Monitoring peripheral perfusion and microcirculation

Arnaldo Dubin[a,b], *Elizabeth Henriquez*[c], *and Glenn Hernández*[c]

Purpose of review
Microcirculatory alterations play a major role in the pathogenesis of shock. Monitoring tissue perfusion might be a relevant goal for shock resuscitation. The goal of this review was to revise the evidence supporting the monitoring of peripheral perfusion and microcirculation as goals of resuscitation. For this purpose, we mainly focused on skin perfusion and sublingual microcirculation.

Recent findings
Although there are controversies about the reproducibility of capillary refill time in monitoring peripheral perfusion, it is a sound physiological variable and suitable for the ICU settings. In addition, observational studies showed its strong ability to predict outcome. Moreover, a preliminary study suggested that it might be a valuable goal for resuscitation. These results should be confirmed by the ongoing ANDROMEDA-SHOCK randomized controlled trial. On the other hand, the monitoring of sublingual microcirculation might also provide relevant physiological and prognostic information. On the contrary, methodological drawbacks mainly related to video assessment hamper its clinical implementation at the present time.

Summary
Measurements of peripheral perfusion might be useful as goal of resuscitation. The results of the ANDROMEDA-SHOCK will clarify the role of skin perfusion as a guide for the treatment of shock. In contrast, the assessment of sublingual microcirculation mainly remains as a research tool.

Keywords
capillary refill time, peripheral perfusion, sublingual microcirculation, videomicroscopy

INTRODUCTION

Microvascular alterations plays a key role in the pathogenesis of shock. Even when systemic hemodynamics has been normalized by resuscitation, ongoing microcirculatory abnormalities might hamper tissue perfusion and oxygenation. This form of cardiovascular compromise – the so-called microcirculatory shock – requires another kind of assessment beyond the monitoring of systemic hemodynamic and oxygen transport variables [1]. Accordingly, blood pressure, cardiac output, or systemic oxygen delivery might be misleading for fully understanding the pathophysiologic condition, targeting the resuscitation, and predicting the outcome. On the contrary, monitoring tissue perfusion might theoretically give relevant information for such purposes.

The first approach for monitoring tissue perfusion in critically ill patients has been the evaluation of peripheral perfusion, particularly skin perfusion, which still is the main tool for this purpose. On the other hand, some technological developments allowed the introduction of hand-held videomicroscopy for the bedside assessment of the microcirculation. Consequently, a growing body of evidence suggests that the evaluation of sublingual microcirculation could provide relevant information. Nevertheless, several controversies remain about the usefulness of both, peripheral perfusion and microcirculation, especially as goals of resuscitation. In this brief review, we summarize the achievements and futures challenges concerning the monitoring of skin perfusion and sublingual microcirculation in critically ill patients.

[a]Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, La Plata, [b]Servicio de Terapia Intensiva, Sanatorio Otamendi y Miroli, Buenos Aires, Argentina and [c]Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

Correspondence to Arnaldo Dubin, Cátedra de Farmacología Aplicada, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Calle 42 No. 577, 1900 La Plata, Argentina. Tel: +54 91150102431; e-mail: arnaldodubin@gmail.com

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KEY POINTS

- Monitoring tissue perfusion might be relevant for shock resuscitation.
- Assessment of skin perfusion by means of capillary refill time is a suitable goal of resuscitation.
- The ANDROMEDA-SHOCK study, an ongoing randomized controlled trial, will clarify the role of peripheral perfusion as a guide for the treatment of septic shock.
- The bedside monitoring of sublingual microcirculation is now feasible in critically ill patients.
- Although there are controversies about the characteristics of normal and septic microcirculation, the main limitation for the clinical application of sublingual microcirculation is the analysis of videos.

SKIN PERFUSION

Sympathetic activation, a compensatory response during shock, redistributes flow away from the skin. Since this territory lacks flow autoregulation, skin perfusion assessment plays a pivotal role in the monitoring of critically ill patients, particularly during acute circulatory dysfunction [1,2]. Indeed, the whole pathophysiological process from early subtle circulatory dysfunction to advanced shock can be followed through this clinical window, even during resuscitation. Clinical reperfusion is also confirmed by the transition from a cold clammy skin to a warm vasodilatory state. Moreover, skin perfusion assessment represents somehow a direct clinical visualization of the local microcirculation. The presence of a warm skin, however, might sometimes fail to reflect either the severity of septic shock or the perfusion in other microvascular beds.

Technical issues

Subjective assessment of the temperature [3] or mottling of the skin [4,5], and capillary refill time (CRT) can be easily used to monitor peripheral perfusion [6,7]. However, CRT assessment is susceptible to factors that can profoundly affect results, such as environmental, skin and core temperatures, age, ambient light, and the duration, amount and site of pressure application [6,7,8▪].

The issue of interobserver reliability has also been raised [9,10], but recent although conflicting data, tend to support an acceptable agreement when observers are previously trained with standardized procedures [7,11]. van Genderen *et al.* [11] showed a good overall agreement in CRT assessment between different examiners. Ait-Oufella *et al.* [7] demonstrated that CRT is highly reproducible in septic shock patients with an excellent inter-rater concordance. In contrast, although CRT exhibited a good correlation with objective variables of skin perfusion in another study, agreement between observers was poor [9]. Eventually, difficulties in implementing routine CRT assessment can be overridden by education, training, and standardization of the technique, and by reducing the impact of ambient-related factors.

Its simplicity makes this approach a very attractive tool for perfusion monitoring in resource-limited or pre-ICU settings, and a robust body of evidence supports the strong prognostic value of abnormal peripheral perfusion in the ICU context [3–7,8▪,11,12▪]. However, the most interesting recent data concern the kinetics of recovery of peripheral perfusion during early resuscitation [6,13], its potential representativeness of the perfusion status of physiologically more relevant territories such as the hepato-splanchnic region [14▪], its usefulness as part of a multimodal perfusion monitoring [1,13,15▪], and its role as a potential resuscitation target [16].

Kinetics of recovery

Skin perfusion is a flow-sensitive variable, meaning that it might respond rapidly to flow-increasing maneuvers such as fluid loading in preload-dependent patients. Indeed, some recent data provide a dynamic view of peripheral perfusion response to resuscitation in septic shock patients [6,13]. Hernandez *et al.* [6] showed that CRT was the first variable to normalize, as early as 2 h after starting ICU-based resuscitation, when compared with other peripheral or metabolic-related perfusion indicators. This was confirmed by analyzing the dynamics of recovery of several variables in a cohort of ultimately surviving septic shock patients. CRT was already normal in almost 70% of the patients after 2 h of fluid resuscitation, as compared with only 15% in the case of lactate [13]. Therefore, a rapid-response time variable like CRT could be useful to monitor treatments with strong physiologic impact such as fluid loading. A prospective study performed in a cohort of 95 patients just admitted to the emergency department found that patients exhibiting a normal CRT after the very first fluid bolus had a hospital mortality of less than 10% as compared with 55% in patients with abnormal values [8▪]. The failure to respond to very early resuscitation might identify patients with a more severe circulatory dysfunction and could represent a signal for early triage to the ICU.

Peripheral perfusion and the hepato-splanchnic region

The hepato-splanchnic region is particularly vulnerable to the neurohormonal response to shock [17]. Early and intense vasoconstriction triggered by the activation of the adrenergic, renin–angiotensin and vasopressin responses might induce local hypoperfusion, which if prolonged could induce massive translocation of proinflammatory mediators. However, as a difference with the skin, this territory exhibits some degree of flow autoregulation and more complex regulatory mechanisms that provide some degree of protection during circulatory dysfunction [17]. On the contrary, there is no clinical technique to monitor this process.

An unresolved issue is if peripheral perfusion normalization implies a parallel reperfusion of the hepato-splanchnic region, as both share a common regulatory mechanism, the adrenergic tone. Data are scanty, but a recent study in septic shock patients subjected to early resuscitation tends to support this hypothesis. Peripheral perfusion normalization was correlated with improvement in the pulsatility index of highly relevant vessels such as the mesenteric, splenic, renal, and hepatic arteries, and thus with perfusion of visceral organs [14▪].

Multimodal perfusion monitoring

Persistent hyperlactatemia has been proposed as the fundamental resuscitation target in septic shock [18]. However, there are several controversial issues that challenge this recommendation. First, sources of lactate not related to hypoperfusion such as stress-related hyperlactatemia or decreased hepatic clearance might contribute in an unknown number of cases [2,15▪,19,20]. Moreover, pursuing additional resuscitation in nonhypoperfusion-related cases could lead to the risk of over-resuscitation. In this sense, a normal peripheral perfusion in septic shock patients with hyperlactatemia might suggest nonhypoperfusion related sources and was associated with less morbidity and mortality in a recent study [15▪]. Second, in accordance with recent studies, skin perfusion allows a real-time response assessment of reperfusion as compared with lactate, which exhibits biphasic recovery kinetics [13]. Therefore, peripheral perfusion assessment appears to play an important role in multimodal perfusion monitoring in septic shock.

Skin perfusion as a potential resuscitation target

Some recent clinical data suggest that targeting peripheral perfusion during septic shock resuscitation might improve outcome [16]. van Genderen *et al.* [16] performed a randomized controlled trial comparing two resuscitation protocols; one targeted at normal peripheral perfusion and the other to standard management in 30 ICU patients. The study demonstrated that targeting peripheral perfusion is safe, and associated with less fluid administration and organ dysfunctions.

Using skin perfusion to target fluid resuscitation in septic shock has also several potential drawbacks. First, some variables used for this purpose, such as CRT and mottling, show some degree of subjectivity and interobserver variability [9,10]. Second, it cannot be well evaluated in some settings such as dark skin patients. Third, and more importantly, the corpus of evidence that supports that improvement of peripheral perfusion is associated with resolution of profound tissue hypoperfusion or hypoxia is still scanty. However, the excellent prognosis associated with CRT recovery, the rapid-response time to fluid loading, the simplicity of its assessment, its availability in resource-limited settings, and recent data suggesting that it might change in parallel to perfusion of physiologically more relevant territories such as the hepatosplanchnic region, constitute a strong background to promote studies evaluating its usefulness to guide fluid resuscitation in septic shock patients.

An important ongoing study, ANDROMEDA-SHOCK (NCT03078712), launched by the Latin America Intensive Care Network will be finished shortly and might give relevant answers. It is a randomized controlled trial comparing peripheral perfusion versus lactate targeted resuscitation in early septic shock, aimed at major outcomes with the hypothesis that the former is associated with decreased mortality and morbidity.

MICROCIRCULATION

Patients with septic shock characteristically display sublingual microvascular abnormalities, which were repeatedly found by several investigators. The sublingual microcirculatory alterations are more severe in nonsurvivors than in survivors from septic shock and are frequently associated to hyperlactatemia and high requirements of vasopressors [21–24]. Alterations observed on admission only improve in survivors while persist in patients who eventually die from either shock or multiorgan failure. Moreover, the microcirculatory alteration is an independent predictor of outcome [25]. In addition, the microvascular abnormalities might respond to different therapeutic approaches such as fluid resuscitation, vasopressors, and inotropes [21].

Although the evidence points out sublingual microcirculation as an appealing goal for guiding

resuscitation, different questions remain controversial and preclude its clinical implementation at the present.

Characteristics of sublingual microcirculation in septic shock

In early studies that characterized the microcirculation by eye, the main features were decreases in total density of small microvessels and proportion of perfused vessels (PPV), along with increased heterogeneity [22]. In contrast, software-assisted analysis demonstrated that, compared with healthy volunteers, septic shock patients have a preserved total length of microvessels, whereas the PPV and the perfused vascular density are reduced [23]. Nevertheless, the most striking manifestation is the increased heterogeneity of microvascular perfusion.

Some of the controversies related to the characteristics of sublingual microcirculation in critically ill patients might arise from an insufficient description of the normal microvascular pattern in healthy individuals. Some small studies reported data about PPV and microvascular flow index (MFI) that seem very low for a normal population. For example, a study found in healthy volunteers aged under 25 years ($n = 20$) that PPV and MFI were 0.92 ± 0.06 and 2.85 [2.75–3.0] [mean ± SD and median (Interquartile range), respectively]. Similarly, in those over 55 years ($n = 20$), the figures were 0.88 ± 0.09 and 2.81 [2.66–2.97] [26]. Another study showed in 10 volunteers that PPV was 0.92 [0.91–0.93] [27]. Thus, both studies showed unexpectedly low ranges of microvascular variables in normal subjects [26,27]. In contrast, a larger study in healthy volunteers found values of 1.00 ± 0.00 and 2.97 ± 0.03 for PPV and MFI, respectively [28] (Fig. 1). Accordingly, the frequently quoted cutoff value of MFI less than 2.6 for the identification of an abnormal microcirculation [29] might be questioned. Another relevant issue is that sublingual microcirculation remains remarkable stable across a wide range of age [28] (Fig. 1).

The large variation reported in the normal values of PPV and MFI might be produced by different degrees of compression artifacts. An observational study that assessed sublingual microcirculatory variables in healthy volunteers over three consecutive days found a variability over time in the PPV of 3.9% for small vessels, 4.9% for medium vessels, and 18.8% for large vessels [30]. Since large vessels should be continuously perfused, the high variability in the measurement of their PPV might reflect how hand-held videomicroscopy is prone to compression artifacts.

Consequently, the avoidance of compression artifacts should be a main caution in the video-acquisition. Accordingly, a score that assesses the

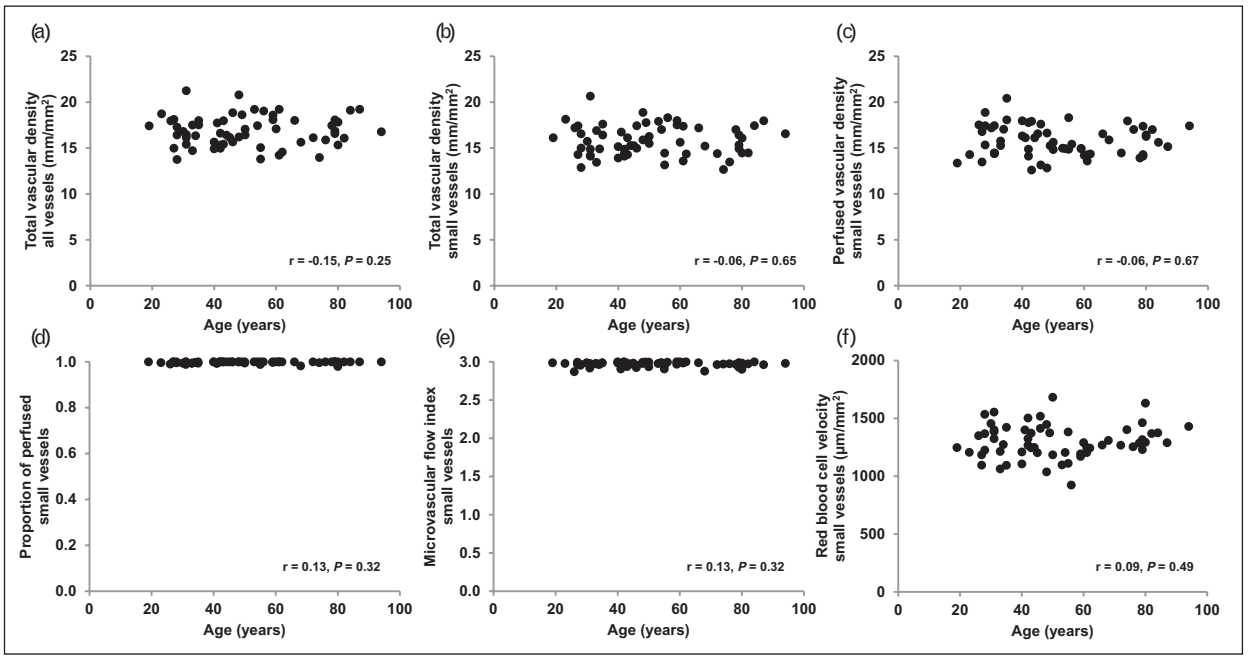

FIGURE 1. Microcirculatory variables in healthy volunteers and outpatients with cardiovascular risk factors as function of age. Panel (a) total vascular density of all vessels. Panel (b) total vascular density of small vessels. Panel (c) perfused vascular density of small vessels. Panel (d) proportion of perfused of small vessels. Panel (e) microvascular flow index of small vessels. Panel (f) red blood cell velocity of small vessels. Proportion of perfused vessels and microvascular flow index remarkably remain in a range of 1.00 ± 0.00 and 2.97 ± 0.03 regardless of age. Reproduced with permission [28].

quality of videos has been introduced [31]. By considering illumination, duration, focus, content, stability, and pressure, it assigns a score of optimal (0 points), suboptimal but acceptable (one point), or unacceptable (10 points) to each category. Any video with a cumulative score at least 10 points (range, 0–60) should be considered unacceptable for further analysis. More recently, a similar evaluation has been proposed [32▪].

Another controversial issue is the presence of hyperdynamic capillary flow as part of the septic microcirculation. Although commonly advocated, it has never been demonstrated in patients with septic shock. On the contrary, slow red blood cell (RBC) velocities were described in that condition [23]. Hyperdynamic flow implies a rather than normal flow; that is, the presence of RBC velocities higher than those found in healthy individuals. Indeed, its definition should take into account the RBC velocity from normal subjects. Accordingly, a study performed in patients with normodynamic and hyperdynamic (cardiac index >4.0 l/min/m^2) septic shock showed that both groups of patients had reduced perfused vascular density and RBC velocity and increased flow heterogeneity compared with that of healthy subjects [33▪]. Fast RBC was not found, even in patients with high cardiac output (Fig. 2). These results support the conclusion that microcirculatory function is frequently dissociated from systemic hemodynamics in septic shock.

Dissociation of microcirculation from systemic hemodynamics in other critical conditions

Probably, hemodilution is the most paradigmatic condition in which microcirculation is dissociated from systemic and regional hemodynamics. Increases in cardiac output and organ blood flows are associated with decreased perfused capillary density in the majority of microvascular beds [34▪]. In addition, the occurrence of hyperdynamic microvascular flow is also controversial. During progressive hemodilution, there are lineal increases in RBC velocity in central nervous system [35] and heart [36]. The behavior, however, is more complex in other territories. For example, U-shaped changes of RBC velocity have been found in muscle [37] and skin [38]. On the other hand, in sublingual mucosa and intestinal mucosa and serosa, any reduction in hemoglobin was strongly associated with decreased RBC velocity [34▪]. Therefore, hyperdynamic microcirculatory flow can be found in hemodilution but is not a ubiquitous phenomenon.

Reperfusion injury is another situation where the complete normalization of systemic cardiovascular variables can fail to adequately recruit the microcirculation. Although coherence between macrocirculation and microcirculation is evident in the fast microvascular improvement after retransfusion in hemorrhagic shock, some degree of dissociation is still present, since most of the microvascular variables stayed altered [39▪].

Sublingual mucosa as a suitable window for microcirculatory monitoring

Microvascular alterations can be easily monitored in the sublingual mucosa. Moreover, evidence suggests that sublingual microcirculatory alterations are related to outcome in patients with septic shock. The predictive ability, however, is not straightforward in a general ICU population [29]. In addition, different microvascular beds might be dissociated each other [40–42]. In patients with abdominal sepsis, mortality is not associated to sublingual but to intestinal microvascular abnormalities [41]. Experimental models also suggest that gut mucosal microcirculation might be more susceptible to septic and hemorrhagic shock [43,44].

The relationship between sublingual microcirculation and skin perfusion is also complex. Some studies showed a different compromise of both territories in patients with septic shock [42]. In spite of this, similar improvements in sublingual perfused vascular density and central-peripheral temperature have been described after a fluid challenge [41].

The proper analysis of the microcirculatory videos

The characterization of microcirculation should include variables of density, perfusion, and heterogeneity. The analysis of the videos can be performed by eye [21] or assisted by software [23]. Both approaches are well correlated [23] but are time-demanding and not suitable for the clinical implementation of the microcirculation as goal of resuscitation. On the contrary, automatic analyses developed at the present do not work properly enough [45▪,46▪]. Consequently, the real-time visual evaluation has arisen as an attractive approach. Even though some studies claimed that this approach might be valid, their results are conflictive [47,48,49▪]. The interchangeability between on-line and off-line MFI is poor, with 95% limits of agreement between both methods that are clinically unacceptable [47,48,50]. In addition, some of these studies considered as normal cutoff values of MFI

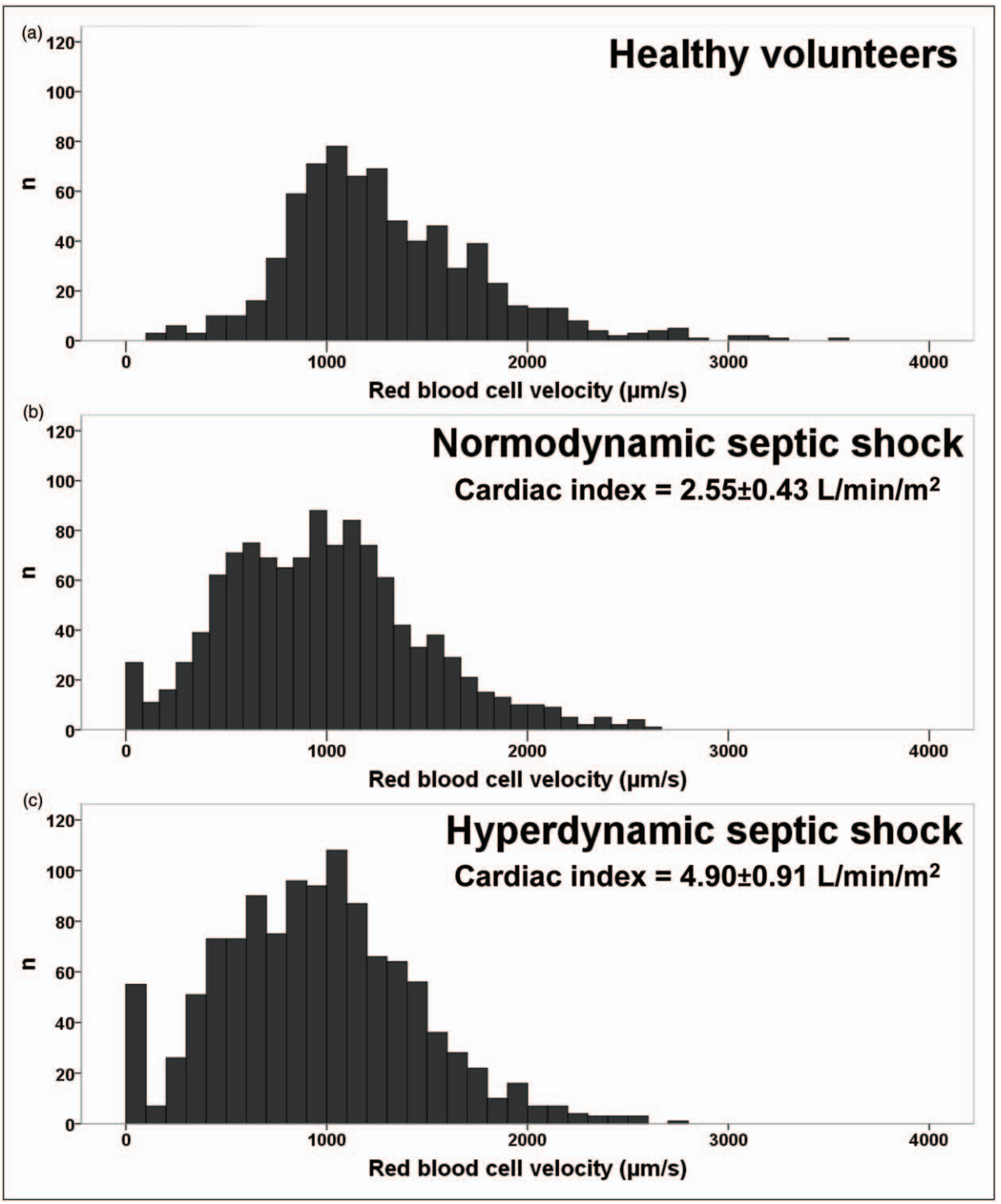

FIGURE 2. Histograms of red blood cell velocity in (a) healthy volunteers, (b) patients with normodynamic septic shock, and (c) patients with hyperdynamic septic shock. Although cardiac index is quite different ($P < 0.0001$), patients with normodynamic and hyperdynamic septic shock show lower red blood cell velocity than healthy volunteers. In addition, high red blood cell velocity is absent in septic microvessels. Reprinted with permission of the American Thoracic Society. Copyright© 2018 American Thoracic Society [33▪]. *Annals of the American Thoracic Society* is an official journal of the American Thoracic Society.

less than 2.5, total vascular density less than 8 mm/mm^2, and PPV less than 0.75 [48,49▪], which actually are severe derangements. Unfortunately, the real-time visual evaluation is misleading.

CONCLUSION

The optimization of tissue perfusion and oxygenation is the final goal of resuscitation. For this purpose, the monitoring of both skin perfusion

and sublingual microcirculation are potentially valuable tools. Hopefully, the ongoing results of the ANDROMEDA-SHOCK study will clarify the role of CRT as a guide for resuscitation of septic shock. In contrast, technical difficulties associated with the assessment of the videos are still the limiting step for the widespread clinical monitoring of the sublingual microcirculation. Therefore, it still remains as a research tool.

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Conflicts of interest

There are no conflicts of interest.

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