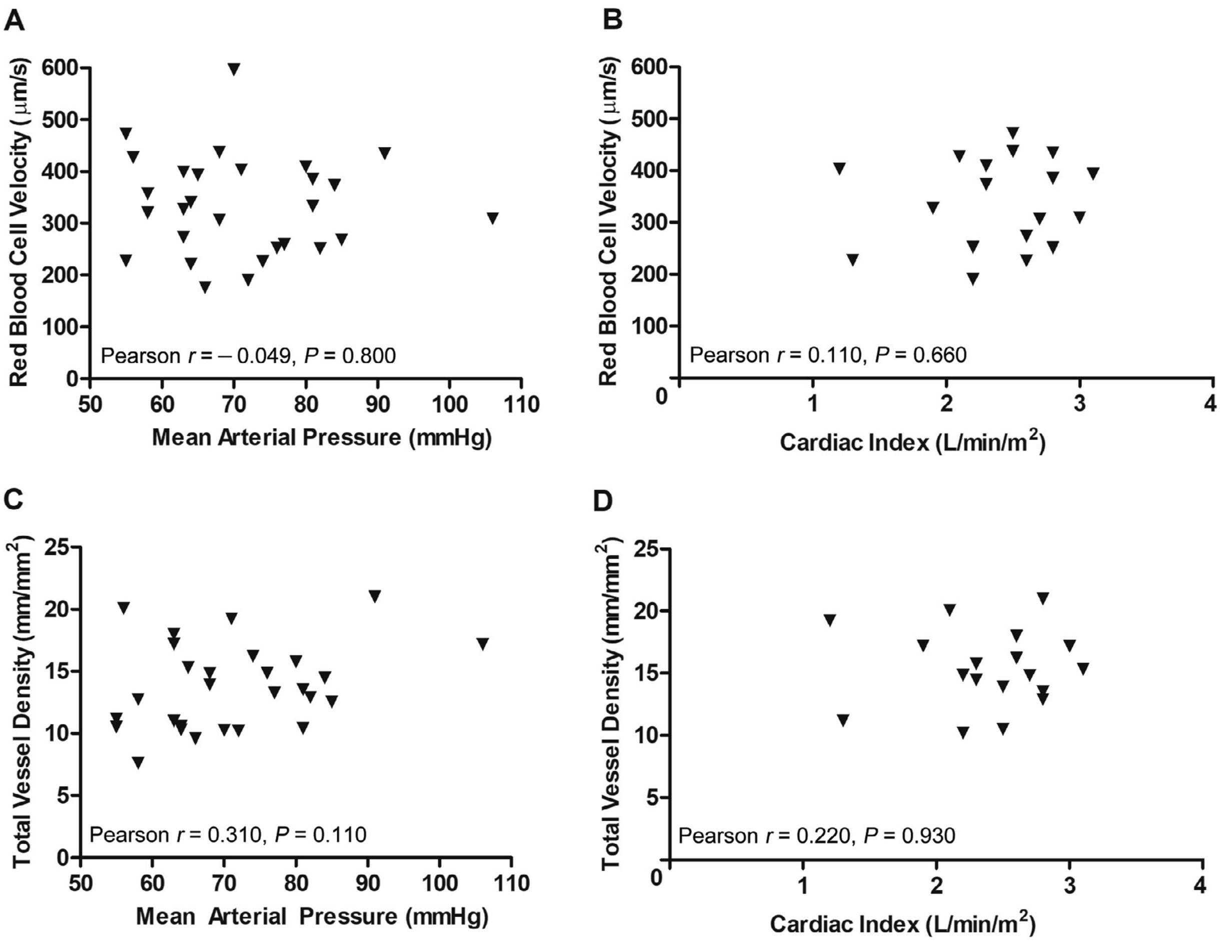

Fig. 2. The correlation between intestinal microcirculation and macrohemodynamic parameters. **(A)** Correlation between RBCv and MAP (*n*=28). **(B)** Correlation between red blood cell velocity and CI (*n*=18). **(C)** Correlation between TVD and MAP (*n*=28). **(D)** correlation between total vessel density and cardiac index (*n*=18). CI: Cardiac index; MAP: Mean arterial pressure; RBCv: Red blood cell velocity; TVD: total vessel density.

Table 2
Intraoperative factors during HVM ($n = 28$).

Item	Data
SBP (mm Hg)	105 ± 19
MAP (mm Hg)	71 ± 12
Heart rate (beats/min)	69 ± 10
CI (L/min/m^2), $n = 18$	2.4 ± 0.5
SVV (%), $n = 18$	9 ± 5
CVP (mm Hg), $n = 15$	9 ± 4
SaO_2 (%)	99 ± 2
Temperature (°C)	36.2 ± 0.5
Volume of crystalloids administered prior to imaging (L)	1.1 (0.74–1.50)
Thoracic epidural anesthesia (*n*, %)	11 (39%)
Noradrenaline (*n*, %)	7 (25%)

Values are presented as the mean ± standard deviation or median (IQR).
CI: Cardiac index; CVP: Central venous pressure; HVM: Handheld vital microscopy; MAP: Mean arterial pressure; SVV: Stroke volume variation; SBP: Systolic blood pressure.

sented in Table 2. The CI, which represents the flow on a systemic level, showed no significant association with RBCv, with a Pearson's r of 0.110 ($P = 0.660$). The CVP, which can be used to detect a state of fluid overload that would be indicative of tissue edema, showed no association with TVD. The volume of crystalloids administered prior to imaging also had no significant correlation with microcirculatory parameters, with Spearman's r-values of −0.130 ($P = 0.520$) for TVD and 0.33 ($P = 0.089$) for RBCv. Seven patients received noradrenaline during HVM, with a mean dosage of 0.20 ± 0.15 mg/h. The microcirculatory parameters did not differ significantly between patients who received noradrenaline and those who did not. Patients who received noradrenaline had an RBCv of 328 ± 101 μm/s and a TVD of 15.8 ± 3.6 mm/mm^2 compared with 336 ± 97 μm/s ($P = 0.850$) and 13.0 ± 3.2 mm/mm^2 ($P = 0.060$), respectively, in patients without noradrenaline.

The small intestine was imaged in 21 patients. In these patients, blood pressure was monitored invasively, and neither RBCv ($r = -0.114$, $P = 0.620$) nor TVD ($r = 0.165$, $P = 0.47$) were significantly correlated with MAP.

Discussion

We studied the serosal microcirculation of the intestine during abdominal surgery in 28 patients using HVM. We found that neither RBCv nor TVD were significantly associated with blood pressure under conditions concomitant with abdominal surgery. During surgery, blood pressure is one of the fundamental measurables on which hemodynamic management is based. Since the monitoring of perfusion and oxygenation in target organs is not performed in standard clinical practice, blood pressure is often used as a proxy measurement for these variables. However, microcirculation does not always correlate with systemic variables; the possibility for this absence of correlation has previously been described for sublingual microcirculation during aortic surgery [15]. Additionally, after major abdominal surgery, a lowered sublingual microcirculation was associated with postoperative complications, although the MAP did not differ in these patients [4]. However, other systemic variables, such as CI or stroke volume, may be more closely associated with the microcirculatory flow than blood pressure; the same association has also been described for sublingual microcirculation during major abdominal surgery [16]. When patients with preload dependence were given a fluid challenge, both microvascular flow and stroke volume improved, whereas MAP and heart rate remained unchanged [16]. We found the CI to be uncorrelated with microcirculatory parameters, although this parameter was only available in 18 patients. The lack of coherence between microcirculation and both blood pressure and CI has previously been reported in an animal model of abdominal surgery. In pigs, SBP increased from a MAP of 60–75 mmHg following norepinephrine administration, resulting in an increase in CI, whereas intestinal microvascular flow remained constant [17]. Our study was conducted in patients undergoing elective surgery; therefore, the perfusion parameters were typically within normal values, as were the macrohemodynamic variables. However, coherence with blood pressure and the impact of therapeutic interventions could differ in postoperative settings or in patients in shock. During abnormal hemodynamic states, such as ischemia or hypertension, the microcirculation could display a different correlation with macrohemodynamics than observed under these study conditions. Interpatient variability also requires consideration, since optimal blood pressure may differ between patients. Therefore, this study highlights a future clinical use for HVM to aid anesthesiologists, surgeons, and other perioperative physicians in the optimization of individual patient care. The HVM device could potentially be used intraoperatively to determine the optimal blood pressure associated with the preservation of microcirculatory function in the intestine, which could then be targeted as a goal for individualized perioperative hemodynamic management. However, for this process to be implemented in clinical care, intraoperative microcirculatory parameters must be associated with clinical outcomes. Currently, the effects of changes in the RBCv or TVD on bowel viability and postoperative complications remain unclear. Additionally, although we imaged both the small intestine and the colon, the microcirculation may behave differently in these components of the gastrointestinal tract. Another clinical use for HVM might be the assessment of anastomotic perfusion during abdominal surgery, since there exist instances in the literature that associate perioperative disturbances in perfusion with anastomotic leakage that arises pursuant to abdominal surgery [2]. In prior studies, we identified compromised serosal perfusion at the planned anastomosis during colorectal surgery; however, none of these patients developed anastomotic leakage [9,10]. One explanation may be that oxygenation can remain adequate even during reduced perfusion; this has been reported for rectal microcirculation after cardiac surgery [18].

Conclusion

In 28 patients undergoing abdominal surgery, we found no association between serosal intestinal microcirculation, as visualized using HVM, and blood pressure.

Funding

Financial support for this study was provided solely from institutional or departmental sources.

Ethical Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by relevant local and institutional ethics committees. Informed consent was obtained from all individual participants included in the study. Trial registry number: ClinicalTrials.gov identifier NCT02688946.

Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: C.I. has received honoraria and independent research grants from Fresenius-Kabi, Bad Homburg, Germany; La Jolla Pharmaceutical Co., La Jolla, CA, USA; and Cytosorbents Monmouth, NJ, USA. C.I. has developed SDF imaging and is listed as the inventor on related patents commercialized by MicroVision Medical (MVM), under a license from the Academic Medical Center (AMC). He receives no royalties or benefits from this license. He has been a consultant for MVM in the past but has not been involved with this company for >5 years, and he holds no shares of stock in MVM. Braedius Medical, a company owned by a relative of C.I., has developed and designed the IDF device used in this study. C.I. has no financial relationship of any sort with Braedius Medical and has never owned shares of, or received consultancy or speaker fees from, Braedius Medical. The MicroTools software is being developed by M.P.H. and is owned by Active Medical BV, of which C.I. and M.P.H. are shareholders. Active Medical runs a website called microcirculationacademy.org, which offers educational courses and services related to clinical microcirculation and provides more information regarding MicroTools. The other authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material which is a HVM imaging sequence of the intestinal serosa can be found in the online version, at doi:10.1016/j.jointm.2021.03.003.

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