International Study on Microcirculatory Shock Occurrence in Acutely Ill Patients

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The work was performed in the ICUs of participating hospitals (listed in **Appendix 1**) and was coordinated from the ICU of Medical Center Leeuwarden, Leeuwarden, The Netherlands. Members of the microSOAP Study Group are also listed in Appendix 1.

Drs. Vellinga and Boerma, Ms. Koopmans, and Drs. Donati, Dubin, Shapiro, Pearse, Bakker, and Ince conceived and designed the study. Drs. Vellinga and Boerma, Ms. Koopmans, and Drs. Donati, Dubin, Shapiro, Pearse, Machado, Fries, Akarsu-Ayazoglu, Pranskunas, Hollenberg, Balestra, van Iterson, van der Voort, Sadaka, Minto, Aypar, Hurtado, Martinelli, Payen, van Haren, Holley, Pattnaik, Gomez, Mehta, Rodriguez, Ruiz, Canales, Duranteau, Spronk, Jhanji, Hubble, Chierego, Jung, Martin, Sorbara, Bakker, and Ince performed data acquisition. Drs. Vellinga and Boerma, Ms. Koopmans, and Drs. Tijssen and Ince were responsible for data analysis. Dr. Tijssen provided statistical expertise. Drs. Vellinga and Boerma, Ms. Koopmans, and Drs. Donati, Dubin, Shapiro, Pearse, Tijssen, Bakker, and Ince interpreted the data. Drs. Vellinga, Boerma, and Ince wrote the manuscript draft. All authors revised the manuscript for important intellectual content and approved the article.

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Objectives: Microcirculatory alterations are associated with adverse outcome in subsets of critically ill patients. The prevalence and significance of microcirculatory alterations in the general ICU population are unknown. We studied the prevalence of microcirculatory alterations in a heterogeneous ICU population and its predictive value in an integrative model of macro- and microcirculatory variables.

Design: Multicenter observational point prevalence study.

Setting: The Microcirculatory Shock Occurrence in Acutely ill Patients study was conducted in 36 ICUs worldwide.

Patients: A heterogeneous ICU population consisting of 501 patients.

Interventions: None.

Measurements and Main Results: Demographic, hemodynamic, and laboratory data were collected in all ICU patients who were 18 years old or older. Sublingual Sidestream Dark Field imaging was performed to determine the prevalence of an abnormal capillary microvascular flow index (< 2.6) and its additional value in predicting hospital mortality. In 501 patients with a median Acute Physiology and Chronic Health Evaluation II score of 15 (10–21), a Sequential Organ Failure Assessment score of 5 (2–8), and a hospital mortality of 28.4%, 17% exhibited an abnormal capillary microvascular flow index. Tachycardia (heart rate > 90 beats/min) (odds ratio, 2.71; 95% CI, 1.67–4.39; $p < 0.001$), mean arterial pressure (odds ratio, 0.979; 95% CI, 0.963–0.996; $p = 0.013$), vasopressor use (odds ratio, 1.84; 95% CI, 1.11–3.07; $p = 0.019$), and lactate level more than 1.5 mEq/L (odds ratio, 2.15; 95% CI, 1.28–3.62; $p = 0.004$) were independent risk factors for hospital mortality, but not abnormal microvascular flow index. In reference to microvascular flow index, a significant interaction was observed with tachycardia. In patients with tachycardia, the presence of an abnormal microvascular flow index was an independent, additive predictor for in-hospital mortality (odds ratio, 3.24; 95% CI, 1.30–8.06; $p = 0.011$). This was not true for nontachycardic patients nor for the total group of patients.

Conclusions: In a heterogeneous ICU population, an abnormal microvascular flow index was present in 17% of patients. This was not associated with mortality. However, in patients with tachycardia, an abnormal microvascular flow index was independently associated with an increased risk of hospital death. (*Crit Care Med* 2014; XX:00–00)

Key Words: in vivo microscopy; microcirculation; sidestream dark field imaging; tachycardia

The presence and significance of microcirculatory alterations in the early phase of critical illness, including sepsis and heart failure, has been widely explored (1–4). Although various techniques can provide information on microvascular dysfunction, discrimination of capillary and venule perfusion appears to be of paramount importance and relies on direct in vivo microscopy methods, including Sidestream Dark Field (SDF) imaging (5–7). Sublingual microcirculatory abnormalities identified by SDF are considered clinically relevant and are independently associated with an increased risk of morbidity and mortality (1, 2, 8–13). Conventional hemodynamic monitoring appears to fall short in detecting this "microcirculatory shock": a common finding is the absence of a clear association between the microcirculation and macrohemodynamic variables, such as cardiac

output and blood pressure (8, 9, 11–18). Therefore, the microcirculation has the potential to be an important additional target for monitoring both organ perfusion and treatment efficacy (3, 19–21). Although conventional goal-directed therapy is associated with improvement of capillary perfusion, persisting microcirculatory abnormalities, despite fulfillment of resuscitation endpoints, are related to adverse outcome (1, 12, 13). Interventions intended to ameliorate microcirculatory dysfunction have shown varying results and lack a clear association with improved outcome (18, 20, 22–25). To further understand the role of microcirculatory monitoring and microcirculation-directed interventions, knowledge of the prevalence of microcirculatory alterations in the general intensive care population is of utmost importance. To date, our knowledge is predominantly based on single-center studies in high mortality subgroups in the early phases of critical illness. This implies that data on the prevalence of microcirculatory alterations in the general, heterogeneous intensive care setting are not currently available. Observational studies in multicenter settings, such as the Sepsis Occurrence in Acutely ill Patients and European Prevalence of Infection in intensive Care trials, are valuable tools and have contributed greatly to our knowledge of the prevalence of diseases (26, 27). We applied a similar study design, focusing on current ICU patient characteristics and hemodynamic monitoring, in a worldwide multicenter setting. Furthermore, we evaluated the prevalence and prognostic value of microcirculatory alterations in our heterogeneous ICU population. In this article, we present our main findings.

MATERIALS AND METHODS

Patient Inclusion

The Microcirculatory Shock Occurrence in Acutely ill Patients (microSOAP) (NCT01179243) study was scheduled for September 5–9, 2011 (28). ICU patients who were 18 years old or older, regardless of their underlying disease, were eligible for inclusion. All centers obtained medical ethics approval (or a waiver, if applicable). Written informed consent for included subjects was obtained in accordance with local applicable laws. The exclusion criteria were a lack of informed consent and patient-related factors that substantially interfered with SDF imaging, such as recent maxillofacial surgery or mucosal bleeding or injury. Funding consisted of an unrestricted grant from a local hospital fund.

Data Collection

The data on patient characteristics, hemodynamics, laboratory values, and treatment were collected together with simultaneous SDF imaging of the sublingual microcirculation. Being a point prevalence study, data were collected on the same day for all patients in a given ICU or ICU subunit.

The noninvasive SDF technique consists of a handheld camera, emitting stroboscopic green light with a wavelength within the absorption spectrum of hemoglobin (5). When placed on mucosal surfaces, the stroboscopic light is absorbed by hemoglobin, thereby visualizing blood vessels by depicting erythrocytes as black dots (29–31). Images were obtained and analyzed in agreement with internationally accepted consensus (29, 30).

Data Analysis

SDF Analysis. SDF clips were blindly analyzed offline in a random order by a preselected group of well-trained SDF researchers. Aiming for consensus, images were excluded in cases of pressure artifacts, instability, or inadequate focus that substantially interfered with the analysis. The coefficient of variation for the analysis was calculated based on 10 randomly selected SDF images.

Computer-assisted analysis (AVA 3.0 software; MicroVision Medical, Amsterdam, The Netherlands) was performed in line with international consensus. The semiquantitative microvascular flow index (MFI), ranging from 0 (no flow) to 3 (continuous flow), and percentage of perfused vessels (PPV) provide information on convexity. MFI is scored as the predominant type of flow in every image quadrant for every image. For each patient, the average MFI was calculated (12, 29, 30, 32). Total vessel density (TVD) and perfused vessel density (PVD), both in mm/mm^2, provide information on diffusion. The image analysis is described in detail elsewhere (29, 30). Being the minimum reported value for the lower bound of the 95% CI of MFI in healthy volunteers, a small vessel (< 20 μm) MFI less than 2.6 was considered as abnormal (4, 12, 33, 34). Microcirculatory variables pertain to small vessels, unless indicated otherwise.

Statistical Analysis. Patient data were described using descriptive statistics. Student *t* test, the Mann-Whitney *U* test, or Fisher exact test were used to test for differences between variables. Backwards stepwise multivariable logistic regression analysis was applied to identify predictors of hospital mortality. For multivariable models, an area under the curve (AUC) was calculated. Logistic regression analysis was repeated in patients with tachycardia, a post hoc-defined subgroup based on a significant interaction between tachycardia (heart rate [HR], > 90 beats/min) and an abnormal MFI. To correct for unavailability of data, multiple imputation analysis was used (20 imputations). Lactate values and microcirculatory variables were not imputated. Hosmer and Lemeshow goodness-of-fit test was used to describe the fit of the model. Statistical analysis is described in detail in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/B26). The data were analyzed using SPSS 21.0 (IBM, New York, NY) and GraphPad Prism 5.04 (GraphPad Software, La Jolla, CA) and are presented as the median (interquartile range) or mean ± SD, unless indicated otherwise. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

All Patients

Patient Inclusion. Of 753 screened patients, 531 patients were included from 36 ICUs worldwide (**Fig. 1**). The majority of

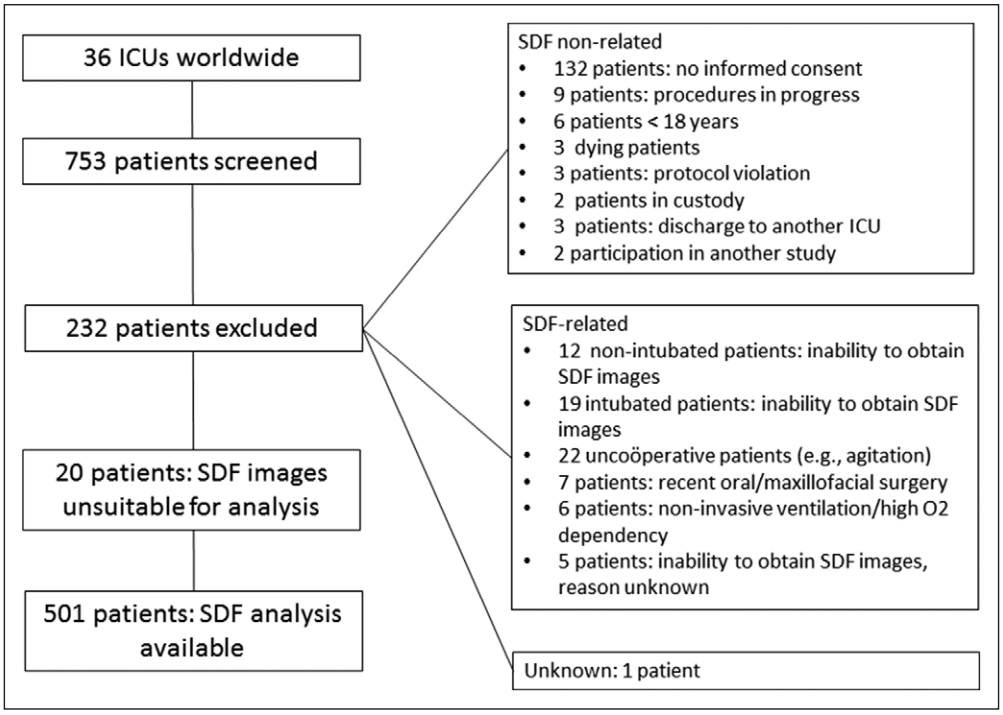

Figure 1. Overview of screened, included and excluded patients. Reasons for exclusion are divided into Sidestream Dark Field imaging (SDF) related and SDF non-related (including absence of informed consent).

exclusions (68%) were not SDF related, with 57% attributable to the lack of informed consent. Twenty patients (3.8%) were excluded because of insufficient SDF image quality, and 501 patients (81% of the eligible patients) were available for further analysis.

General Characteristics. Baseline characteristics of the study population are shown in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B26). Patients were 62 years old (51–73 yr) with an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 15 (10–21) and a Sequential Organ Failure Assessment (SOFA) score of 5 (2–8). The most common reasons for ICU admission were surgery (33%) and sepsis (17%).

Microcirculatory Variables. An abnormal MFI was observed in 86 patients (17%). The number of adequately resuscitated patients, as determined by the attending physician, did not differ between patients with and without an abnormal MFI (85% vs 78%, $p = 0.15$). In patients with an abnormal MFI, we observed a higher heterogeneity index (0.80 [0.40–1.32] vs 0.00 [0.00–0.35], $p < 0.001$) and a lower PPV (0.92 [0.87–0.95] vs 0.98 [0.96–1.00], $p < 0.001$) and PVD (17.21 ± 3.95 vs 18.83 ± 3.88 mm/mm^2); however, TVD did not differ (18.93 ± 3.98 vs 19.32 ± 3.99 mm/mm^2, $p = 0.41$) (supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/B26). No differences in microcirculatory variables were observed between different admission diagnoses. The coefficient of variation for the SDF analysis varied from 0% ± 0% for large vessel MFI and 2% ± 2% for small vessel MFI to 7% ± 4% for the (perfused) De Backer score.

Outcome. Hospital nonsurvivors (28.4%) displayed higher APACHE II and SOFA scores, lower hemoglobin, and a higher HR and arterial lactate level (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B26). Multivariable logistic regression identified higher APACHE II score, a stay in ICU more than 24 hours before SDF, arterial lactate level more than 1.5 mEq/L, tachycardia, lower mean arterial pressure (MAP), renal replacement therapy, use of a vasopressor, and being admitted to ICU because of sepsis, respiratory insufficiency, or cardiac disease as independent predictors of hospital mortality (for odds ratios [ORs], see **Table 1**) (AUC for this model, 0.83; 95% CI, 0.79–0.87; $p < 0.001$).

Integrating Micro- and Macrohemodynamic Monitoring

The use of macrohemodynamic monitoring other than blood pressure and HR appeared to be very limited (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B26). The measurement of cardiac output and S(c)vo_2 was restricted to 6.2% and 20%, respectively. Furthermore, the percentage of patients with hypotension, defined as a MAP less than 65 mm Hg, was as low as 8%. However, tachycardia, defined as a HR more than 90 beats/min (bpm), was present in 204 patients (41%). This threshold was confirmed for our database as the optimal cutoff value for hospital mortality with a sensitivity of 66% and a specificity of 62% (AUC, 0.69 [0.63–0.74]; $p < 0.001$). Tachycardia was significantly less frequent in patients who had been admitted to the ICU less than 24 hours prior, compared with other patients (47% vs 27%, $p < 0.001$). Patients with tachycardia had significantly higher APACHE II and SOFA scores and lower hemoglobin levels. No significant differences were observed in lactate levels (1.3 [0.9–2.1] vs 1.2 [0.9–2.0] mEq/L, $p = 0.28$). Vasopressor use was more frequent in patients with a HR more than 90 bpm (37% vs 26%, $p = 0.007$) (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B26). No significant difference was observed between patients with or without tachycardia in terms of the number of subjects considered adequately resuscitated (78% vs 81%, $p = 0.50$). In contrast, these data for patients with and without hypotension (MAP < 65 mm Hg) were 48% and 82%, respectively ($p < 0.001$).

Tachycardia was an independent predictor of hospital mortality (HR > 90 bpm 41%, HR ≤ 90 bpm 19%, $p < 0.001$; OR, 2.71 [1.67–4.39], $p < 0.001$) (Table 1 and **Fig. 2**). In patients with tachycardia, not only lactate levels more than 1.5 mEq/L but also an abnormal MFI was one of the independent, additional

TABLE 1. Multivariable Logistic Regression for Variables Associated With Hospital Mortality

Variable	OR (95% CI)	*p*
Hospital mortality[a]		
Acute Physiology and Chronic Health Evaluation II	1.05 (1.02–1.08)	0.001
Stay in ICU > 24 hr before SDF	2.81 (1.53–5.21)	0.001
Lactate level > 1.5 mEq/L[b]	2.15 (1.28–3.62)	0.004
Heart rate > 90 bpm	2.71 (1.67–4.39)	< 0.001
Mean arterial pressure (mm Hg)	0.979 (0.963–0.996)	0.013
Use of any vasopressor	1.84 (1.11–3.07)	0.019
Renal replacement therapy	2.26 (1.07–4.80)	0.034
Reason for ICU admission[c]		0.022
Surgery (reference category)	1.00	
Sepsis	2.07 (1.02–4.22)	0.045
Trauma/hemorrhage/other	1.58 (0.74–3.35)	0.239
Respiratory insufficiency/cardiac disease	3.44 (1.73–6.87)	< 0.001
Neurological disorders	2.32 (0.96–5.58)	0.061
Hospital mortality for heart rate > 90[d]		
Lactate level > 1.5 mEq/L[b]	2.84 (1.36–5.92)	0.005
Stay in ICU > 24 hr before SDF	2.92 (1.19–7.14)	0.020
Abnormal microvascular flow index[e]	3.24 (1.30–8.06)	0.011
Use of any vasopressor	2.91 (1.48–5.74)	0.003
Reason for ICU admission[c]		0.022
Surgery (reference category)	1.00	
Sepsis	3.08 (1.27–7.45)	0.013
Trauma/hemorrhage/other	1.04 (0.37–2.97)	0.935
Respiratory insufficiency/cardiac disease	3.54 (1.38–9.08)	0.008
Neurological disorders	1.63 (0.43–6.16)	0.473

OR = odds ratio, SDF = Sidestream Dark Field imaging.

[a]Multivariable logistic regression for hospital mortality (all patients). Average Nagelkerke $R^2 = 0.37$ (range, 0.36–0.41) ($p < 0.001$), average Hosmer and Lemeshow chi-square = 5.303 (range, 1.383–9.400), $p = 0.710$ (range, 0.310–0.994).

[b]As compared with patients with a lactate < 1.5 mEq/L or no lactate measurement available.

[c]As compared with patients with surgery as admission diagnosis.

[d]Multivariable logistic regression for hospital mortality for patients with heart rate > 90 beats/min ($n = 204$). Nagelkerke $R^2 = 0.32$ ($p < 0.001$), Hosmer and Lemeshow chi-square, 5.576 ($p = 0.59$). $p = 0.022$ for overall effect of admission diagnosis. Because Acute Physiology and Chronic Health Evaluation II score was not included in this model, models in all imputations were equal.

[e]Microvascular flow index < 2.6 for vessels < 20 μm.

risk factors for in-hospital death (68% vs 38%, $p = 0.002$; OR 3.24 [1.30–8.06], $p = 0.011$) (Table 1). AUC (95% CI) for this model was 0.79 (0.73–0.86; $p < 0.001$). In contrast, an abnormal MFI did not have an additional predictive value in patients with a HR less than or equal to 90 bpm (Fig. 2).

DISCUSSION

By including more than 500 patients with a variety of underlying diseases, the microSOAP trial is presently the largest prospective study investigating the prevalence and significance of microcirculatory alterations in a heterogeneous ICU population. Applying a predefined threshold, an abnormal MFI was observed in 17% of patients (4). In the mixed ICU population, lactate levels and several macrohemodynamic variables, but not microcirculatory variables, were independent predictors of hospital mortality. After post hoc identification of a high-risk tachycardic subpopulation, abnormal microcirculatory blood flow was an additional independent risk factor for death.

In our study, the likelihood of microcirculatory abnormalities was lower than reported previously. This may in

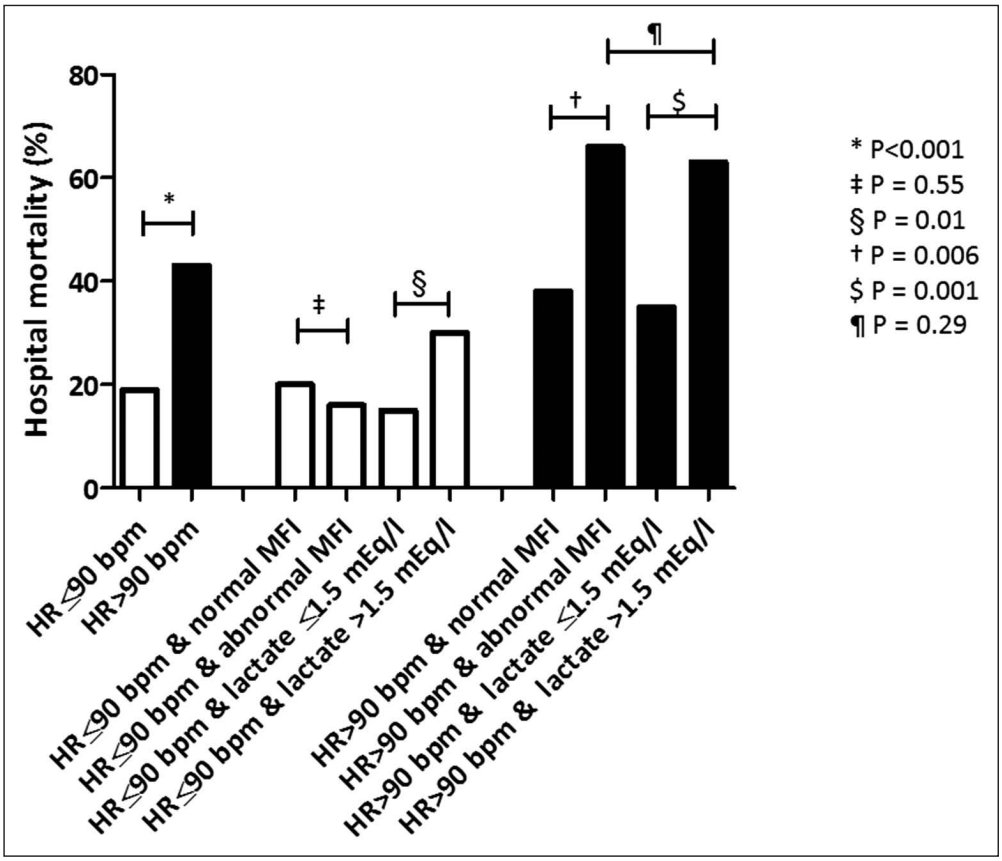

Figure 2. Hospital mortality for subgroups of patients with and without tachycardia (heart rate [HR], > 90 beats/min [bpm]). Normal microvascular flow index (MFI), i.e., MFI ≥ 2.6 for vessels < 20 μm. Abnormal MFI, MFI < 2.6 for vessels < 20 μm. $p < 0.05$ is considered statistically significant.

part be explained by patient selection: our patients were less severely ill than the patients in previously studied subgroups. Furthermore, the majority of studies are restricted to the early phase of critical illness. In the present study, the smaller number of patients in subgroups such as sepsis did not allow in-depth subgroup analysis. Furthermore, abnormal microcirculatory blood flow was not an independent risk factor in the overall population, whereas a significant difference in abnormal microcirculatory blood flow variables has been observed between survivors and nonsurvivors in various studies. However, previous smaller studies primarily focused on high mortality subgroups. Indeed, in a recent study in early normotensive sepsis, MFI was 3.00 (2.73–3.00) (35).

The observed association between macrohemodynamic variables, lactate levels, and mortality confirms the present clinical paradigm (36–46). Notably, a single measurement of blood pressure or HR, irrespective of disease state and timeframe, provided predictive value.

The prognostic significance of tachycardia is well-recognized, especially in cardiac disease, but also in different phases of critical illness (44, 45, 47–50). In line with previous literature and our data, we used a cutoff value of 90 bpm for further analysis (45, 49–51). Using this cutoff value at ICU discharge resulted in similar differences in mortality in patients with multiple organ dysfunction syndrome as observed in our study population (45).

In contrast to previous literature, we found indications for an association between macro- and microcirculatory variables: an abnormal MFI was an independent predictor for hospital death in subjects with tachycardia. This was independent of inotrope use. Linking microcirculatory abnormalities with hypotension was impossible due to the low prevalence of patients (8%) with a MAP less than 65 mm Hg. However, tachycardia was present in 41% of patients and was not confined to patients included within the first 24 hours of ICU admission. Furthermore, the attending physician considered resuscitation adequate at the moment of data acquisition, irrespective of the presence of tachycardia. These data are in agreement with the fulfillment of resuscitation goals in the existing guidelines, in which HR is not an endpoint. In addition, some patients appear to display a well-compensated microcirculatory blood flow under conditions of increased stress, including tachycardia, whereas others do not. Persisting microcirculatory shock has been related to adverse outcome, and accordingly, patients in whom microcirculatory perfusion increases during the course of their disease may have an increased chance of a better outcome (3, 52). Therefore, the ability to preserve microcirculatory perfusion under conditions of stress appears to be key to a more favorable clinical course.

This study has several limitations. A capillary MFI less than 2.6 was a priori defined as the threshold for an abnormal MFI. MFI was chosen because of the possibility of bedside evaluation of this variable, in contrast to the mandatory offline analysis for other variables (53). This could maximize the clinical applicability of the findings. The threshold value was based on previous studies describing the range of MFI in healthy volunteers (4, 12, 33, 34). In order to minimize false-positive findings, the minimum reported lower bound of the 95% CI in healthy volunteers was used as threshold value (12). A capillary MFI less than 2.6 has been shown to be the optimal cutoff value for the response to fluid administration (19). Although SDF enables direct visualization of capillaries, several other techniques, such as near-infrared spectroscopy and laser Doppler flowmetry, are also useful in providing information on the microcirculation (6).

Due to the design of the study, data on the incidence of microcirculatory flow abnormalities cannot be estimated. Presumably, our data underestimate the true incidence of microcirculatory dysfunction, as it has been observed that these alterations attenuate over time (1, 22, 54). Furthermore, no information on the relevance of changes of both macro- and microcirculatory variables over time can be provided. Because of a significant interaction between tachycardia and an abnormal MFI, analysis in the subgroup of patients with tachycardia was appropriate, nevertheless being a post hoc analysis. Despite being the largest prospective study in this field so far, lower numbers of patients per subgroups may have masked clinically relevant differences.

Approximately one third of all screened patients were not included in the study, predominantly due to a lack of informed consent. However, the vast majority of reasons for noninclusion were not related to sublingual in vivo microscopy, and only 3.8% of the included patients were excluded because of inadequate SDF image quality. In agreement with previous literature, the coefficient of variation for our analysis was good (9, 12, 30). Furthermore, by aiming for consensus between SDF researchers, we aimed to keep differences in analysis to a minimum. It must be mentioned, however, that although improved technology is forthcoming, the current need for detailed offline analysis is a severe impairment of the practical bedside applicability of this technique (55). Finally, the limited macrohemodynamic monitoring did not allow for an extensive evaluation of a possible relationship between $S(c)vO_2$ or cardiac output and microcirculatory variables. Our data reflect daily clinical practice in critical care and seem to be in contrast with an overwhelming interest for more advanced hemodynamic monitoring in the current literature.

CONCLUSIONS

This study provides an estimation of the prevalence of microcirculatory abnormalities in a heterogeneous ICU population and may serve as a basis for future studies. In this general ICU population, an abnormal MFI is not associated with mortality, whereas the presence of an abnormal MFI independently predicts an increased risk of dying in patients already at risk for adverse outcome due to tachycardia. Our data bridge the gap between micro- and macrocirculatory dysfunction, suggesting that microcirculatory monitoring could be a potentially clinically important extension of conventional hemodynamic monitoring. Future research could seek to unravel the underlying mechanisms of microcirculatory shock and potential therapeutic options.

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