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Research Article

Postoperative Observational Study of Sublingual Microcirculation After Caesarean Sections with Side Stream Dark-Field Imaging Technique

Oscar Lindström[1], Jesper Sjöstedt[2], Peter Bansch[3] and Ulf Schött[4]*

[1]Medical Graduate. Institution of Clinical Sciences Lund, Lund University Lund, Sweden.

[2]Medical Graduate. Institution of Clinical Sciences Lund, Lund University, Lund, Sweden.

[3]Institution of Clinical Sciences Lund, Lund University and Skane University Hospital, Department of Anaesthesiology And Intensive Care, Lund, Sweden.

[4]Institution of Clinical Sciences Lund, Lund University and Skane University Hospital, Department of Anaesthesiology and Intensive Care, Lund, Sweden

***Corresponding Author**: Ulf Schött, Institution of Clinical Sciences Lund, Lund University and Skane University Hospital, Department of Anaesthesiology and Intensive Care, Lund, Sweden.

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Abstract

Background: The ultimate effects of resuscitation in patients with hemodynamic instability are assumed to be in the microcirculation. By monitoring sublingual microcirculation using Sidesteam dark-field imaging (SDF), microcirculatory function can be evaluated. Sublingual microcirculatory dysfunction identified with SDF is associated with increased risk of morbidity and mortality in multiple clinical scenarios. Previous studies suggest microvascular alterations in a number of pathological conditions, but still more information about microcirculatory alterations in different pathologies is needed.

Aim/Hypothesis: The aim of our study was to investigate the prevalence of sublingual microcirculatory alterations in Post-OP Caesarean sections, Post-OP liver resections and a heterogeneous ICU population using the SDF-imaging with AVA4 software. A secondary objective was to evaluate the AVA4 software's effectiveness in researching the microcirculation.

Methods: Data on patient diagnosis, type of surgery, systemic hemodynamics variables and laboratory values were collected together with simultaneous SDF imaging of the sublingual microcirculation, supplemented with retrospective acquisition of data from medical records. Data analysis was made using Kruskal-Wallis test and Linear regression.

Results: 22 patients were included in this study. No group proved any significant difference from the control group of healthy volunteers in any of the chosen microcirculatory parameters. There were no linear relations between the microvascular parameters and blood-lactate levels (all patients) or blood-lactate levels (liver resections).

Conclusion: Due to small sample size this study was unable to prove any significant differences between microvascular parameters between patient groups compared to healthy volunteers. To achieve more definite results a larger study population is needed.

Keywords: *Postoperative; Sublingual; Microcirculation; Side Stream*

Abbreviations

SDF: Side Stream Dark-field; ICU: Intensive Care Unit; Post-OP = Post-Operative Unit

Introduction

The ultimate effects of resuscitation in patients with hemodynamic instability is assumed to be in the microcirculation where the blood-cellular exchange takes place. Conventional hemodynamic monitoring appears to fall short in detecting microcirculatory alterations. Macro-hemodynamic variables, such as cardiac output and blood pressure, are only surrogate markers for organ microcirculation [1]. Monitoring of the microcirculation has therefore the potential to be an important additional target for optimizing organ perfusion and preventing organ failure or death [2]. Recently, the Side Stream Dark-field (SDF) imaging technique has allowed bedside observation of the sublingual microcirculation in vivo. The sublingual microcirculation is an accessible location to examine, and has also been shown to excellently mirror the splanchnic microcirculation [3]. Sublingual microcirculatory dysfunction identified by SDF is associated with increased risk of morbidity and mortality in multiple clinical scenarios [4,5].

The newly released AVA4 software allows for automatic quantification of microvascular parameters based on the round-table conference organized in Amsterdam in 2005. Evaluated parameters include measures of vessel density (total and perfused vessel density) and of vascular perfusion (proportion of perfused vessels) [1]. These scores answers two questions of clinical interest when evaluating the microcirculation: the extent of vascularization of the mucosa and how many vessels are perfused. Previous studies suggest microvascular alterations in a number of pathological conditions such as septic- and cardiogenic shock, but still more information about microcirculatory alterations in different pathologies is needed.

Patients undergoing Caesarian sections are expected to have hemodynamic alterations and are thereby of interest when evaluating microcirculatory abnormalities [6]. In another type of surgery - liver resection, hypovolemia is maintained to relieve portal tension that otherwise would interfere with surgical procedure with increased bleeding and time to achieve wound hemostasis. Inadequate circulation in addition to metabolic failure secondary to the liver resection is a common complication in these patients. Patients undergoing Caesarian sections are prone to blood loss and receive fluids and vasoconstrictive therapy to compensate for hypovolemia [7]. Standard therapeutic procedures after liver resections and Caesarian sections are focused on optimizing macro-hemodynamic variables, but therapy efficacy has not been evaluated in regard of the microcirculation with modern noninvasive techniques like SDF. Also, hemodynamic instability is a common problem in intensive care unit (ICU) patients. Additional information about microvascular alterations in these patient groups could be used to further optimize therapeutic procedures in regard to microcirculation to prevent post-operational complications.

The aim of our study was to investigate the prevalence of sublingual microcirculatory alterations in postoperative Caesarean sections and for comparison postoperative liver resections and a heterogeneous ICU population using SDF-imaging with AVA4 software. A healthy volunteer group was used as a reference group. The newly released AVA4 software has not been widely tested in clinical trials and a secondary objective was to evaluate its effectiveness in researching the microcirculation.

Material and Methods

Twenty-eight patients staying in Post-OP unit, ICU or Neuro-ICU who were 18 years or older, and were treated for circulatory abnormalities, were eligible for inclusion. The exclusion criteria were a lack of informed consent and patient-related factors that substantially interfered with SDF imaging, such as being highly dependent on oxygen therapy or mucosal bleeding or injury. Patients with contagious diseases that would interfere with the SUS Lund health and safety policies were also excluded. Five healthy volunteers were also studied as a control group.

The work was carried out in accordance with the Code of Ethics of the World Medical Association (Helsinki Declaration) of 1975, as revised in 1983. The study was approved by the Regional Ethical Board, Lund, Sweden (DNR 309) and registered at Clinicaltrials.com with identification number NCT01037803. The study was a prospective screening study. No power analysis was performed.

The SDF technology is non-invasive, does not hurt and is not inconvenient for the patients. Each measurement takes less than 5 minutes to perform and can be done repetitively. Written and oral informed consent for included subjects was obtained from the patient or next-of-kin.

Fluid therapies are chosen and administered by the ICU doctor in charge and was not involved in the study.

Data on patient diagnosis, type of surgery, systemic hemodynamics variables (fluid balance, urine output, blood pressures, heart rate, pulse pressure variation, Sp02), laboratory values (hemoglobin, arterial lactate and mixed venous saturation), and fluid inotropic or vasoconstrictor therapy were collected together with simultaneous SDF imaging of the sublingual microcirculation, supplemented with retrospective acquisition of data from medical records.

The SDF-device consists of a handheld camera surrounded by LED's emitting stroboscopic green light that is absorbed by erythrocytes, making them appear on screen as black dots against a light mucosal surface yielding a high-contrast picture of blood flow [8]. Short film sequences are recorded and are automatically analyzed by the AVA4 software in regards to pre-determined parameters [9]. Several factors could potentially interfere with image analysis by the AVA4 software. For image acquisition, four requirements based on accepted consensus were taken in consideration: elimination of secretions, adequate focus and contrast, avoidance of pressure artifacts, and high quality recordings. The AVA4 software automatically registers adequate focus, stability and brightness. To minimize variance, a minimum of three film sequences (usually at least five) were taken at different sublingual locations for each measurement and patient.

Collected SDF-film sequences were manually evaluated to ensure a quality that allows for automatic analysis by the AVA4 software. SDF film sequences with lack of image quality were discarded. The AVA4 software automatically analyses collected SDF-images in regards to pre-determined parameters based on accepted consensus chosen to evaluate microcirculation [9]. Collected data is presented as De Backer Density (calculated by AVA4 registering the number of vessels crossing arbitrary lines divided by the total length of the lines), Proportion of Perfused Vessels (PPV), Total Vessel Density, Perfused Vessel Density, Vessel Length and Perfused Vessel Length.

Statistical Analysis

The data were analyzed using Microsoft Excel to calculate average values from a collected minimum of three sublingual locations from each measuring period. Data were then transferred to GraphPad Prism 6 (GraphPad Software, La Jolla, CA) and presented as a boxplot diagram with max, 75% percentile, median, 25% percentile and min values. To determine whether any group proved significant difference compared to the control, healthy volunteers without oxygen inhalation was used for reference. P-values were calculated using Kruskal-Wallis test. A p-value < 0.05 was considered statistically significant.

Results and Discussion

Out of 28 screened patients a total of 22 patients were included in this study. Five Post-OP patients were excluded because of insufficient number of patients in that particular patient group. One Caesarian section patient was excluded due to insufficient SDF image quality. The remaining patients were: 4 Post-OP Caesarean section patients, 5 Post-OP liver resection patients and 13 ICU-patients with different diagnosis (4 with sepsis, 4 with cardiogenic shock, 3 with sub-arachnoid bleeding, 1 with multi organ failure, 1 with acute abdomen). 5 healthy volunteers with 15L/min oxygen were also studied. No group proved any significant difference from the control group of 5 healthy volunteers without oxygen therapy in any of the chosen microcirculatory parameters. (De Backer Density, p=0.065; PPV, p=0.464; Small vessel PPV, p=0.225; Total vessel density, p=0.397; Perfused vessel Density, p=0.134; Perfused Small Vessel Density, p=0.288) (Figure 1). Data tables are presented in appendix.

There were no linear relations between the microvascular parameters and blood-lactate levels (all patients, (Figure 2)) or blood-lactate levels (liver resections, (Figure 3)).

Due to negligible alternations in macro-hemodynamic parameters and laboratory values (with the exception of lactate) within our patient groups, no attempt of correlating these with microcirculatory parameter was made.

Our initial objective with this research project was to use the Micro vision SDF technique to study fluid resuscitation in the intensive care unit. However, during the limited time we had access to a fully operational SDF-system there were not enough hemodynamically unstable patients accessible for measurement before and after fluid resuscitation with crystalloid or colloid intravenous fluid therapy. This is otherwise a controversial area – how to optimize hemodynamics, which goal parameters to achieve and what type of fluid to administrate [10]. Instead we chose to observe micro-circular alternations in more accessible patients.

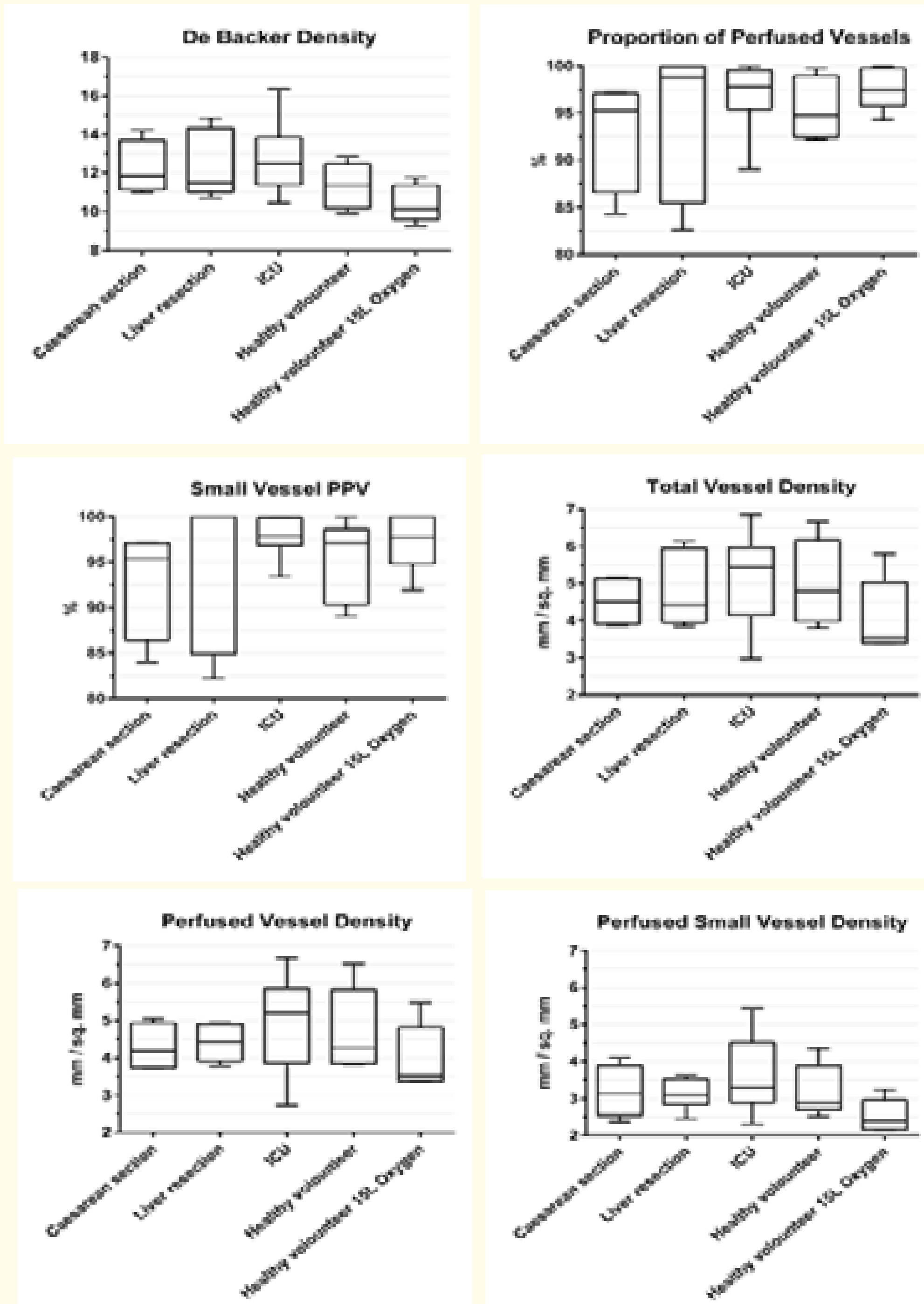

Figure 1: *Boxplots showing Max, 75% percentile, Median, 25% percentile and Min values of parameters: De Backer Density, Proportion of Perfused vessels, Small Vessel PPV, Total Vessel Density, Perfused Vessel Density and Perfused Small Vessel Density for groups: Caesarean section, Liver resection, ICU-patients, Healthy volunteers and Healthy volunteers with 15L oxygen.*

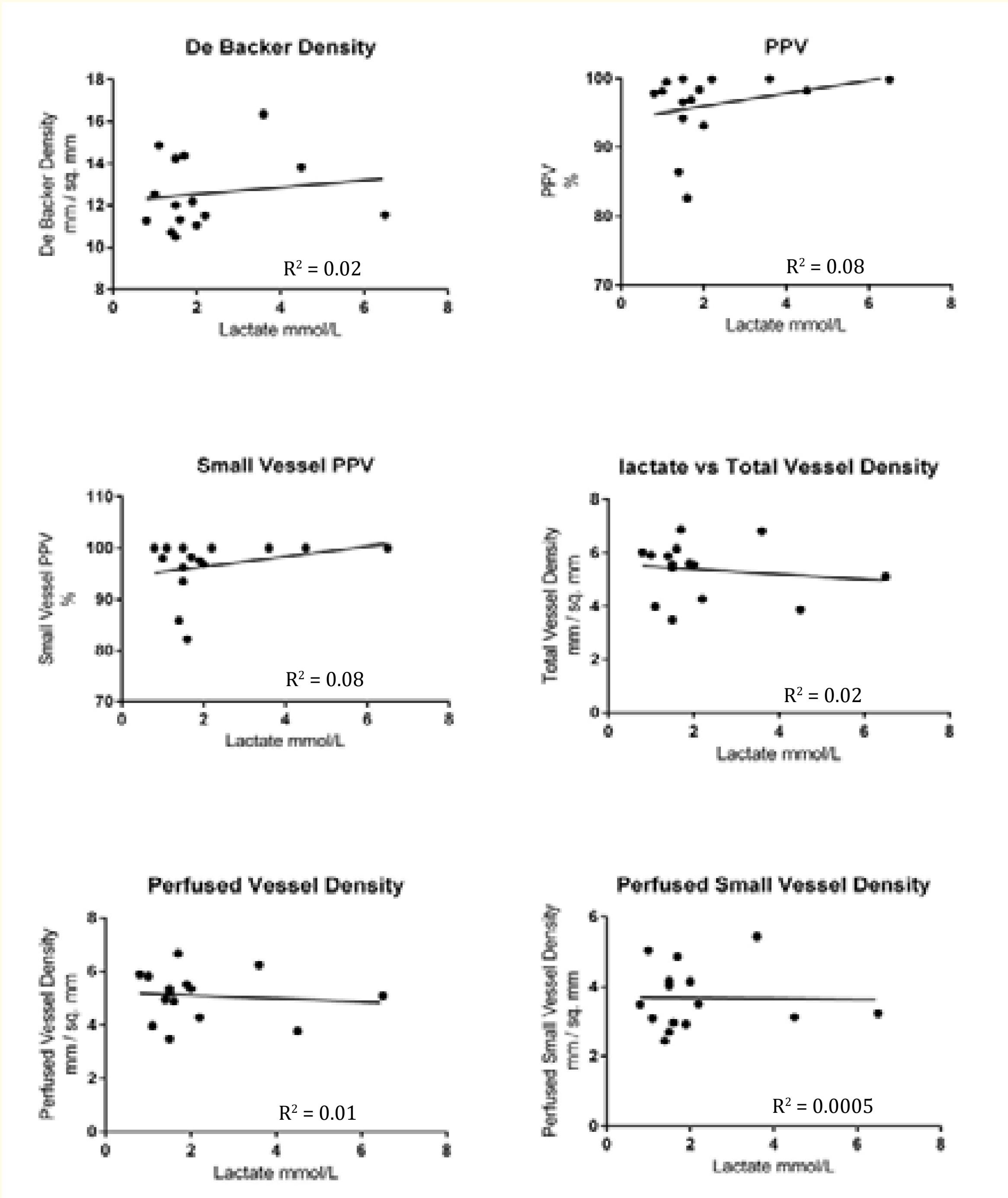

Figure 2: *Linear regressions between lactate and microcirculatory parameters (De Backer Density, Proportion of Perfused vessels, Small Vessel PPV, Total Vessel Density, Perfused Vessel Density and Perfused Small Vessel Density).*

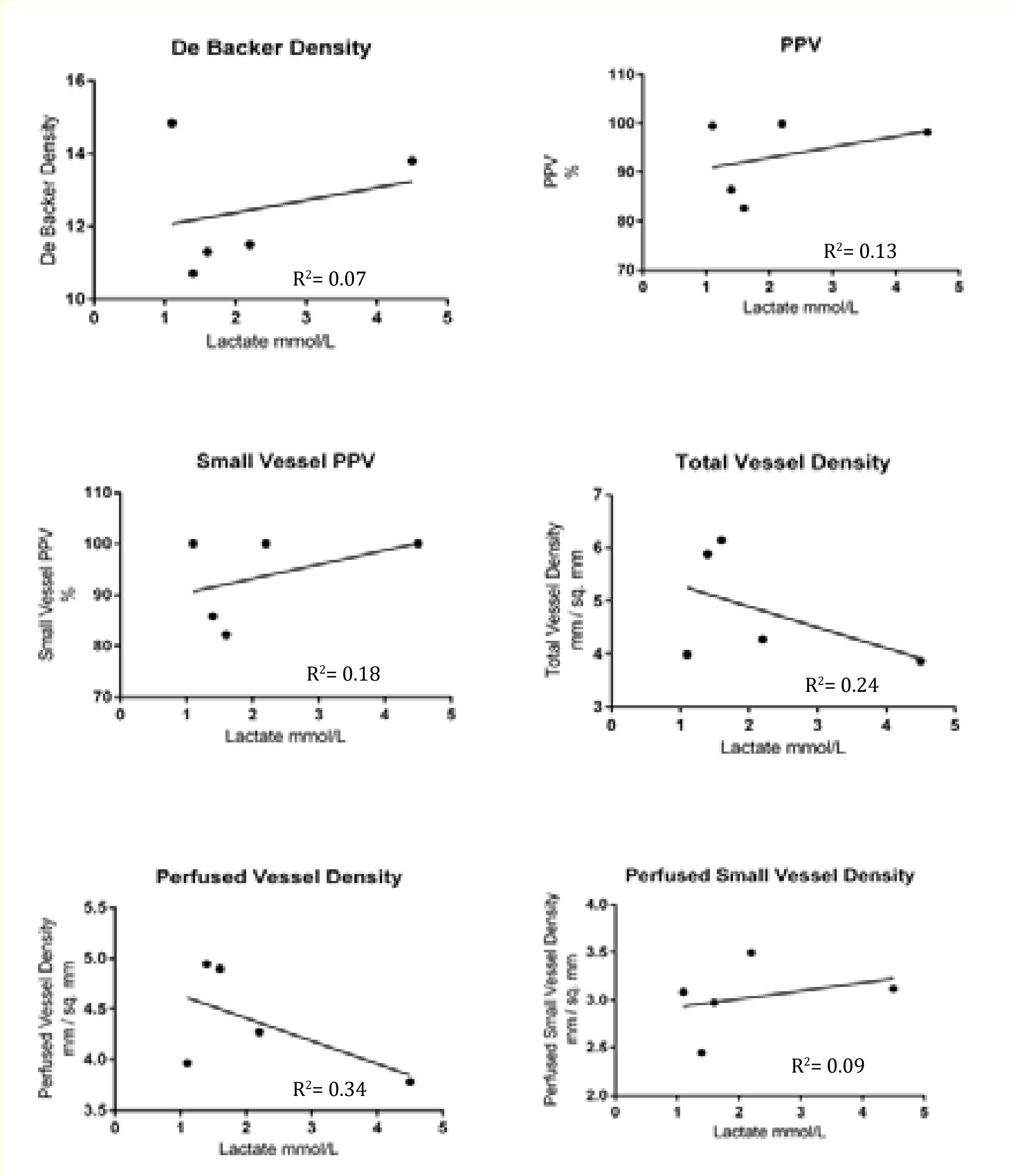

Figure 3: *Linear regressions between lactate levels and microvascular parameters (De Backer Density, Proportion of Perfused vessels, Small Vessel PPV, Total Vessel Density, Perfused Vessel Density and Perfused Small Vessel Density) in liver resection patients.*

The AVA4 Software arrived late in April and due to technical difficulties with the Microvision camera only two weeks of data collection and a limited number of patients was assessed. The small sample size used in this study could not establish any significant difference in the microcirculation between the patient groups and the healthy volunteers. Due to the high variance of the microcirculatory parameters observed, a larger sample size is needed to prove possible differences within and between groups.

It has previously been suggested that oxygen inhalation therapy has coronary and retinal vasoconstrictive effects [11]. The majority of the patients in our study were administered oxygen therapy. We used a healthy volunteer group to, with high flow 15L/min oxygen inhalation in horizontal position, evaluate potential oxygen therapy interference with our study. However, we failed to reach significance due to small sample size and oxygen therapy should despite of our results be taken in consideration when evaluating our study results.

Patients undergoing liver resections are kept hypovolemic intraoperatively to decrease portal tension. Postoperatively, patients are often administered fluids and vasopressors for hemodynamic stabilization. It is possible that microcirculatory alterations can be observed during the hypovolemic stages, but may stabilized over time after surgery. In our study measurements were made within 30 minutes arriving in the Postoperative Care Unit and many patients still had high blood lactate levels that could indicate inadequate circulation in addition to metabolic failure secondary to the liver resection. The lack of correlation between lactate and microcirculatory parameters in our small series of patients does not support inadequate microcirculation in these patients. Probably this reflects our selection of patients being relatively stable and not in circulatory shock. The time after arrival in the post-OP could be of interest when observing microvascular alterations in liver resections but has not been taken in consideration in this study. Future studies of patients undergoing liver resections should include multiple observations of microcirculatory alterations in single patients in relation to time after surgery with repetitive measurements.

The SDF-technology has proved to be a valuable tool for evaluating microcirculatory abnormalities in relation to morbidity and mortality [9]. Before the release of the AVA4 software, analysis of the sublingual microcirculation was done by researchers manually evaluating the Microvascular Flow Index, perfusion and level of heterogeneity, of the microcirculation, with the help of AVA3 (or previous releases) in a 20s-film sequence. This is a time-consuming task that is highly dependent on the competence the researchers. The newly released AVA4 software (2015-04-28) has made analysis of sublingual microcirculation more user-friendly, automatically evaluating perfusion of vessels and vessel density in short film sequences of approximately 1 second. However, we found several drawbacks with the new software. The reduction in length of the film sequences has made collected SDF analysis more accessible for novice users but has also abandoned the established consensus of calculating the flow quality (using microvascular flow index MFI) based on a 20s-film sequence. A heterogeneity index HI is calculated based on acquired MFI data. Since AVA4 is a newly released software, studies have not yet evaluated its efficiency in analyzing microvascular function in the absence of MFI and HI. The absence of MFI quantification eliminates the opportunity of evaluating flow quality and heterogeneity; two parameters put in focus in most previous studies evaluating microcirculatory function. MFI abnormalities have been shown to correlate with adverse outcome in septic patients [9] However, a newly released study has failed to find correlation between MFI and mortality in a heterogeneous ICU population [6]. It is therefore possible that MFI – and thus also HI – as indicators of microvascular flow quality and heterogeneity will be abandoned in the future.

AVA4 uses real-time indicators of adequate focus, stability and brightness; an effort to minimize image quality variance. However, these indicators tend to be unreliable, indicating adequate focus and brightness with low correlation with the operator's view of the image quality. Since the sublingual images cannot be recorded without fulfilled requirements of the AVA4 software, image quality may suffer and can potentially interfere with data analysis. SDF images collected in this study show a lack of quality in many instances, interfering with image analysis. This could have had been avoided if operators where allowed free rein without restrictions from the AVA4 software. A better solution would be to keep indicators as guidance of image quality, but remove their influence on image capturing.

Optimal assessment of SDF-technology is to utilize sublingual images of microcirculation to adjust treatment to optimize vascular perfusion in critically ill patients. A limitation to the use of the current SDF-device in clinical practice is that the patients of which information about the sublingual microcirculatory status has the most potential are also the most inaccessible; patients in severe crisis are often anxious and highly dependent on oxygen therapy, both factors interfering with data acquisition. Hence, SDF-imaging is better suited for observation of intubated and stable patients in the OP- and Post-OP room, defeating the purpose of evaluating microvascular flow in the critically ill.

Appendix

Table showing: Number of patients, Minimum, 25% percentile, Median, 75% percentile, Maximum, Mean and std. deviation values for each parameter: De Backer Density, Proportion of Perfused vessels, Small Vessel PPV, Total Vessel Density, Perfused Vessel Density and Perfused Small Vessel Density values for each group: Caesarean section, Liver resection, ICU-patients, Healthy volunteers and Healthy volunteers with 15L oxygen.

De Backer Density	Caesarean section	Liver resection	ICU	Healthy volunteer	Healthy volunteer 15L oxygen
Number of patients	4	5	13	5	5
Minimum	10.99	10.71	10.48	9.92	9.26
25% Percentile	11.14	11.01	11.40	10.20	9.59
Median	11.86	11.51	12.50	11.38	10.15
75% Percentile	13.70	14.33	13.86	12.50	11.38
Maximum	14.22	14.84	16.34	12.86	11.77
Mean	12.23	12.44	12.72	11.35	10.42
Std. Deviation	1.406	1.787	1.639	1.193	0.9782

Proportion of Perfused Vessels	Caesarean section	Liver resection	ICU	Healthy volunteer	Healthy volunteer 15L oxygen
Number of patients	4	5	13	5	5
Minimum	84.35	82.67	89.04	92.21	94.31
25% Percentile	86.63	85.50	95.37	92.48	95.80
Median	95.22	98.86	97.82	94.71	97.51
75% Percentile	97.13	99.94	99.52	99.00	99.75
Maximum	97.19	99.99	99.97	99.73	99.94
Mean	93.00	94.46	96.94	95.53	97.72
Std. Deviation	6.009	7.789	3.191	3.338	2.246

Small Vessel PPV	Caesarean section	Liver resection	ICU	Healthy volunteer	Healthy volunteer 15L oxygen
Number of patients	4	5	13	5	5
Minimum	83.99	82.23	93.44	89.07	91.92
25% Percentile	86.45	84.93	96.86	90.32	94.79
Median	95.36	100.0	97.82	97.14	97.76
75% Percentile	97.09	100.0	99.90	98.65	100.0
Maximum	97.15	100.0	100.0	100.0	100.0
Mean	92.97	94.68	97.87	95.02	97.47
Std. Deviation	6.173	8.326	1.896	4.521	3.308

Total Vessel Density	Caesarean section	Liver resection	ICU	Healthy volunteer	Healthy volunteer 15L oxygen
Number of patients	4	5	13	5	5
Minimum	3.886	3.863	2.965	3.815	3.403
25% Percentile	3.915	3.957	4.146	3.987	3.407
Median	4.511	4.433	5.437	4.805	3.532
75% Percentile	5.146	5.950	5.967	6.183	5.032
Maximum	5.190	6.150	6.862	6.862	5.792
Mean	4.524	4.792	5.175	5.029	4.082
Std. Deviation	0.6741	0.9849	1.222	1.166	1.021

Perfused Vessel Density	Caesarean section	Liver resection	ICU	Healthy volunteer	Healthy volunteer 15L oxygen
Number of patients	4	5	13	5	5
Minimum	3.724	3.783	2.730	3.808	3.364
25% Percentile	3.731	3.921	3.863	3.850	3.376
Median	4.190	4.431	5.211	4.278	3.530
75% Percentile	4.937	4.911	5.855	5.829	4.817
Maximum	5.041	4.948	6.680	6.518	5.490
Mean	4.286	4.410	4.957	4.727	3.983
Std. Deviation	0.6547	0.4834	1.187	1.132	0.900

Perfused Small Vessel Density	Caesarean section	Liver resection	ICU	Healthy volunteer	Healthy volunteer 15L oxygen
Number of patients	4	5	13	5	5
Minimum	2.363	2.448	2.295	2.519	2.153
25% Percentile	2.539	2.838	2.901	2.689	2.167
Median	3.132	3.101	3.298	2.908	2.393
75% Percentile	3.886	3.528	4.509	3.882	2.972
Maximum	4.115	3.625	5.434	4.354	3.250
Mean	3.186	3.123	3.648	3.210	2.534
Std. Deviation	0.7200	0.4177	0.9772	0.7145	0.4551

Conclusion

Probably due to small sample size this study was unable to prove any significant differences between micro-vascular parameters or lactate in the different patient groups compared to healthy volunteers. To achieve more definite results a larger study population is needed. The newly released AVA4 software and its effectiveness to monitor the microcirculation is unclear.

Conflict of interest

There are no financial interest or any other conflict of interests for any of the authors.

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