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Changes in peripheral perfusion relate to visceral organ perfusion in early septic shock: A pilot study☆

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ABSTRACT

Purpose: To correlate clinical indicators of peripheral perfusion with visceral organ vascular tone in 30 septic shock patients.
Materials and Methods: In a prospective pilot study, capillary refill time, the Mottling score, and peripheral temperature were determined within 24, 48, and 72 hours after intensive care unit admission. Simultaneously, pulsatility indices in the liver, spleen, kidneys, and intestines were measured by Doppler ultrasonography. Correlation analyses were calculated, applying an adjusted significance level ($P < .0125$) to correct for multiple testing.
Results: Significant relationships were observed between the pulsatility index of selected organs and the capillary refill time (intestines: $r = 0.325$, $P = .007$), and the Mottling score (kidneys: $r = 0.396$, $P = .006$), but not peripheral temperature (all $r < 0.14$, $P > .05$). An association over time was observed for the capillary refill time and pulsatility index of the liver ($P = .04$) and intestines ($P = .03$) as well as for the Mottling score and the kidneys' pulsatility index ($P = .03$), but not for peripheral temperature and any visceral organs' pulsatility index.
Conclusions: Capillary refill time and skin mottling may be correlated with the pulsatility index, a sonographic surrogate of vascular tone, of visceral organs in early septic shock.

1. Background

Macrocirculatory parameters show a poor correlation to microcirculatory perfusion in severe sepsis and septic shock [1,2]. As the microcirculation is the ultimate target of resuscitation, normal microcirculatory perfusion would be the ideal resuscitation end point. Due to its strict control by the sympathetic nervous system, the microcirculation of the skin is first to shut down in circulatory compromise [3]. Because it is easily accessible to clinical evaluation, it has been suggested as a potential end point of shock resuscitation [3]. Already in the early days of critical care medicine, Joly and Weil [4] reported that the temperature of the great toe was an indicator of shock severity and predictive of outcome. Recently, new findings have been added to this initial observation. First, cold extremities were found to be an independent predictor of mortality in patients with cardiogenic shock [5]. In addition, a cool periphery was related to low cardiac output in critically ill patients [6]. Patients with abnormal peripheral perfusion, assessed by either skin temperature or color, had higher odds of hyperlactatemia and organ failure [7] and a high risk of death [8]. Even in postsurgery patients with a very low incidence of death, skin perfusion as assessed by the capillary refill time was related to increased morbidity [9]. In septic shock patients, Ait-Oufella et al [10] showed that the capillary refill time measured at 6 hours of resuscitation was related to lactate levels, organ dysfunction, and mortality. Second, early normalization of parameters of skin perfusion including the capillary refill time was associated with survival from septic shock [11] and has been suggested as an indicator to stop fluid resuscitation in septic shock [12,13]. So far, however, it remains unclear why patients with abnormal peripheral perfusion have increased morbidity and mortality. From a pathophysiologic point of view, it is currently assumed that peripheral and visceral organ perfusion is minimized by sympathetic nervous system activation in circulatory shock to preserve vital organ (brain, heart, lung) perfusion. Thus, abnormal peripheral perfusion could relate to visceral organ hypoperfusion, organ dysfunction, and ultimately death.

In this pilot study, we assessed the relationship between skin perfusion (capillary refill time, skin mottling, and subjective assessment of

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peripheral skin temperature) and visceral organ perfusion as assessed by the pulsatility index in patients during early septic shock resuscitation as well as its relationship to organ function and mortality.

2. Materials and methods

This analysis was designed as a prospective pilot study and conducted in a 23-bed multidisciplinary intensive care unit (ICU) of a tertiary university teaching hospital from December 2012 until May 2014. The study protocol was approved by the Ethical Committee of the Land Salzburg (Nr. 415-E/1543/5-2012). Written informed consent was obtained from all study patients or their next of kins.

2.1. Patients

Patients admitted to the study ICU because of septic shock were eligible for study enrollment during the first 24 hours after ICU admission. *Septic shock* was defined as the presence of an infectious focus together with a systemic inflammatory response syndrome and arterial hypotension (mean arterial blood pressure <65 mm Hg) despite fluid loading [14]. Patients younger than 18 years, pregnant women, and patients with known (micro)vascular diseases (eg, peripheral arterial occlusive disease, vasculitis), and/or arrhythmic pulse (for technical reasons when assessing the pulsatility index) were excluded. Baseline data of the 30 study patients are detailed in Table 1. No patient was lost to follow-up.

2.2. Management of septic shock

The clinical management of sepsis and septic shock in this study population followed contemporary recommendations of the Surviving Sepsis Campaign guidelines [14]. Fluid resuscitation was not performed according to central venous pressure but indicated and guided by clinical as well as laboratory signs of systemic tissue hypoperfusion such as cold peripheral temperature, prolonged capillary refill time, skin mottling, oliguria, and arterial hyperlactatemia. In patients with severe septic shock receiving high norepinephrine support, the mean arterial blood pressure target was adjusted individually accepting lower targets as long as systemic tissue perfusion improved or was maintained.

Table 1
Characteristics of patients at study inclusion

n	30
Age (y)	64 ± 14
Male sex, n (%)	14 (46.7)
BMI (kg/m^2)	27.1 ± 6.5
Comorbidities, n (%)	
Chronic arterial hypertension	13 (43.3)
Diabetes mellitus	10 (33.3)
Coronary artery disease	7 (23.3)
Chronic obstructive pulmonary disease	5 (16.7)
Chronic renal insufficiency	2 (6.7)
Sepsis focus, n (%)	
Pneumonia	14 (46.7)
Peritonitis	10 (33.3)
Cholangitis/cholecystitis	2 (6.7)
Other	4 (13.4)
Microbiology-proven sepsis, n (%)	27 (90)
Surgical source control, n (%)	12 (40)
Time between ICU admission and first antibiosis (h)	1.8 ± 1.8
Adequate empirical antibiosis, n (%)	25 (83.3)
SAPS II (points)	47 ± 18
SAPS III (points)	65 ± 15
Maximum SOFA (points)	14 ± 3
Norepinephrine, n (%)	30 (100)
Norepinephrine dose at study inclusion (μg kg^{-1} min^{-1})	0.19 ± 0.14
Dobutamine, n (%)	8 (26.8)
Dobutamine dose at study inclusion (μg kg^{-1} min^{-1})	3.9 ± 2.8
Pulmonary artery catheter, n (%)	5 (16.7)
Mechanical ventilation, n (%)	25 (83.3)
RIFLE criteria, n (%)	
Risk	7 (23.3)
Injury	3 (10)
Failure	9 (30)
Extracorporeal membrane oxygenation, n (%)	2 (6.7)
ICU length of stay (d)	13 ± 16
ICU mortality, n (%)	6 (20)
28-d mortality, n (%)	7 (23.3)
90-d mortality, n (%)	11 (36.7)

2.3. Data collection

The following data were collected at study enrollment: age, sex, body mass index, comorbid conditions, sepsis focus, microbiology results, need for surgical source control, time between ICU admission and first antibiosis, adequacy of empirical antibiosis, the Simplified Acute Physiology Score II and III [15,16], and the Sepsis-related Organ Failure Assessment (SOFA) score [17]. Within 24, 48, and 72 hours after ICU admission, the following measurements were performed: heart rate, arterial blood pressure, central venous pressure, diuresis during the preceding hour, arterial lactate levels, base deficit, the RIFLE criteria [18], central body temperature, and catecholamine doses. At ICU discharge, need for mechanical ventilation, renal replacement therapy, extracorporeal membrane oxygenation, a pulmonary artery catheter, length of ICU stay, and ICU mortality were documented. At 28 and 90 days after study inclusion, survival status was assessed.

2.4. Measurements of peripheral perfusion and the sonographic pulsatility indices

Assessment of peripheral perfusion and measurement of the sonographic pulsatility indices were performed simultaneously with the above-mentioned parameters within the first 24, 48, and 72 hours after ICU admission. Peripheral perfusion was assessed by 3 different clinical methods: capillary refill time, the Mottling score, and the subjective assessment of peripheral skin temperature. Capillary refill time was measured by counting after applying gentle pressure to the skin over the lateral aspect of the distal index finger. The degree of skin mottling in the lower extremity was evaluated using the Mottling score [8]. Peripheral skin temperature was determined by touching the patient's hands and subjectively categorizing temperature as either warm or cold to the examiner's hand. As for sonographic measurements, evaluation of peripheral perfusion was conducted by 1 of 2 investigators (A.B., M.W.D.) to keep interobserver variability at a minimum.

The pulsatility index is a Doppler sonography–derived measure of the variability of blood velocity. It is a dimensionless figure, with low values indicating low and high values indicating high vascular tone [19–21]. Using a standard sonography machine (Vivid S6; GE Healthcare, Vienna, Austria) and a convex sector transducer (2-6 MHz), we measured the pulsatility index in the kidneys, liver, spleen, and intestines (Fig. 1). The artery of interest in each organ (kidney: arcuate or interlobar artery; liver: intraparenchymal artery; spleen: subbranch of the splenic artery; intestines: artery in the intestinal wall located in the lower left abdominal quadrant) was identified by the color Doppler method. The sample volume of the pulsed-wave Doppler was then placed into the artery of interest and the blood flow signal recorded over several heart beats. Measurements were performed in the kidneys and spleen in 3 areas (upper/anterior pole, between poles, lower/posterior pole) and averaged. Pulsatility indices of the left and right kidney were then averaged (Spearman correlation coefficient, 0.6; $P < .001$) and only analyzed if the RIFLE criteria did not exceed the level of risk (defined as elevation of serum creatinine by <150% or oliguria <6 hours [18]). The reason for this was that higher degrees of acute kidney injury in sepsis have been associated with marked changes in renovascular resistance [22]. In the liver, the blood flow signal was collected in the left and right lobe. In the intestinal wall, up to 3 measurements were averaged from adjacent arteries. Using the EchoPAC software (GE Healthcare), the pulsatility index was calculated offline (Fig. 1).