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Oscillation frequency of skin microvascular blood flow is associated with mortality in critically ill patients

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Background: Microcirculatory dysfunction has been hypothesized to play a key role in the pathophysiology of multiple organ failure and, consequently, patient outcome. The objective of this study was to investigate the differences in reactive hyperemia response and oscillation frequency in surviving and non-surviving patients with multiple organ dysfunction syndrome.
Methods: Twenty-nine patients (15 survivors; 14 non-survivors) with two or more organ failures were eligible for study entry. All patients were hemodynamically stabilized, and demographic and clinical data were recorded. A laser Doppler flowmeter was used to measure the cutaneous microcirculatory response. Reactive hyperemia and oscillatory changes in the Doppler signal were measured during 3 min before and after a 5-min period of forearm ischemia.
Results: Non-survivors demonstrated a significantly higher multiple organ dysfunction score when compared with survivors ($P = 0.004$). Norepinephrine administration was higher in non-survivors ($P = 0.018$). Non-survivors had higher arterial lactate levels ($P = 0.046$), decreased arterial pH levels ($P = 0.001$) and decreased arterial P_{O_2} values ($P = 0.013$) when compared with survivors. A higher oscillation frequency of the skin microvasculature at rest ($P = 0.033$) and after an ischemic stimulus ($P = 0.009$) was observed in non-survivors. The flow motion frequency observed in reactive hyperemia was associated with the severity of multiple organ dysfunction ($P = 0.009$) and, although not statistically significant, with the arterial lactate concentration ($P = 0.052$).
Conclusion: Increased skin microvascular oscillation frequency at rest and in the hyperemic state after an ischemic stimulus is associated with increased mortality in patients suffering from multiple organ dysfunction. The underlying mechanism could be a response of the skin microvasculature to an impaired oxygen utilization of the skin tissue.

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Key words: Flow motion; microcirculation; multiple organ dysfunction; outcome; reactive hyperemia.

THE contribution of the microcirculation to the pathophysiology of multiple organ dysfunction syndrome (MODS) is still a matter of intense discussion and investigation. Studies on the role of microcirculatory function and dysfunction in critically ill patients have rendered heterogeneous results. Although impaired capillary perfusion and failure of improvement in microvascular dysfunction have been identified as risk factors of adverse outcome in septic patients (1, 2), regional parameters of microvascular function do not reflect the severity of established MODS in hemodynamically stable patients (3).

Reactive hyperemia (RH) is a measure of regional vascular reactivity in response to tissue hypoxia involving capillaries, arterioles and small arteries. The increase in regional blood flow after vascular occlusion is directly related to the severity and duration of ischemia (4). Hyperemia occurs because, during the period of occlusion, tissue hypoxia and several metabolites produced during the hypoxic state (e.g. adenosine) dilate arterioles and decrease the vascular resistance. After restoration of the perfusion pressure, the flow is increased because of the reduced vascular resistance. During hyperemia, oxygen is replenished and vasodilator metabolites are washed out of the tissue, causing the resistance vessels to regain their normal vascular tone and thereby to return the flow to normal levels. The longer the period of occlusion, the greater the metabolic stimulus for vasodilation, leading to increases in peak RH and the duration of hyperemia. In general,

the ability of an organ to exhibit RH reflects the autoregulative capacity of its microcirculation (5).

Vasomotion and flow motion have been observed and reported in animal and human microvascular studies using various techniques (6). Vasomotion is the phenomenon of rhythmic periodic contractions and dilations in a microcirculatory network under various physiological and pathophysiological conditions. Vasomotion and flow motion are characterized by two distinct frequency ranges, namely α or fast waves, with a frequency of 3–20 cycles/min, and β- or slow waves, with a frequency of 0.5–3 cycles/min (7, 8). Until recently, vasomotion was considered as a normal physiological phenomenon (9). Later studies raised the perception that vasomotion economizes tissue perfusion, optimizes blood flow distribution and has a positive influence on tissue oxygenation (10–12). In a study by Young and Cameron (13), flow motion was significantly increased in patients with sepsis, compared with cardiac surgery patients and healthy volunteers, further indicating an association between tissue oxygenation and flow motion patterns. Schmidt (14) critically reviewed whether vasomotion occurs under physiological conditions, and concluded that vasomotion is most prevalent in low-flow conditions.

Thus, the present study was conducted to further elucidate the association between microcirculatory function and outcome in patients suffering from MODS. The relationship between different degrees of MODS and RH, as well as skin microvascular flow motion, was investigated by laser Doppler velocimetry. It was hypothesized that there is an association between RH and differences in flow motion patterns in hemodynamically stable, resuscitated patients with different degrees of multiple organ dysfunction and, consequently, with patient outcome.

Materials and methods

The study protocol was approved by the ethics committee of Innsbruck Medical University. The study was performed in a 12-bed general and surgical intensive care unit (ICU) in a tertiary university teaching hospital.

Study patients

Fifteen consecutive patients with a MODS score of > 4 and ≤ 8 and with an expected mean mortality rate of 3.8%, and 14 patients with a MODS score of ≥ 9 and with an expected mean mortality rate of 58%, were included in the study protocol. Multiple organ dysfunction was assessed using a modified Goris MODS score (15, 16). Expected mortality data were collected from results on ICU mortality of 2783 patients admitted to our ICU during the last 4 years. The exclusion criteria were as follows: a history of peripheral arterial vascular occlusive disease, insulin-dependent diabetes mellitus, traumatic injury to the upper extremities or previous polyneuropathy. In order to avoid the influence of hypoxia and acidosis on the measured microvascular parameters, patients were only included after initial stabilization and treatment of hypoxia ($P_aO_2 > 60$ mmHg) and metabolic acidosis (pH > 7.3). All patients were mechanically ventilated, analgo-sedated using midazolam and sufentanil or morphine, and invasively monitored using arterial, central venous and pulmonary artery catheters. All patients were fluid resuscitated using a colloidal solution (gelatine) until the stroke volume could no longer be increased; corresponding pulmonary capillary wedge pressures were then used for guidance of further fluid loading. If the stroke volume index remained below 25 ml/m^2/beat or the cardiac index below 2.0 l/min/m^2 despite adequate fluid therapy, continuous milrinone infusion was started. Norepinephrine infusion was administered to all patients who could not achieve a mean arterial pressure of more than 65 mmHg with volume and/or inotropic therapy. Continuous veno-venous hemofiltration using average filtration rates of 20–30 ml/min was applied in all patients with acute renal failure. No patient was hemofiltrated for other non-renal indications. During the study period, no patient received activated protein C.

Data collection

The following data were documented in all study patients: age, sex, body mass index, pre-existing comorbidities, admission diagnosis, American Society of Anesthesiology Classification Score, Simplified Acute Physiology Score II (SAPS II), calculated from the worst physiological values within the first 24 h after ICU admission, and the presence of systemic inflammatory response syndrome (SIRS) and sepsis (17, 18).

The hemodynamic parameters measured included the heart rate, mean arterial pressure, central venous pressure, cardiac index, stroke volume index, mean pulmonary arterial pressure and pulmonary capillary wedge pressure. Arterial and mixed venous acid–base status, blood oxygen tension and saturation, hemoglobin and arterial lactate concentrations were also determined (Rapidlab 860; Chiron Diagnostics, Medfield, MA). The systemic oxygen delivery index (DO_2I), systemic oxygen consumption index (VO_2I) and oxygen extraction ratio (ER) were calculated according to standard formulae.

Reactive hyperemia measurements

Skin microvascular blood flow and RH response after arterial occlusion in the patient forearm were assessed by laser Doppler velocimetry (Periflux 4001, Perimed, Järfälla, Sweden). Laser Doppler measurements are based on the principle that light, scattered by moving red blood cells, experiences a frequency shift proportional to the velocity of the red blood cells. The Periflux 4001 uses laser light with a wavelength of 770–790 nm. A fiberoptic guide-wire (PF407, Perimed) conducts laser light to the tissue and carries back-scattered light back to a photodetector. Calibration of the laser Doppler flowmeter device was performed using the manufacturer's original calibration kit (Perimed). Setting of the zero value was conducted on the surface of a white compact synthetic material [perfusion units (PU) = 0]. The second value of the calibration curve (PU = 250) was derived by measurement in a motility standard fluid provided by the manufacturer (Perimed). The fraction of scattered light that is Doppler shifted in this solution is exactly 250 ± 5 PU. During the examination period, the electrode was placed on the volar aspect of the forearm and was held in place by the adhesion force generated by a surrounding thin transparent silicone rubber patch of approximately 2 cm in diameter using a self-adhesive ring. The skin microvascular blood flow was recorded in relative PU. Forearm ischemia was produced with a sphygmomanometer cuff wrapped around the arm over the brachial artery and inflated to 300 mmHg for 5 min.

After a resting period of 30 min, pre-occlusive baseline PU (BL-PU) and the baseline area under the curve (BL-AUC) were recorded for 3 min (Fig. 1). During reperfusion, the post-ischemic peak PU (MAX-PU) and the area under the curve (RH-AUC) were measured. After the measurements, the differences between MAX-PU and BL-PU, and between RH-AUC and BL-AUC, were calculated. To determine the magnitude of RH, the following formula was used: [100 × (RH-AUC – BL-AUC)/BL-AUC] (%). Measurements were stopped when, for a period of at least 5 min, stable PU values were recorded after reperfusion.

Flow motion analysis

For flow motion analysis, the Doppler signal tracing (3 min) was divided into nine blocks of 20 s each before the induction of ischemia and during the reperfusion measurements, respectively, to avoid the well-known leakage phenomenon of the fast Fourier transformation analysis algorithm. Fast Fourier transformation analysis was performed for single blocks to obtain a quantitative description of oscillatory frequency components. The frequency resolution of the fast Fourier transformation was 0.5 cycles/min, which corresponds to 0.0083 Hz. After computing a power spectrum for each block, median values were averaged to reflect the final power spectrum for pre-ischemic and reperfusion oscillations. Frequencies corresponding to heart rate or mechanical ventilation were discarded.

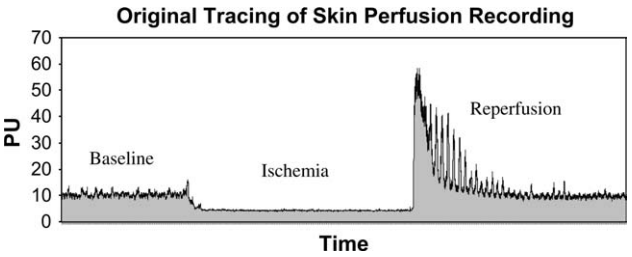

Fig. 1. Original laser Doppler flowmeter tracing of the skin. Skin microvascular blood flow was recorded in relative perfusion units (PU) in a survivor. Forearm ischemia was produced after a 3-min baseline measurement with a sphygmomanometer cuff wrapped around the arm over the brachial artery, and inflated to 300 mmHg for 5 min. Measurements were stopped when, for a period of at least 5 min, stable PU values were recorded after reperfusion. For an analysis of reactive hyperemia and flow motion, see text.

Statistical analysis

The study patients were grouped into survivors (n = 15) and non-survivors (n = 14) according to their outcome at discharge from the ICU.

As the trial was considered to be a pilot study, no power-analyzed sample size estimation could be performed. The normality assumption was tested using the Shapiro–Wilk test. The normality assumption was not fulfilled for the following parameters: norepinephrine requirements, arterial lactate concentration, magnitude of RH and flow motion during RH. Continuous demographic and clinical data were compared by paired Student's t-test (Gaussian distribution) and Wilcoxon signed-ranked test (non-Gaussian distribution). Correlation coefficients were tested using Pearson's correlation (Gaussian distribution) and Spearman's correlation (non-Gaussian distribution). Significance was assumed at $P < 0.05$. All data are given as mean values ± standard deviation, if not indicated otherwise.

Results

Demographic data

Table 1 presents the characteristics and demographic data of the study patients. Non-survivors were

Table 1

Characteristics and demographic data of survivors and non-survivors.

	Survivors ($n = 15$)	Non-survivors ($n = 14$)	*P*
Demographic data			
Age (years)	52.3 ± 16.0	67.6 ± 10.2	0.007
Sex (male/female)	11/4	8/6	0.377
BMI (kg/m^2)	26.4 ± 3.6	25.1 ± 3.6	0.378
Diagnosis			
Cardiac surgery	5/15 (33.3)	4/14 (28.6)	0.791
Abdominal surgery	2/15 (13.3)	7/14 (50.0)	0.033
Trauma	6/15 (40.0)	3/14 (21.4)	0.297
Others	2/15 (13.3)	0/14 (0.0)	0.168
Clinical syndromes			
SIRS	9/15 (60.0)	10/14 (71.4)	0.535
Sepsis	3/15 (20.0)	0/14 (0.0)	0.168
Septic shock	3/15 (20.0)	4/14 (28.6)	0.605
Scoring systems			
MODS	6.5 ± 2.7	9.4 ± 2.0	0.004
ASA	3.7 ± 0.5	4.0 ± 0.5	0.097
SAPS II	11.5 ± 3.4	15.9 ± 2.4	0.001

ASA, American Society of Anesthesiologists Physical Status Classification; BMI, body mass index; MODS, multiple organ dysfunction syndrome; SAPS II, Simplified Acute Physiology Score II; SIRS, systemic inflammatory response syndrome.
Values are given as mean ± standard deviation; percentages are given in parentheses.

Table 2

Systemic hemodynamics, systemic oxygen transport variables, serum lactate concentrations, and norepinephrine and milrinone requirements in survivors and non-survivors.

	Survivors ($n = 15$)	Non-survivors ($n = 14$)	*P*
Systemic hemodynamics			
HR (beats/min)	87 ± 17	94 ± 17	0.311
MAP (mmHg)	79 ± 13	76 ± 10	0.413
PCWP (mmHg)	15 ± 4	17 ± 4	0.208
CI (l/min/m^2)	4.2 ± 1.6	3.9 ± 1.0	0.524
SVI (ml/m^2/beat)	48.6 ± 15.2	41.8 ± 9.5	0.186
Oxygen transport variables			
D_{O_2}I (ml/min/m^2)	607 ± 201	504 ± 115	0.124
V_{O_2}I (ml/min/m^2)	168 ± 50	141 ± 35	0.130
ER (%)	28.1 ± 4.2	28.1 ± 4.7	0.978
Arterial blood gas analysis			
pH	7.43 ± 0.07	7.32 ± 0.08	0.001
P_{aCO_2} (mmHg)	40.3 ± 6.7	44.0 ± 8.4	0.219
P_{aO_2} (mmHg)	114.1 ± 20.2	95.2 ± 16.5	0.013
Arterial lactate (mmol/l)	1.8 ± 1.0	3.4 ± 2.7	0.046
Vasopressor and inotropics			
Norepinephrine (μg/kg/min)	0.24 ± 0.29	0.54 ± 0.31	0.018
Milrinone (μg/kg/min)	0.44 ± 0.15	0.44 ± 0.09	0.956

CI, cardiac index; D_{O_2}I, systemic oxygen delivery index; ER, systemic oxygen extraction ratio; HR, heart rate; MAP, mean arterial blood pressure; P_{aCO_2}, arterial carbon dioxide tension; P_{aO_2}, arterial oxygen tension; PCWP, pulmonary capillary wedge pressure; SVI, stroke volume index; V_{O_2}I, systemic oxygen consumption index.
Values are given as means ± standard deviation.

significantly older than survivors. A significantly higher proportion of patients were admitted to the ICU after abdominal surgery in the non-survivor group. There was no difference in the incidence of SIRS or sepsis/septic shock between the groups. Non-survivors demonstrated a significantly higher SAPS II and MODS score when compared with survivors. The mean stay in the ICU before study inclusion was 9 ± 8 days in all patients: 8 ± 8 days in survivors and 10 ± 8 days in non-survivors.

Systemic hemodynamics and oxygen transport variables

No differences were seen in systemic hemodynamic parameters and oxygen transport variables between the groups (Table 2). Non-survivors required higher norepinephrine dosages than survivors. No difference in inotropic support was observed between the groups. P_{aO_2} was significantly higher in survivors, although no patient in the present study had $P_{aO_2} <$ 60 mmHg. Non-survivors had higher arterial lactate levels, concomitant with a decreased pH value, than survivors.

Reactive hyperemia and flow motion

No difference in RH was observed between non-survivors and survivors (Table 3). Non-survivors experienced a higher oscillation frequency of skin microvasculature at baseline and after an ischemic stimulus in the hyperemic state. The flow motion frequency observed in RH was significantly associated with the severity of MODS (Fig. 2). In addition, there was a trend towards a correlation between a higher oscillation frequency during RH and arterial lactate concentrations. No further correlations were observed between the oscillation frequency and systemic hemodynamic and oxygen transport/consumption variables.

Discussion

In this study, the frequency of oscillation in the skin vascular bed was increased in non-survivors under resting conditions and after an ischemic stimulus in the hyperemic state. No difference in the RH response was observed between the two groups. The magnitude of oscillation frequency correlated well with the degree of multiple organ dysfunction and, although not statistically significant, with the arterial lactate levels. This study has demonstrated, for the first time, a correlation between microvascular

Table 3

Reactive hyperemia and flow motion.

	Survivors ($n = 15$)	Non-survivors ($n = 14$)	*P*
Reactive hyperemia			
BL-PU	16 ± 12	16 ± 9	0.945
AUC-BL	2590 ± 1541	2761 ± 1599	0.781
MAX-PU	69 ± 44	56 ± 40	0.426
AUC-RH	4440 ± 2763	4608 ± 3340	0.888
Δ-PU	53 ± 39	40 ± 33	0.365
Δ-AUC	1849 ± 1515	1846 ± 1841	0.997
Magnitude RH (%)	72 ± 54	63 ± 44	0.638
Flow motion			
BL (Hz)	8.9 ± 4.8	12.8 ± 4.3	0.033
RH (Hz)	7.8 ± 4.3	13.1 ± 4.5	0.009

AUC-BL, baseline area under the curve; AUC-RH, reactive hyperemia area under the curve; BL, baseline; BL-PU, baseline perfusion units; Δ-AUC, difference between AUC-RH and AUC-BL; Δ-PU, difference between MAX-PU and BL-PU; magnitude RH, 100 × (RH-AUC − BL-AUC)/BL-AUC; MAX-PU, maximum perfusion units; RH, reactive hyperemia.
Data are given as means ± standard deviation.

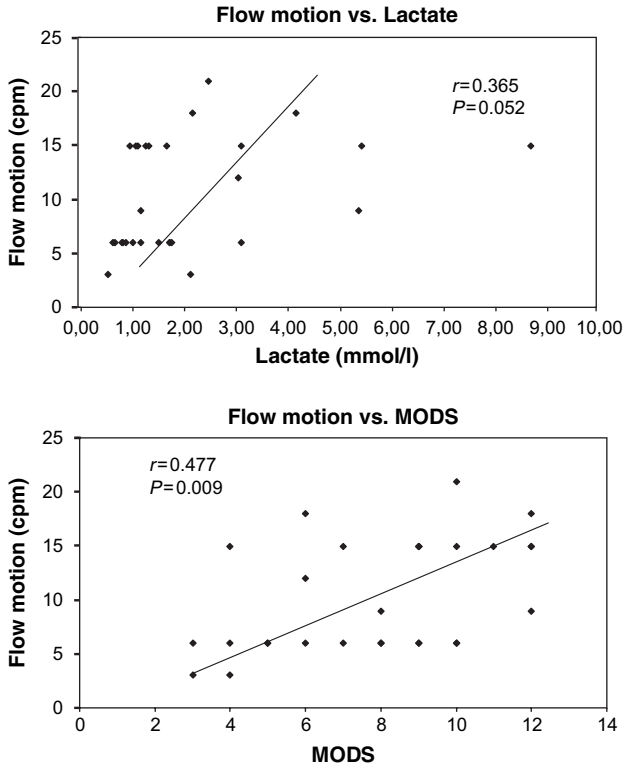

Fig. 2. Scatter plots of flow motion correlation analysis in survivors and non-survivors. The flow motion frequency (cycles per minute, cpm) in reactive hyperemia correlates significantly with the severity of multiple organ dysfunction syndrome (MODS). In addition, there is a trend towards higher oscillation of the vascular bed and serum lactate levels. r, Pearson's correlation coefficient; P, the correlation is significant (two-sided) at the 0.05 level.

flow motion in the skin vascular bed and mortality in patients suffering from MODS.

The ability of an organ to increase regional blood flow after vascular occlusion reflects the autoregulative capacity of its microcirculation (5). No difference in regional vascular reactivity (assessed as the degree of RH response to a defined period of forearm ischemia in the skin) was found between non-survivors and survivors. However, increased arterial lactate levels and a decreased arterial pH indicated some tissue hypoxia in non-survivors. As a result of the autoregulative capacity of the microcirculatory bed, it might be suggested that the magnitude of the RH response must be increased in patients with signs of tissue hypoxia. The present evidence of a lack of difference in RH between survivors and non-survivors could be interpreted as an impaired ability of the microvasculature to react on an ischemic stimulus. For example, Haisjackl et al. (5) described a reduced RH response in the skin of critically ill patients when compared with healthy volunteers. The magnitude of RH response correlated well with the degree of physiological derangement. As adrenergic vasoconstrictors have been shown to decrease the peak RH response by more than 20%, it is conceivable that the higher dosages of norepinephrine infused in non-survivors may have masked an increased RH response in these patients (19). An alternative interpretation is that the RH response remains intact, and the difference between survivors and non-survivors is the result of the oxygen supply not reaching the tissue because of capillary perfusion failure in non-survivors. This cannot be documented by the methods used in the present study.

Vasomotion can be described as rhythmic oscillations in arteriolar vascular tone as a result of local changes in smooth muscle constriction and dilation. Vasomotion induces alterations in red blood cell velocity, called flow motion, which affects microcirculatory transit times and probably facilitates gas exchange between microvessels and tissue (10). The frequency of vasomotion is significantly enhanced during abnormal conditions associated with low blood pressure, hypoperfusion and decreased tissue oxygen tension (10, 20). For this reason, it is speculated that vasomotion may serve as a protective mechanism for the supplied tissue under conditions of ischemia (6). In this study, microvascular flow motion was enhanced under resting conditions and after an ischemic stimulus in the RH phase in non-survivors relative to survivors. In addition, the frequency of flow motion correlated well with the degree of multiple organ dysfunction and, although

not statistically significant, with arterial lactate levels; this could be interpreted as a response of the microvasculature to hypoxia or decreased oxygen utilization of the skin. The precise mechanisms responsible for possible impairment of tissue oxygen utilization are unclear, and were not investigated in this study, but may include reduced functional capillary density, disseminated cell death, limitation in oxygen delivery or a general decrease in tissue metabolism (21, 22).

Mechanisms contributing to the evolution of flow motion during periods of limited oxygen supply to tissue are not clear. Bertuglia et al. (23) found that hypoxia enhances the activity of rhythmic oscillations of terminal arterioles. Thus, it seems that changes in the pattern of flow motion contribute to the microvascular response to limited oxygen supply. This raises the question of whether vasomotion may be beneficial by improving tissue oxygenation. In a study by Rücker et al. (24), the metabolic state was investigated in perfused rat hind limbs by NADH (reduced form of nicotinamide adenine dinucleotide) fluorescence intravital microscopy. Vasomotion was induced by a decrease in blood flow. By comparing NADH fluorescence in preparations with and without vasomotion, the authors observed that vasomotion improved blood flow to tissues, and maintained NADH fluorescence in the tissues. It was concluded that vasomotion has a beneficial effect on tissue oxygenation in adjacent tissue as a result of an improvement in microvascular blood flow.

Interestingly, we found no correlation between the frequency of flow motion and the dosage of norepinephrine in the present study. It is known from previous reports that oscillations of arterioles can be induced in healthy subjects by various vasopressors, such as norepinephrine (25), phenylephrine (26) and arginine vasopressin (27). Again, the exact mechanism responsible for this phenomenon has not been investigated. It is difficult to say whether this observation is also present in pathophysiological states, such as vasodilatory shock, requiring vasopressor agents to maintain perfusion pressure. Our study group investigated the oscillation frequencies in the skin microcirculation by laser Doppler flowmetry in vasodilatory shock patients during infusion of either norepinephrine or norepinephrine + arginine vasopressin (28). No differences were found in the response of the oscillation frequency, detected by laser Doppler flowmetry, despite significant differences in mean arterial blood pressure.

Skin blood flow decreases significantly with age in healthy subjects (29). In addition, the response to ischemia is reduced significantly in older healthy forearm skin relative to young skin, which may possibly be attributed to a poorer vascularity of the skin or a decreased skin thickness (30). Otherwise, the flow motion frequency in the skin remains similar in both young and old subjects, with a mean frequency of 4.9 cycles/min (31). In this study, no significant differences in baseline blood flow or RH response were observed between survivors and non-survivors, although non-survivors were significantly older. The difference in age between the groups was probably too low to observe differences in the microcirculatory blood flow at rest and RH response between the groups.

One general drawback of studies investigating microvascular phenomena in diseased animals and humans is the problem of the heterogeneity of regional blood flow and metabolic changes, not only when comparing different organs, but also within one particular organ system (32). Therefore, measurements in the skin may not be representative of other organs. Furthermore, the method applied in this study does not allow any direct observation of the microvascular bed, or direct measurements of metabolic changes associated with microcirculatory dysfunction. Moreover, the human skin is unique in its vascular anatomy, the richness of its vascular supply and its innervation. Cutaneous vessels have a dense distribution of α-adrenergic receptors, but β-receptors are sparse or even absent. Thus, all catecholamine agents at physiologically relevant levels and all exogenous pharmacological doses principally act as vasoconstrictors. This is in striking contrast to any 'internal organ', e.g. the gastrointestinal tract, kidney or heart, which possess strong vasodilating mechanisms and exert a much more pronounced metabolic control of blood flow when compared with skin or skeletal muscle. Under stress conditions, such as hypothermia or blood loss, skin blood flow can be reduced to almost zero. For this reason, the skin of patients can also act as a window to the physiological derangement during critical illness. Finally, it is conceivable that, if measurements had been repeated at other time points before or after randomization, the microcirculatory response might have been different from that reflected by measurements taken in this study protocol.

Increased skin microvascular flow motion during rest and after an ischemic stimulus is associated with increased mortality in critically ill patients. The oscillation frequency correlates well with the severity of multiple organ dysfunction. We suggest that the underlying mechanisms could be the response of the

microvasculature to hypoxia or decreased oxygen utilization of the tissue within the skin.

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