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BRIEF REPORT

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Disparity between skin perfusion and sublingual microcirculatory alterations in severe sepsis and septic shock: a prospective observational study

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Abstract *Objective:* Measurement of central-to-toe temperature difference has been advocated as an index of severity of shock and as a guide for circulatory therapy in critically ill patients. However, septic shock, in contrast to other forms of shock, is associated with a distributive malfunction resulting in a disparity between vascular compartments. Although this disparity has been established between systemic and microcirculatory parameters, it is unclear whether such disparity exists between skin perfusion and microcirculation. To test this hypothesis of disparity, we simultaneously measured parameters of the two vascular compartments, in the early phase of sepsis. *Design:* Prospective observational study in patients with severe sepsis/septic shock in the first 6 h of ICU admission. Simultaneous measurements of central-to-toe temperature difference and sublingual microcirculatory orthogonal polarization spectral imaging, together with parameters of systemic hemodynamics. *Setting:* 22 bed mixed-ICU in a tertiary teaching hospital. *Patients:* 35 consecutive patients in a 12-month period. *Measurements and results:* In 35 septic patients and a median APACHE II score of 20, no correlation between central-to-toe temperature gradient and microvascular flow index was observed ($r_s = -0.08$, $p = 0.65$). Also no significant correlation between temperature gradient/microvascular flow index and systemic hemodynamic parameters could be demonstrated. *Conclusions:* During the early phase of resuscitated severe sepsis and septic shock there appears to be no correlation between sublingual microcirculatory alterations and the central-to-toe temperature difference. This finding adds to the concept of a dispersive nature of blood flow under conditions of sepsis between microcirculatory and systemic hemodynamics.

Keywords Orthogonal polarization spectral imaging · Microcirculation · Peripheral circulation · Temperature gradient · Skin perfusion · Sepsis

Introduction

Over the last decades it has become clear that despite correction of systemic hemodynamics, the incidence of organ dysfunction and mortality remains high in sepsis. Already in 1969 Joly and Weil [1] identified the cold toe as a new and easily accessible parameter of severity of circulatory shock. The authors observed a correlation between an increment in central-to-toe temperature difference (ΔT) and adverse outcome in a mixed ICU population. 30 years later this was confirmed with a subjective assessment of skin temperature [2]. In a mixed surgical population cool skin temperature was associated with lower cardiac output and central venous oxygen saturation and higher lactate levels as opposed to warm skin temperature, thus using skin perfusion as a marker for systemic hypoperfusion. How-

ever, Weil and Shubin [3] had earlier reclassified circulatory shock to identify distributive shock, including septic shock, as a different entity, in which there is an inability of blood to reach the exchange sites. This concept was confirmed by microcirculatory measurements made in septic patients after the introduction of sublingual orthogonal polarization spectral (OPS) imaging [4]. It has become clear that the discordance between systemic hemodynamic parameters and the microcirculatory alterations is most prominent during sepsis [5], as opposed to other forms of shock. These alterations have also been identified as markers for morbidity and mortality [6] whereas systemic hemodynamic parameters failed to do so under septic conditions [7].

However, no investigations exist as to what extent skin perfusion is correlated with microcirculatory abnormalities during sepsis. Since ΔT is easily obtainable in the clinical setting, we conducted an observational study [8] in human sepsis to answer the question: is there a relationship between ΔT and microcirculatory alterations during sepsis? Based on our understanding of distributive shock we expected a disparity between these two parameters.

Materials and methods

Imaging technique

The OPS technique, as described in detail elsewhere [4], consists of a hand-held device that illuminates an area of interest with polarized light, while imaging the remitted light through a second polarizer. If a wavelength within the hemoglobin absorption spectrum (e.g., 548 nm) is chosen, red blood cells will appear dark.

Imaging and analysis procedure

OPS imaging and semiquantitative analysis was performed as described in detail elsewhere [9]. The overall microvascular flow index (MFI) is an average score over a maximum of 12 quadrants (three regions × four quadrants per region) derived from the overall flow impression of all vessels with a particular range of diameter in a given quadrant.

Setting and patient selection

We performed a single-center prospective observational study in a tertiary teaching-hospital with a 22-bed mixed ICU. During a 12-month period patients with severe sepsis/septic shock, according to international criteria [10], were included. Patients were included only when the source of the sepsis was suspected or confirmed (e.g., infiltrate on chest X-ray plus positive sputum gram stain/culture, fecal spill in the abdominal cavity observed during surgical procedure). Age under 18 years, (diabetic) peripheral vascular disease and a body mass index higher than 35 were contraindications for enrolment. A local ethics and scientific committee approved of the study protocol and written informed consent was obtained from the patients or their surrogate decision makers, according to applicable laws.

Protocol and data collection

Patients were admitted to the ICU directly from the emergency department or operation room. All patients were ventilated and sedated with morphine/midazolam. By protocol, none of the patients received vasodilatory therapy, steroids, or activated protein C before the OPS images were obtained. Before measurement fluid resuscitation was applied until repeated volume challenges did not increase stroke volume (SV) 10% or more, or when central venous pressure (CVP) reached 15 mmHg. Mean arterial pressure (MAP) was maintained at a minimum level of 60 mmHg with dopamine up to 10 μg/kg per minute and additional norepinepherine. Cardiac index (CI) and SV were measured by esophageal Doppler technology (CardioQ, Deltex Medical, West Sussex, UK). ΔT was calculated as the difference between rectal and skin temperature; skin temperature was measured by a probe on the dorsum of the foot (Philips Medical Systems 21078A, Eindhoven, The Netherlands) under constant room temperature. SvO_2 was not measured routinely. Age, gender, length of stay (LOS), Acute Physiology And Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure Assessment (SOFA) scores were calculated after 24 h [11, 12].

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 12.0.1 for Windows, Chicago IL, USA) was used for statistical analysis. Data are presented in medians and interquartile ranges (IQR). Nonparametric rank correlation is expressed as Spearman's rho (r_s). For subgroup analysis a Bonferroni correction was applied. A two-sided p value less than 0.05 is considered statistically significant.

Results

Thirty-five ICU sepsis patients with a median APACHE II score of 20 (14–23) were enrolled; 20 patients also engaged in a previous reported study [13]. All patients fulfilled the entry-criteria; cultures confirmed the source of sepsis in all cases. Baseline characteristics and hemodynamic parameters are summarized in Table 1. ICU and in-hospital mortality were 25.7% and 32.4% respectively,

Table 1 Characteristics study population ($n = 35$) (*APACHE*, Acute Physiology and Chronic Health Evaluation; *SOFA*, Sepsis-Related Organ Failure Assessment; *PEEP*, Positive End Respiratory Pressure; *n*, number of patients)

Gender: M/F	21/14
Age, median (years)	65 (56–77)
APACHE II score, median (IQR)	20 (14–23)
SOFA score, median (IQR)	7 (6–9)
Use of ventilator	35
PEEP level, median (cmH_2O; IQR)	12 (10–15)
Continuous venovenous hemofiltration (*n*)	2
Norepinepherine (*n*)	8
Median dose, ($\mu g\,kg^{-1}\,min^{-1}$; IQR)	0.02 (0–0.17)
Dopamine (*n*)	23
Median dose ($\mu g\,kg^{-1}\,min^{-1}$; IQR)	6 (4–10)
Source of sepsis	
Abdominal	28
Pneumonia	7
Heart rate, median (beats/min; IQR)	107 (92–119)
Mean arterial pressure, median (mmHg; IQR)	71 (66–81)
Central venous pressure, median (mmHg; IQR)	11 (8–14)
Cardiac index, median ($l\,min^{-1}\,m^{-1}$; IQR)	4.5 (3.5–5.3)
Central-to-toe temperature difference, median (°C; IQR)	3.2 (2.2–6)
Lactate, median (mmol/l; IQR)	2.5 (1.3–3.4)

with an ICU LOS of 7 (IQR 3–13) days and an in-hospital LOS of 20 (IQR 11.8–35.3) days. All measurements were obtained in the first 6 h of ICU admission.

Primary outcome of the study, the relation between MFI and ΔT, appeared to be absent; nonparametric rank correlation (r_s) was –0.08 ($p = 0.65$, Fig. 1). After

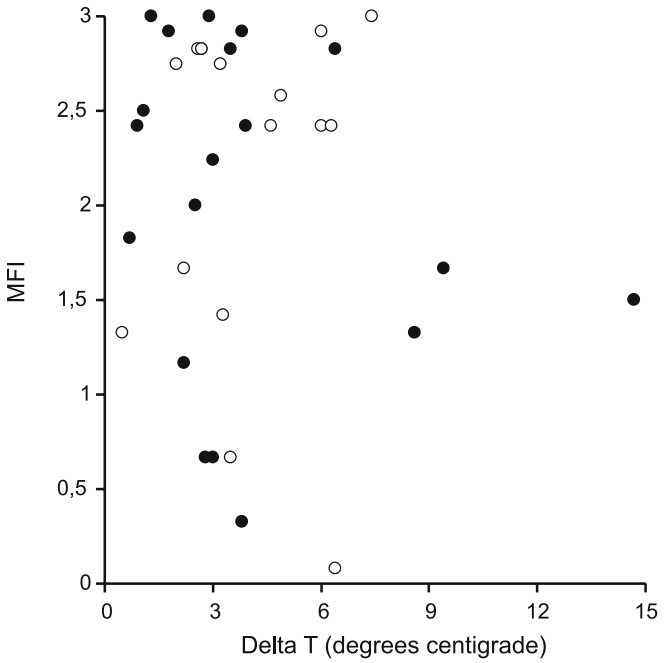

Fig. 1 Scatter of microvascular flow index (*MFI*) of small vessels (< 20 μm) in the sublingual region vs. the central-to-toe temperature gradient (*ΔT*); *open symbols*, severe sepsis; *filled symbols*, septic shock. Spearman's rank correlation −0.08, $p = 0.65$

Table 2 Correlation between microvascular flow index (*MFI*) of small vessels (< 20 μm), central-to-toe temperature difference (*ΔT*), and systemic hemodynamic parameters/parameters of morbidity in study population; data presented as Spearman's rank correlation values ($n = 35$), (*SOFA*, Sepsis-Related Organ Failure Assessment; *APACHE*, Acute Physiology and Chronic Health Evaluation)

	MFI		ΔT	
	r_s	*p*	r_s	*p*
Heart rate	0.12	0.50	0.03	0.85
Mean arterial pressure	0.17	0.33	0.38	0.18
Cardiac index	−0.06	0.74	−0.15	0.39
Central venous pressure	0.13	0.49	0.1	0.59
Norepinepherine dose	0.17	0.34	0.04	0.82
Dopamine dose	0.10	0.58	0.10	0.58
Lactate	−0.17	0.37	0.1	0.59
SOFA	0.18	0.29	−0.08	0.64
APACHE II	−0.2	0.24	0.05	0.76

subgroup analysis r_s in severe sepsis was –0.04 ($n = 16$, $p = 0.87$) and in septic shock –0.23 ($n = 19$, $p = 0.35$). Secondary outcome was the relationship between MFI and ΔT, on the one hand, and systemic hemodynamic parameters and parameters of morbidity/mortality on the other. Correlation coefficients between MFI/ΔT and macro-hemodynamic parameters such as heart rate (HR), CI, MAP, CVP, lactate, and use of inotropic and vasopressors agents or parameters of morbidity (APACHE II and SOFA) were all statistically nonsignificant (Table 2). There was no difference between median MFI/ΔT of survivors and nonsurvivors (2.42 and 2.42; 3.3 and 3, respectively).

Discussion

The presented study demonstrates a lack of correlation between ΔT and OPS-derived sublingual microcirculatory alterations during sepsis after initial resuscitation. Although one may consider ΔT as an index of skin perfusion, this gradient has also been associated with systemic hemodynamic variables [14]. Previous studies demonstrated a good relationship between central-to-toe temperature difference and severity of shock [1, 2]. In patients with circulatory shock ΔT during therapy was associated with outcome, predicted fluid responsiveness in correlation with plasma arginine vasopressin concentrations in preterm infants, and discriminated between circulatory and noncirculatory causes of dyspnea [14].

However, during sepsis and septic shock microcirculatory abnormalities rather than systemic hemodynamic parameters seem to be the predominant factor [5], and heterogeneity of flow between and within microcirculatory units seems to be a characteristic finding. In previous years research using OPS imaging has added to the understanding of the pathophysiological role of microcirculatory alterations in the distributive defects seen in sepsis. Per-

sistence of OPS-derived microcirculatory abnormalities was found to be associated with prognosis, in contrast to all available systemic hemodynamic parameters [6]. The observed lack of correlation between ΔT and MFI therefore adds to these previous data on the dispersion between systemic and microcirculatory alterations in sepsis after initial resuscitation. Alternatively, skin perfusion itself might not reflect systemic hemodynamics in sepsis, as suggested by nonsignificant correlations between ΔT and systemic hemodynamics in our study (Table 2). Interestingly, Vincent and coworkers [15] also reported a poor correlation between ΔT and cardiac output during septic shock, as opposed to other forms of shock.

Limitations of the study are enclosed in the method of semiquantitative analysis used. Whether the flow score from 0 to 3 is linear or nonlinear remains to be established; until now it is technically impossible to measure exact red blood cell flow velocities in individual vessels in OPS-derived images. In the case of a completely nonlinear relationship between the semiquantitative flow score and exact flow speed the observed relationship between MFI and ΔT would be influenced considerably. Using ΔT as the single parameter of skin perfusion is another limitation of the study. Laser Doppler has the ability to detect altered vascular reactivity, especially in conditions of ischemia-reperfusion. Under nonseptic conditions laser-Doppler imaging of the dorsum of the foot showed a linear relationship with skin temperature [16]. Recently, transcutaneous pO_2 measurement of the skin with near infrared spectroscopy has become available. However, until now its use is poorly validated in the ICU setting. Finally, thermoregulatory effects of opioids in general cannot be ruled out, whereas the influence of midazolam has been reported to be futile [17].

Conclusions

During the early phase of resuscitated severe sepsis and septic shock there appears to be no correlation between sublingual microcirculatory alterations and the central-to-toe temperature difference. This finding adds to the concept of a dispersive nature of blood flow under conditions of sepsis between microcirculatory and systemic hemodynamics.

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