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Association of Microcirculation, Macrocirculation, and Severity of Illness in Septic Shock: A Prospective Observational Study to Identify Microcirculatory Targets Potentially Suitable for Guidance of Hemodynamic Therapy

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Abstract

Purpose: Clinically unapparent microcirculatory impairment is common and has a negative impact on septic shock, but specific therapy is not established so far. This prospective observational study aimed at identifying candidate parameters for microcirculatory-guided hemodynamic therapy. **ClinicalTrials.gov:** NCT01530932. **Materials and Methods:** Microcirculatory flow and postcapillary venous oxygen saturation were detected during vaso-occlusive testing (VOT) on days 1 (T0), 2 (T24), and 4 (T72) in 20 patients with septic shock at a surgical intensive care unit using a laser Doppler spectrophotometry system (O2C). **Results:** Reperfusional maximal venous capillary oxygen saturation ($SvcO_2max$) showed negative correlations with Simplified Acute Physiology Score II (SAPSII)/Sequential Organ Failure Assessment (SOFA) score, norepinephrine dosage, and lactate concentration and showed positive correlations with cardiac index (CI). At T24 and T72, $SvcO_2max$ was also inversely linked to fluid balance. With respect to any predictive value, $SvcO_2max$ and CI determined on day 1 (T0) were negatively correlated with SAPS II/SOFA on day 4 (T72). Moreover, $SvcO_2max$ measured on day 1 or day 2 was negatively correlated with cumulated fluid balance on day 4 ($r = -.472$, $P < .05$ and $r = -.829$, $P < .001$). By contrast, CI neither on day 1 nor on day 2 was correlated with cumulated fluid balance on day 4 ($r = -.343$, $P = .17$ and $r = -.365$, $P = .15$). **Conclusion:** In patients with septic shock, microcirculatory reserve as assessed by $SvcO_2max$ following VOT was impaired and negatively correlated with severity of illness and fluid balance. In contrast to CI, $SvcO_2max$ determined on day 1 or day 2 was significantly negatively correlated with cumulative fluid balance on day 4. Therefore, early microcirculatory measurement of $SvcO_2max$ might be superior to CI in guidance of sepsis therapy to avoid fluid overload. This has to be addressed in future clinical studies.

Keywords

microcirculation, postcapillary saturation, macrocirculation, septic shock, fluid balance, therapy guidance, laser Doppler spectrophotometry

Introduction

Septic shock is a leading cause of death in intensive care medicine,[1,2] and altered microcirculation has been a well-recognized problem in critically ill patients and particularly in patients with sepsis for more than a decade.[3] Microcirculatory dysfunction plays an important role in pathophysiology of septic shock.[4] The main causal mechanisms are vasoactive substances such as nitric oxide and endothelin, altered endothelial cell surfaces, and microvascular occlusion by activated coagulation and leukocytes.[5] Furthermore, there is evidence from vaso-occlusive testing (VOT) with near-infrared spectroscopy (NIRS) and direct visualization of

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perfused vessels by sidestream dark-field imaging (SDI) techniques that impaired microcirculation is associated with organ dysfunction and increased mortality.[3,6,7] However, microcirculatory monitoring has not been incorporated in routine sepsis care so far.[8,9] Instead, in clinical practice, circulatory therapy is still guided by point-of-care laboratory diagnostics and macrocirculatory indices,[10] and the current approach of restoring effective tissue perfusion is to optimize vascular filling and global hemodynamics.[4]

Aggressive volume therapy initially reduces lactate levels,[11-14] and vasopressors and inotropes are useful in the presence of systemic vasoparalysis and septic cardiomyopathy. Results of recent multicenter studies, however, are of concern, as in critically ill patients presenting with septic shock, classic early goal-directed therapy combining fluid resuscitation, vasopressors, and inotropes did not reduce mortality.[15,16]

Thus, more knowledge on pathophysiologically relevant parameters at the level of microcirculation is required to establish "microcirculatory-guided therapy,"[14,17] which in the future may allow for better treatment success in sepsis and septic shock than currently obtained by macrocirculation-guided therapy. We used a relatively new device combining well-known laser Doppler flowmetry (LDF) with white light spectroscopy (WLS) to investigate the relationship between micro- and macrocirculation as well as severity of illness in patients with septic shock with the aim to identify target variables potentially suitable for future microcirculatory-guided therapy.

Material and Methods

A prospective observational study was performed in a 25-bed surgical intensive care unit (ICU) in the Department of Anaesthesiology and Surgical Intensive Care of the University Medical Centre, Mannheim, Germany. Design and reporting followed the STROBE statement recommendations (http://www.strobe-statement.org/). Enrollment of patients started in August 2012 and ended in April 2014. Presented data sets are part of a larger combined clinical and laboratory observational trial comprising 3 groups of patients: patients with septic shock, patients with noninfectious systemic inflammatory response syndrome, and age- and sex-matched patients waiting for elective minor surgery without systemic inflammation. Each individual was analyzed with respect to specific laboratory and immune cell activation parameters including microRNA expression profiling (manuscript in preparation).

Ethics

The local ethics committee provided ethical approval (Medical Faculty of Mannheim, Germany). Patients were not able to give consent for inclusion in the study, and therefore, relatives gave assent on every patient's behalf, and patients were later given the opportunity to withdraw from the study.

Patients

Patients with sepsis were enrolled on ICU admission if they fulfilled the criteria of a septic shock with recent onset, defined as norepinephrine required for maintaining a systolic blood pressure of 90 mm Hg or mean arterial pressure (MAP) of at least 60 mm Hg, despite appropriate volume resuscitation, in the absence of other causes of hypotension (2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference[18]). Exclusion criteria were age below 18 years, pregnancy, cardiopulmonary resuscitation, glucocorticoid therapy, end-stage renal or liver disease, and previous organ transplantation.

All patients were sedated with fentanyl and midazolam on a Richmond Agitation-Sedation Scale level[19] of −1 to −4 and mechanically ventilated with lung protective ventilator settings supporting spontaneous breathing. Volume therapy, norepinephrine, and dobutamine were titrated to an MAP of >65 mm Hg, cardiac index (CI) >2.5 L/min × m^2, and urine output of more than 0.5 mL/kg body weight per hour. Central venous oxygen saturation (goal >70%), serum lactate concentration (goal <2 mmol/L), and extended cardiocirculatory monitoring guided treatment of septic shock. Early focus control and empirical antibiotics were additional treatment targets according to the Surviving Sepsis Campaign (SSC) guidelines.[20]

Macrocirculation

Macrohemodynamics (MAP, CI), intrathoracic blood volume index (ITBVI), as a volumetric parameter, and systemic vascular resistance index (SVRI) were monitored every 8 hours as part of routine clinical care and before VOT. For this, patients had a femoral or axillary thermistor-tipped arterial catheter (5F/20 cm or 4F/16 cm; PULSION, Germany), and measures were based on the transpulmonary thermodilution technique (PiCCO; PULSION).[21]

Microcirculation

We assessed microcirculation with a VOT maneuver and took measurements at the thenar eminence[22] using 2 optical methods, LDF and WLS, combined with the O2C device (LEA Medical Technology, Giessen, Germany).[23-25] Briefly, the O2C device emits continuous laser light (830 nm) and white light (500-650 nm), which is scattered by tissue and detected at the skin surface. The collected light is split into its spectral components by a charge-coupled device array and is converted into an electrical signal. The laser Doppler shift is detected, and the product of moving erythrocytes is used for the calculation of the relative blood flow in arbitrary units. This is a quantitative assessment of about 1 mm^3 of tissue volume and interindividually comparable if measured at the same body site. White light is used for the detection of oxygen saturation. The change in color of the reflected light is due to a wavelength-dependent absorption of the applied white light and can be used for the calculation of the oxygen saturation of

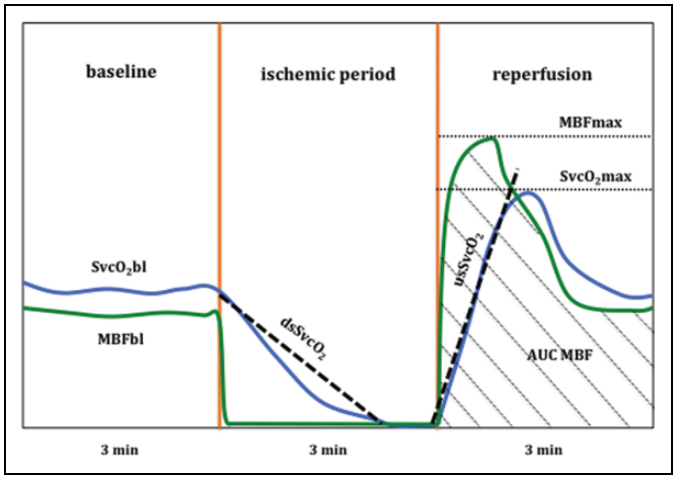

Figure 1. Schematic illustration of vaso-occlusive testing: baseline detection, ischemic period with downslope ($dsSvcO_2$ in %/s) for detecting oxygen uptake, and reperfusion with upslope ($usSvcO_2$ in %/s), indicating recovery, and maximum after cuff deflation; AUC indicates area under the curve; MBF, microcirculatory blood flow; $SvcO_2$, postcapillary venous oxygen saturation (%);

hemoglobin. Measurements with the O2C-device mainly assess the postcapillary venous compartment of the microcirculation, because light is absorbed completely if the vessel diameter is greater than 100 µm[26] and about 70% to 80% of the hemoglobin is located in postcapillary venous system of the microvascular bed.[23,26]

The parameters microcirculatory blood flow (MBF) and postcapillary venous oxygen saturation ($SvcO_2$) were detected in real time (50 Hz) at 2-mm-depth tissue with a gently fixed skin probe (LF 2; LEA Medical Technology). Following an initial 3-minute stabilization period, a cuff was inflated to 250 mm Hg on the proximal forearm for further 3 minutes and quickly removed for reperfusion. Baseline values (baseline MBF [MBFbl], $SvcO_2$bl) were recorded at the end of the stabilization period, the downslope of $SvcO_2$ ($dsSvcO_2$) during the ischemic period, maximum values (MBFmax, $SvcO_2$max) and upslope ($usSvcO_2$) during reperfusion (Figure 1). Microcirculation was assessed within the first day of ICU admission (T0), as well as 24 (T24) and 72 (T72) hours later.

Statistical Analyses

O2CevaTime-Software 20.2.0 (LEA Medical Technology) and SAS 9.4 (SAS Cooperation, Cary, North Carolina) were used for data analysis. We obtained Spearman correlation coefficients for all correlations involving clinical scores and Pearson correlation coefficients for other clinical and hemodynamic parameters. For multiple testing controls, false discovery rate was applied. Paired *t* tests with Bonferroni correction were used for comparison of repeated measures. Simple linear regression was used to estimate the line slope for graphical assessment of the association of selected parameters. For all analyses, a *P* value of less than .05 (2 tailed) was considered statistically significant.

Table 1. Patient Characteristics.[a]

	Septic Shock (n = 20)
Age, years	61.8 ± 16.7
Gender, male	10 (50%)
Source of sepsis	
Abdominal	11 (55%)
Pulmonary	9 (45%)
WBC on admission (cells/nL)	15.0 ± 11
CRP on admission (mg/dL)	221.7 ± 119.4
PCT on admission (µg/L)	4.5 ± 91.7
Organ dysfunction	
Mechanical ventilation	20 (100%)
Vasopressors	20 (100%)
Coagulopathy	12 (60%)
Renal failure (AKIN ≥ 3)	13 (65%)
Hepatic failure	6 (30%)
Comorbidities	
COPD	3 (15%)
Cardiovascular	9 (45%)
Renal	3 (15%)
Diabetes	2 (10%)
Cancer	3 (15%)
ICU	
Length of stay (days)	13.3 ± 8.6
Mortality	6 (30%)

Abbreviations: AKIN, Acute Kidney Injury Network score; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; PCT, procalcitonin; WBC, white blood cell count.
[a]Data are presented as mean ± SD.

Results

General Patient Characteristics

Twenty patients with sepsis were included in the study. After T0, there were 2 dropouts: 1 patient required extracorporeal membrane oxygenation therapy and in the other case relatives withdrew informed consent.

Sources of sepsis were pulmonary or abdominal. Renal failure and coagulopathy were common at baseline (Table 1). The overall ICU mortality was 30%. Average Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) score decreased from T0 to T72 (Table 2). Serum lactate declined and arterial pH increased when T0 and T72 were compared ($P < .001$). Hemoglobin concentration and heart rate declined, whereas MAP increased while fluid balance increased. Cardiac index, ITBVI, and central venous pressure (CVP) were within the recommended range (SSC guidelines), and SVRI was reduced as expected under septic conditions.

Evaluation of Microcirculation at Baseline, During the Ischemic Period, and Measurement of VOT Response

Postcapillary venous oxygen saturation ($SvcO_2$) was determined at baseline ($SvcO_2$bl), and maximum value of reperfusion ($SvcO_2$max) increased over time but did not reach the level of significance (Table 2). The downslope ($dsSvcO_2$)

Table 2. Clinical and Microcirculatory Parameters in Septic Shock.[a]

	T0 (n = 20)	T24 (n = 18)	T72 (n = 18)
SAPS II score	59.2 ± 14.9	53.7 ± 13.9	46.6 + 16.8[b,c]
SOFA score	13.3 ± 3.1	11.4 ± 3.9[b]	9.6 ± 4.7[b,c]
pHa	7.34 ± 0.12	7.38 ± 0.09	7.44 ± 0.06[b,c]
Pao_2/Fio_2 ratio	167 ± 78	191 ± 80	228 ± 59[b,c]
Sao_2 (%)	92.9 ± 4.4	94.9 ± 3.2	95.2 ± 2.7
Hb (g/dL)	10.4 ±2.0	9.8 ± 1.7[b]	9.7 ± 1.0[b]
Lactate (mmol/L)	3.2 ± 2.3	1.8 ± 1.3[b]	1.4 ± 0.8[b]
$ScvO_2$ (%)	73.0 ± 4.9	71.4 ± 8.8	69.6 ± 9.1
Central temperature (°C)	37.1 ± 1.3	37.4 ± 0.6	37.4 ± 0.9
Skin temperature (°C)	33.2 ± 0.5	33.3 ± 0.3	33.3 ± .4
Macrocirculation			
Fluid balance (L)	7.2 ± 4.9	12.6 ± 8.0[b]	15.6 ± 15.1
HR (beats/min)	105.3 ± 18.6	105.4 ± 16.0	94.3 ± 18.6
MAP (mm Hg)	73.6 ± 9.7	77.1 ± 13.0	83.5 ± 16.3[b,c]
CVP (mm Hg)	16.1 ± 5.7	14.8 ± 4.2	14.7 ± 4.2
Noradrenaline (μg/kg/min)	0.59 ± 0.50	0.43 ± 0.31	0.32 ± 0.36
Dobutamine (μg/kg/min)	1.86 ± 3.39	1.59 ± 3.65	0.96 ± 3.03
Cardiac index (L/min/m^2)	4.0 ± 1.3	4.1 ± 1.5	3.9 ± 1.1
ITBVI (mL/m^2)	910 ± 158	920 ± 187	1043 ± 188[c]
SVRI (dyn·s·m^2/cm^5)	1303 ± 451	1375 ± 558	1450 ± 291
Microcirculation			
MBFbl (AU)	121 ± 109	176 ± 122	134 ± 118
MBFmax (AU)	286 ± 138	364 ± 141	314 ± 115
MBF AUC	23 249 ± 19 925	32 889 ± 21 275	26 581 ± 19 005
$SvcO_2$bl (%)	53.3 ± 16.6	60.0 ± 16.5	60.3 ± 14.9
$SvcO_2$max (%)	66.3 ± 10.8	69.8 ± 11.6	70.6 ± 14.9
ds$SvcO_2$ (%/min)	15.3 ± 5.4	17.6 ± 7.7	19.9 ± 9.3
us$SvcO_2$ (%/s)	2.3 ± 1.8	2.1 ± 1.7	3.1 ± 2.9

Abbreviations: AU, arbitrary units; CVP, central venous pressure; ds$SvcO_2$, downslope of the postcapillary venous oxygen saturation; Hb, hemoglobin; HR, heart rate; ITBVI, intrathoracic blood volume index (standard values: 850-1000 mL/m^2); MAP, mean arterial pressure); MBF AUC, area under the curve of microcirculatory blood flow in reperfusion; MBFbl/max, microcirculatory blood flow baseline/maximum; pHa, pH in arterial blood; Sao_2, arterial blood oxygen saturation; SAPS, simplified acute physiology score; SD, standard deviation; $ScvO_2$, central venous oxygen saturation; SOFA, sequential organ failure assessment score; SVRI, systemic vascular resistance index (standard values: 1700-2400 dyn·s·m^2/cm^5; $SvcO_2$bl/max, postcapillary venous oxygen saturation baseline/maximum; us$SvcO_2$, upslope of the postcapillary venous oxygen saturation.

[a]Data are presented as mean ± SD.

[b]$P < .05$ in comparison to T0.

[c]$P < .05$ in comparison to T24.

during ischemia, indicating oxygen uptake, and the upslope (us$SvcO_2$) after start of reperfusion seemed to increase continuously over time, but as standard deviation also increased, statistical significance was missed. Baseline MBF and postischemic response as assessed by maximum blood flow (MBFmax) and the area under the curve (AUC) of reperfusional MBF showed high interindividual variations and did not change significantly over time, although there appeared to be a peak at 24 hours (Table 2).

Associations of Microcirculation and Severity of Illness in Septic Shock

Table 3 gives an overview of significant relationships within the first 4 days of ICU treatment. White light spectroscopy parameters and LDF parameters were linked in manifold ways. Regarding WLS parameters at T0, $SvcO_2$bl was negatively correlated with SAPS II ($P < .05$), and dynamic $SvcO_2$ parameters ($SvcO_2$max, ds$SvcO_2$, us$SvcO_2$) were negatively correlated with SAPS II/SOFA scores ($P < .05$), with the strongest relationship observed between $SvcO_2$max and SAPS II score ($P < .001$) at T0 (see Table 3). At T24, $SvcO_2$max was still correlated with SAPS II and SOFA ($P < .01$) but not at T72 (see also Figure 2). Reperfusional MBF AUC was inversely correlated with SAPS II as well as at T0 ($P < .05$), but not at T24 or T72 (Table 3).

Table 4 shows that $SvcO_2$max at T0 is negatively correlated with indices of illness severity determined at T24 and T72, demonstrating SvcO2max at T0 to be of predictive relevance. Nonetheless, CI determined at T0 was also correlated with illness severity scores determined during the ICU stay.

Associations of Microcirculatory With Routine Hemodynamic and Metabolic Parameters in Septic Shock

At T0, $SvcO_2$max and MBF AUC were positively correlated with CI ($P < .05$; Table 3). The relationship between $SvcO_2$max

Table 3. Correlations of Disease Severity and Clinical and Microcirculatory Parameters.[a]

Correlation Coefficient (*P* Value)		T0	T24	T72
SAPS II	$SvcO_2$bl	**−.468 (<.05)**[b]	−.286 (.25)	−.178 (.48)
	$SvcO_2$max	**−.706 (<.001)**[b]	**−.643 (<.01)**[b]	−.323 (.19)
	ds$SvcO_2$	**−.542 (<.05)**[b]	**−.601 (<.01)**[b]	−.356 (.14)
	us$SvcO_2$	**−.552 (<.05)**[b]	−.408 (.09)	−.440 (.07)
	MBF AUC	**−.472 (<.05)**[b]	.066 (.79)	.390 (.11)
SOFA	$SvcO_2$bl	−.105 (.66)	−.274 (.27)	−.063 (.80)
	$SvcO_2$max	**−.529 (<.05)**[b]	**−.600 (<.01)**[b]	−.282 (.26)
	ds$SvcO_2$	**−.508 (<.05)**[b]	−.384 (.12)	−.205 (.42)
	us$SvcO_2$	**−.502 (<.05)**[b]	**−.481 (<.05)**	−.457 (.06)
	MBF AUC	−.394 (.86)	−.084 (.74)	.177 (.48)
Cardiac index	$SvcO_2$bl	.429 (.07)	.200 (.44)	**.638 (<.05)**
	$SvcO_2$max	**.518 (<.05)**[b]	**.558 (<.05)**	**.528 (<.05)**[b]
	ds$SvcO_2$	**.630 (<.01)**[b]	.399 (.11)	.375 (.17)
	us$SvcO_2$	.026 (.93)	.043 (.87)	.086 (.76)
	MBF AUC	**.507 (<.05)**[b]	−.130 (.62)	.049 (.89)
Norepinephrine	$SvcO_2$bl	−.392 (.09)	−.455 (.05)	**−.567 (<.05)**[b]
	$SvcO_2$max	**−.667 (<.01)**[b]	**−.597 (<.01)**	**−.709 (<.001)**[b]
	ds$SvcO_2$	**−.552 (<.05)**[b]	−.324 (.19)	**−.478 (<.05)**
	us$SvcO_2$	**−.490 (<.05)**	−.401 (.09)	−.430 (.08)
	MBF AUC	−.359 (.09)	−0193 (.44)	.179 (.48)
Lactate	$SvcO_2$bl	**−.573 (<.01)**[b]	−.273 (.27)	−.203 (.42)
	$SvcO_2$max	**−.564 (<.01)**[b]	−.357 (.14)	−.316 (.20)
	ds$SvcO_2$	−.427 (.06)	−.214 (.39)	−.198 (.43)
	us$SvcO_2$	−.340 (.14)	−.341 (.17)	−.447 (.06)
	MBF AUC	−.306 (.19)	−.233 (.35)	.404 (.10)
Fluid balance	$SvcO_2$bl	−.069 (.77)	−.292 (.24)	−.415 (.09)
	$SvcO_2$max	.053 (.82)	**−.560 (<.05)**	**−.561 (<.05)**
	ds$SvcO_2$	.008 (.97)	−.241 (.34)	**−.537 (<.05)**
	us$SvcO_2$	−.104 (.66)	**−.570 (<.05)**	**−.513 (<.05)**
	MBF AUC	.310 (.18)	.294 (.24)	.292 (.24)

Abbreviations: ds$SvcO_2$, downslope of the postcapillary venous oxygen saturation; MBF AUC, area under the curve of microcirculatory blood flow in reperfusion; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment score; $SvcO_2$bl/max, postcapillary venous oxygen saturation baseline/maximum; T0, within 24 hours of ICU admission; T24, second day; T72 fourth day; us$SvcO_2$, upslope of the postcapillary venous oxygen saturation.

[a]Data are presented as Pearson correlation coefficients and as Spearman correlation coefficients for all correlations involving clinical scores. Statistically significant correlations are highlighted with bold print.

[b]The values remain significant after adjustment with false discovery rate.

and CI persisted at later points in time, even if significance was slightly missed after adjustments for T24. At T0, $SvcO_2$max and ds$SvcO_2$ were negatively correlated with norepinephrine dosage and lactate concentration ($P < .01$ and $P < .05$). These inverse correlations with norepinephrine dosage were also seen at T24, in particular for $SvcO_2$max ($P < .05$) and at T72 ($P < .05$ and $P < .001$), but were lost for lactate concentration. Central venous blood oxygen saturation showed no correlation with any recorded LDF or WLS parameter, but CVP was negatively linked to MBF AUC. Figures 2 and 3 provide scatterplots of $SvcO_2$max and MBF AUC correlations with clinical patient characteristics.

$SvcO_2$ indices were not related to fluid balance at T0, but interestingly, in the time course of sepsis, fluid balance became associated with $SvcO_2$-related parameters (Table 3). Early $SvcO_2$max was negatively correlated with fluid balance determined at later time points (Table 5). Accordingly, negative correlations were observed between $SvcO_2$max T0 and fluid balance T72 ($r = -.472$, $P < .05$) and $SvcO_2$max T24 versus fluid balance T72 ($r = -.829$, $P < .0001$). Such correlations were not detected between early measurements of CI at T0 or CI at T24 and cumulated fluid balance values determined later at T72, respectively.

Discussion

We present results on patients with septic shock prospectively analyzed with a laser Doppler spectrophotometry system (O2C) on the day of ICU admission (T0), 24 hours later on day 2 (T24) and on day 4 of treatment (T72). Although previous trials used this device to monitor cerebral microcirculation during neurosurgical procedures[27] and buccal mucosa of patients with sepsis,[24] we applied this method for the first time in combination with VOT in critical care patients with septic shock.

We demonstrate multiple significant correlations between patient's clinical parameters with distinct MBF and numerous $SvcO_2$ parameters. Relationships were strongest for $SvcO_2$max, indicating $SvcO_2$max determined by VOT in the superficial thenar skin layer might be useful for

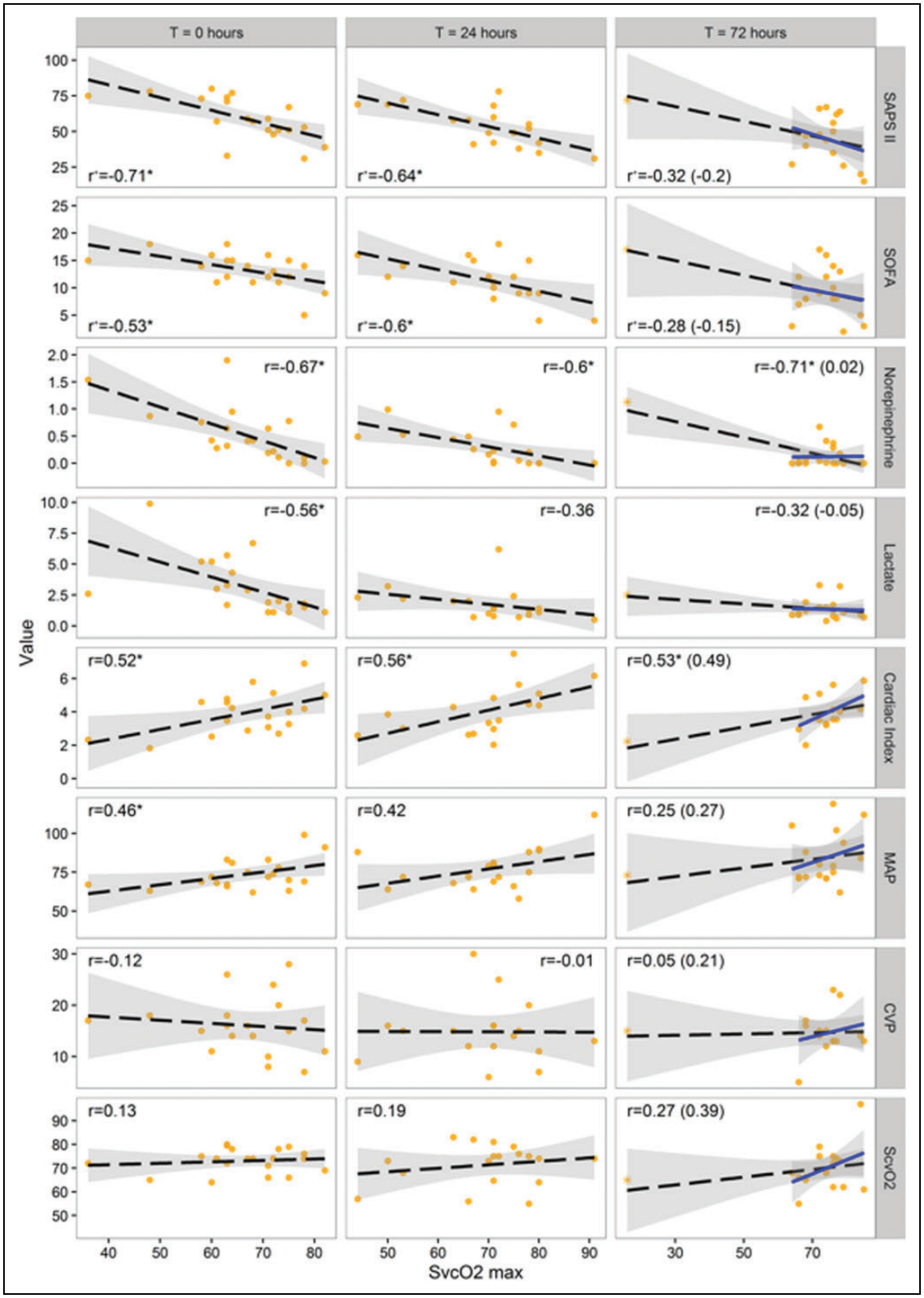

Figure 2. Correlation of clinical characteristics with $SvcO_2$max. Correlations to postischemic maximum of postcapillary venous O_2 saturation ($SvcO_2$max in %); blue correlation line indicates eliminated outliner. Norepinephrine in μg/kg/min; lactate in mmol/L; cardiac index in L/min/m^2. *Note*: Statistical significance for norepinephrine and cardiac index ($P < .08$) at T72 was lost if the obvious outliner was eliminated. CVP indicates central venous pressure; MAP, mean arterial pressure; *r*, Spearman correlation coefficient; SAPS, Simplified Acute Physiology Score; $ScvO_2$, central venous saturation; SOFA; Sequential Organ Failure Assessment score.

Table 4. Correlations of $SvcO_2max$ or CI on Day 1 (T0) With Disease Severity Scores of Day 2 (T24) and 4 (T72).[a]

	T24		T72	
Correlation Coefficient (*P* Value)	SAPS II	SOFA	SAPS II	SOFA
T0 $SvcO_2max$	**−.733 (<.001)**	−.452 (.06)	**−.549 (<.05)**	**−.526 (<.05)**
T0 CI	**−.699 (<.01)**	**−.545 (<.05)**	**−.648 (<.01)**	**−.653 (<.01)**

Abbreviations: CI, cardiac index; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment score; $SvcO_2max$, postcapillary venous oxygen saturation maximum; T0, within 24 hours of ICU admission; T24, second day; T72 fourth day.
[a]Data are presented as Spearman correlation coefficients. Statistically significant correlations are highlighted with bold print.

microcirculatory guidance of hemodynamic therapy at the macrocirculatory level.

Limitations

Optical methods have several technical limitations. Artefacts are frequently caused by surrounding room light or patient movements, and in contrast to SDI, the heterogeneity of impaired microcirculation is not directly recorded.[5] The design of this study is that of a prospective observational one in a single center. We consider this investigation in a small number of patients a hypothesis-generating pilot study. Time-dependent relationships of $SvcO_2max$ were generated as post hoc analyses and should be assessed accordingly.

Technical Aspects

The laser Doppler spectrophotometry system used has been validated in the pig brain[28] and was used in several clinical settings.[23-25,27,29-31] It has not been calibrated for absolute values, but it is suitable for measurements of parameters in the microcirculation.[8,26] Results are closely correlated with those of other blood flow measurement methods and correctly quantify relative changes in skin blood flow.[24,32] However, microcirculatory perfusion is site dependent[32] and intermitted hypoxia leads to altered metabolic signals with long-lasting effects.[33] Accordingly, the relatively poor reproducibility of VOT measurements (coefficient of variation 9.2% ± 1.7%)[25,32] is not surprising. Interindividual variations of skin perfusion are common in critical illness[34] and cause high standard deviation of results. Interestingly, skin perfusion impairment is a strong predictor of 14-day mortality.[35] The advantage of the system used here is the simultaneous assessment of MBF and oxygenation on a quantitative basis in real time, which allows for functional testing of the microcirculatory reserve.[5,8] Vaso-occlusive testing in combination with LDF is a reliable test to detect overall changes in microvascular function,[32] and occlusion longer than 3 minutes does not raise MBFmax.[36]

Major Findings

Our patients had severe organ dysfunction as evidenced by high SOFA and SAPS II scores, elevated average norepinephrine dose requirement,[37] reduced SVRI, high fluid balances, and increased lactate level. Increased needs for vasopressors and fluids in the presence of still decreased SVRI indicate septic vasoplegia with presumed microcirculatory impairments.[3] As pointed out by Kara et al,[38] resuscitation procedures should aim to correct macrohemodynamic variables during critical illness, with the goal of improving tissue perfusion and oxygenation. However, although hemodynamic targets may be reached at the macrocirculatory level, it is often unclear whether therapy leads to a parallel improvement in the microcirculation. Thus, it is important to monitor the microcirculation for guiding therapy at the macrocirculatory level.

When we simultaneously analyzed dynamic parameters at the level of macro- and microcirculation during standardized therapy of our patients with septic shock, we observed multiple correlations, which are in support of the recently coined term of hemodynamic coherence.[38] Accordingly, CI at T0 was significantly correlated with MBF AUC indicating reperfusional MBF to be dependent on the cardiac output (Table 3). With increased MBFmax, $SvcO_2max$ also increased ($r = .489$, $P < .05$), thereby further substantiating a functional relationship between blood flow and venous oxygen saturation at the microcirculatory level. As a result, $SvcO_2max$ increased with CI (Table 3) and like the latter decreased with severity of illness, the need for vasopressive norepinephrine, and increase in lactate levels (see Figure 2).

An inverse association between the perfusion of small vessels and the severity of illness has also been observed by others using a similar SDI method,[7] findings being in agreement with the observation of diminution of microcirculatory flow index when SOFA rose.[39] $DsSvcO_2$ and $usSvcO_2$ determined by NIRS in deeper tissue were also reported to decrease, similar to our findings (Table 3), with the increase in severity of illness as assessed by SOFA score ($r = -.21$, $P < .02$ and $r = -.35$, $P < .001$ respectively).[6,40] In another NIRS study, the upslope distinguished patients with sepsis having SOFA scores of >10 and <10 ($P < .05$).[40] Our data strongly support these findings, based on $SvcO_2max$, not only on the first day but also on the second day of septic shock (Figure 2 and Table 3).

We also observed a significant relationship between both MBF AUC and $SvcO_2max$ with CI (Figure 3), demonstrating a link between microcirculatory and macrocirculatory levels. This observation, however, is in contrast to other clinical trials using the SDI technique[3,7,41-46] or NIRS.[47] For instance, using LDF and a Clark electrode, MBFbl and tissue oxygen pressure were measured and both were elevated while raising MAP up to 90 mm Hg with enhanced norepinephrine rates and

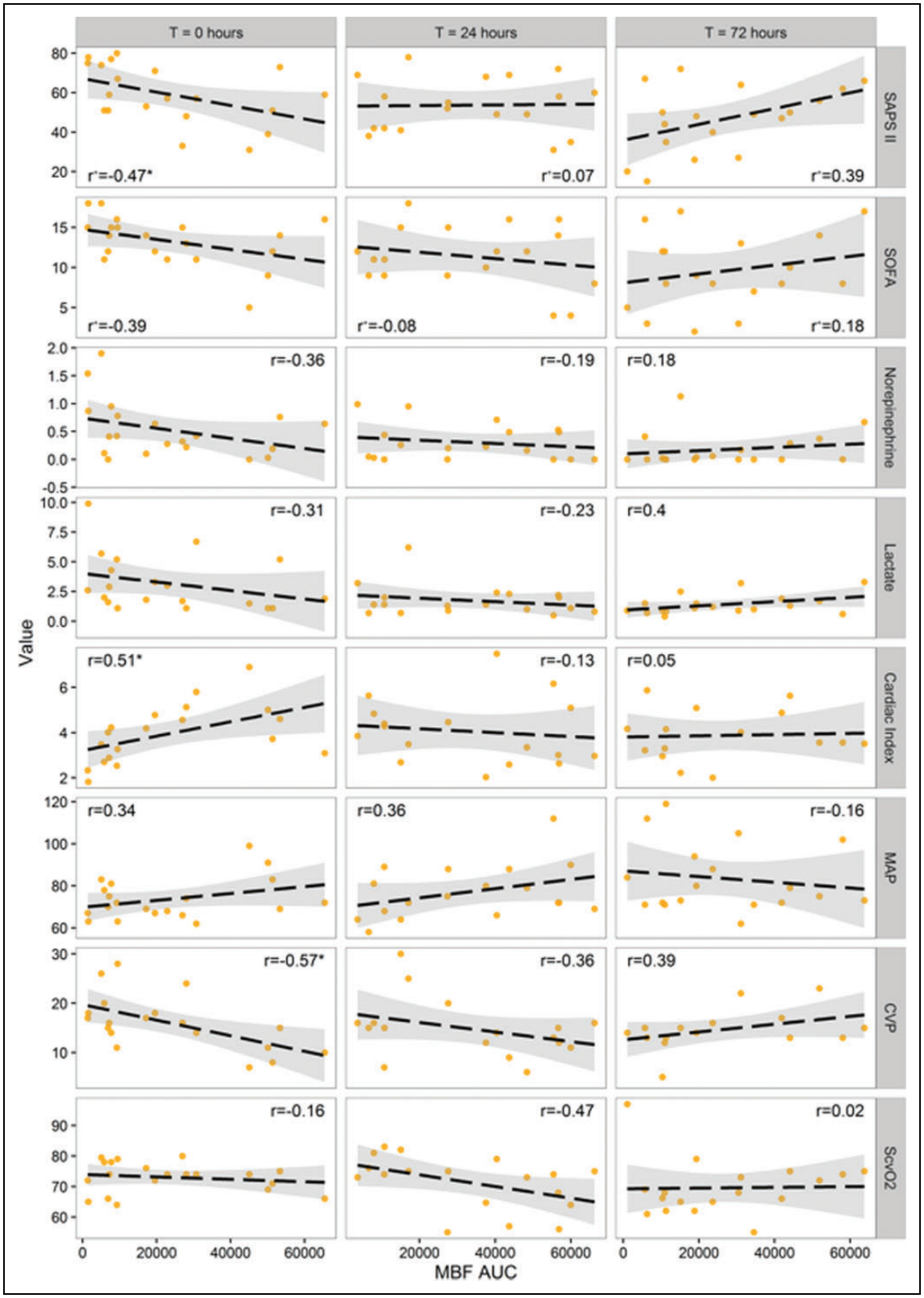

Figure 3. Correlation of clinical characteristics with MBF AUC. Correlations to the area under the curve of reperfusional microcirculatory blood (MBF AUC in arbitrary units). Norepinephrine in μg/kg/min; lactate in mmol/L; cardiac index in L/min/m^2. CVP indicates central venous pressure in mm Hg; MAP, mean arterial pressure in mm Hg; *r*, Spearman correlation coefficient; SAPS, Simplified Acute Physiology Score; $ScvO_2$, central venous saturation; SOFA; Sequential Organ Failure Assessment score.

Table 5. Correlations of $SvcO_2max$ or CI on Day 1 (T0) and 2 (T24) With Fluid Balance of Day 4 (T72).[a]

	T0		T24	
Correlation Coefficient (*P* Value)	SvcO2max	CI	SvcO2max	CI
T72 fluid balance	**−.472 (<.05)**	−.343 (.17)	**−.829 (<.0001)**	−.366 (.15)

Abbreviations: CI, cardiac index; $SvcO_2max$, postcapillary venous oxygen saturation maximum; T0, within 24 hours of ICU admission; T24, second day; T72 fourth day.
[a]Data are presented as Pearson correlation coefficients. Statistically significant correlations are highlighted with bold print.

subsequently CI in patients with septic shock. Specific correlations were not reported.[48] Another group confirmed the lack of any correlation and concluded " . . . increasing MAP above 65 mm Hg . . . might be harmful for some patients, while benefiting others."[42(p7)] However, these different findings are likely to be explained by different tissue depth and methods of microcirculatory perfusion measurement used in previous studies.

Since CI and $SvcO_2max$ were correlated with the severity of illness scores, we asked for possible differences in their predictive values. $SvcO_2max$ determined on day 1 (T0) was negatively correlated with SAPS II/SOFA on day 4 (T72; $r = -.549/-.526$, $P < .05$, Table 4). This was also true for respective measurements of CI and SAPS II/SOFA ($r = -.648/-.653$, $P < .01$). Taken together, the results discussed so far are in line with the physiological concept of hemodynamic coherence, which in our patients with septic shock is obviously detectable by the O2C method.

During the stay of our patients in the ICU, fluid balance became inversely correlated with $dsSvcO_2$, $usSvcO_2$, and $SvcO_2max$ (Table 3). Patients with a larger positive fluid balance were more severely ill, required more norepinephrine, and had higher lactate levels. A positive fluid balance, which at T72 had mounted up to 15 L on average (Table 2), represents a substantial volume load. This additional volume is mostly distributed into the interstitial space and can be expected to have effects on the microcirculation.[14,49] Tissue edema affects oxygen delivery, impairs oxygen and metabolite diffusion, distorts tissue architecture, impedes capillary blood flow and lymphatic drainage, and disturbs cell–cell interactions.[50,51] Microcirculatory blood flow AUC was compromised with rising CVP (Figure 3) and showed the microcirculatory consequence of reduced net organ perfusion pressures[49] due to restrictive right ventricular filling. Others also observed such effects using SDI technology. If CVP was higher than 12 mm Hg, microcirculatory flow index was significantly restricted (odds ratio 2.5).[52] Diastolic dysfunction is common in septic shock (prevalence 40.4%) and a major predictor of mortality (hazard ratio = 6.0, $P < .0001$).[53] Recent findings suggest that common practice of very liberal volume administration in septic shock is of adverse effect and proved to be a predictor for death.[14,51,54] Therefore, easily assessable parameters and interventional trials questioning individual-guided fluid therapy to treat microcirculatory disturbances and in parallel to avoid volume-overloading are needed.[4,10,14]

In this regard, it is interesting to note that $SvcO_2max$ determined at T0 and T24 was negatively correlated with cumulated fluid balance measured at T72 (Table 5). Thus, $SvcO_2max$ detects actual functional microcirculatory capacity and possibly also reflects impairments in barrier functions with subsequent future need for volume replacement. By contrast, such correlations were not observed for CI and late fluid balance (Table 5). Early and repetitive determination of $SvcO_2max$ might hence better support decision-making in fluid therapy as microcirculatory conditions change quickly.

In this small observational study using laser Doppler spectrophotometry in VOT, MBF and $SvcO_2$ indices were correlated with routine intensive care parameters and severity of illness scores. Specifically, simultaneous determination of flow and oxygen delivery/consumption-related phenomena by the integral parameter $SvcO_2max$ appears to be promising in the functional assessment of the microcirculation, especially as $SvcO_2max$ showed good correlation with well-established scores of illness severity in early septic shock, had predictive value, and was associated with limitations of cardiac function, use of vasopressors, and excessive volume load. Additional work is needed for validation of our findings in particular with regard to fluid requirements, but it appears compelling to test $SvcO_2max$ as a target for microcirculation-guided treatment strategies in future studies.

Conclusion

Determination of $SvcO_2max$ was most sensitive in the detection of microcirculatory dysfunction with a laser Doppler spectrophotometry system in septic shock. This parameter was strongly associated with SAPS II and SOFA scores, CI, noradrenaline dosage, and lactate concentration on the first 2 days and with fluid balance in the later course of therapy. $SvcO_2max$ on the first 2 days might hence be of value in prediction of later severity of illness. As compared with CI, $SvcO_2max$ even showed significantly better predictive value for subsequent fluid requirement in our post hoc analyses. Larger trials are needed to clarify whether $SvcO_2max$ can serve as a target for microcirculatory-guided (fluid) therapy in septic shock.

Authors' Note

This is the first printed publication of the shown data; parts were shown during a congress presentation.

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