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EDITORIAL

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Shedding light on microcirculation?

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Hypovolemia due to hemorrhage is a common problem in emergency and intensive care medicine. The clinical signs of severe acute hypovolemia are hardly controversial, and include tachycardia, hypotension, reduced central and peripheral venous filling, cold periphery, oliguria, and as a preterminal symptom, decreased level of consciousness [1]. Impaired microcirculation, observed as reduced skin temperature and decreased capillary perfusion (slow recapillarization), is a well-recognized component of this clinical entity, and tends to recover last during resuscitation. As is the case with many clinical entities, severe hypovolemia is relatively easy to recognize but difficult to define with numbers.

The progression to hemorrhagic shock without treatment is rarely observed (and never should be!) in patients—therefore few data are available on the evolution of hemodynamics, tissue perfusion, and microcirculation in patients with hemorrhage. The symptoms and signs obviously depend on both the rate of bleeding and the total loss of blood—physiologic mechanisms can best protect systemic hemodynamics during slow hemorrhage. In this scenario, clinical signs of reduced capillary perfusion can be present without apparent deterioration of systemic hemodynamics. If hemorrhage is severe enough to cause acute reduction of cardiac output or hypotension, common sense would expect microcirculation to deteriorate as well. Indeed, parallel decreases in cardiac output and microcirculatory blood flow have been observed in some experimental models of hemorrhage and sepsis [2, 3].

In this issue of *Intensive Care Medicine*, Dubin et al. [4] report the effects of hemorrhage on sublingual, ileal serosal, and ileal mucosal microcirculation, and on systemic and mesenteric hemodynamics, in anesthetized sheep. The authors use sidestream darkfield imaging [5] to visualize the microcirculation. This technology is one of many contributions to microcirculatory research by the senior author, Dr. Ince, who has again developed a novel device and made it commercially available to the scientific community. This paper [4] also applies a new software for the measurement of red blood cell velocity in single vessels by generating "space-time diagrams"—a concept earlier proposed by Dr. Ellis's group [6]. Briefly, the software places a center line on a vessel segment, and the red cell motion along the segment distance is plotted against time. The slopes of the resulting lines represent the velocity of the red cells. These lines are manually traced for analysis.

Quantification has been one of the main problems in assessing microcirculation with imaging techniques. Most investigators use semiquantitative analysis of video sequences, where the flow characteristics are visually (subjectively) defined. Either continuous or categorical scores can be calculated to characterize the flow pattern [7]. A consensus statement by a group of investigators has been published in order to solve some problems and variation in quantification [7]. Although the new software to objectively quantify the red blood cell velocity is a welcome step, several fundamental problems remain.

The microcirculation has an inherent variability and heterogeneity, which makes the selection of the measurement area, the duration of the measurement, and the selection of the images crucial. This becomes even more important when a disease or intervention changes the characteristics of the microcirculation. These issues are also relevant for the interpretation of the results of Dubin et al.

Dubin et al. found that hemorrhage reduced sublingual, gut serosal and gut mucosal red blood cell velocities and the semiquantitative microcirculatory flow and flow heterogeneity indices. Capillary density was also reduced, except in the gut serosa. The authors emphasize that the microcirculatory changes were already detectable after the first step of bleeding. In order to put these findings in perspective, several issues need to be considered.

First, how relevant was the hemorrhage? The first 5 ml/kg hemorrhage (approximately 8% of estimated blood volume) increased blood lactate and reduced cardiac output and mesenteric blood flow by 26% (to 74% of the baseline; Table 1), and reduced mixed and mesenteric venous saturation. Such a major cardiac output reduction indicates a very high sensitivity of this model to hemorrhage. This is in sharp contrast to observations in humans [8]. Healthy volunteers bled for 25% of blood volume over 60 min maintained stable systemic hemodynamics halfway through the bleed. Only after 25% loss of blood volume did stroke volume decrease by 19% and cardiac output (calculated from [8]) by 15% ($P = 0.19$ repeated measures ANOVA), without increase in blood lactate. Accordingly, the findings of Dubin et al. on microcirculation should be viewed in the context of the major changes in cardiac output rather than of the (small) percentage of blood loss.

Second, how did microcirculatory changes compare with changes in cardiac output? This is relevant if monitoring microcirculation is considered for monitoring hypovolemia, as proposed by Dubin et al. As can be expected (Table 1), systemic and mesenteric blood flows change almost identically. In contrast to this, changes in red blood cell velocities are substantially smaller at all measurement sites, and do not reflect the deterioration of systemic and regional blood flows.

The third issue is the interpretation of the semiquantitative microvascular flow index, a non-validated modification of a previous one. This index, based on categorical scoring of the predominant flow types, also indicated impairment of microcirculation in all regions, and correlated with red blood cell velocities. Roughly estimated linear regression lines for these correlations (Figure 5 in [4]) suggest a *y*-axis intercept slightly above 200 μm/s of red blood cell velocity at zero microvascular flow index in all studied regions; perhaps, because only vessels with continuous flow were assessed. Since the flow index should approach zero when red blood cell flow velocity approaches zero, its behavior at flow velocities approaching zero may be very different. The robust conclusion that can be drawn from the data [4] is that changes in microcirculation following hemorrhage-induced marked (26%) reduction in cardiac output could also be detected with the microcirculatory flow index.

Since Dubin et al. provide no data on hemorrhage-induced microcirculatory changes without major reductions of cardiac output, their suggestion that sublingual imaging of microcirculation be used to monitor and detect hypovolemia is less than convincing. However, their study does provide interesting insights into the behavior of the microcirculation during hemorrhage.

In a mouse model of hemorrhage-induced hypotension, intestinal mucosal red blood cell velocity and velocity distribution were preserved, and the number of perfused villi decreased only slightly [9]. In contrast, Dubin et al. suggest that hemorrhage causes relevant deterioration of mucosal perfusion. Although the red blood cell velocities decrease less than cardiac output or regional blood flow, the concomitant reduction of capillary density and possibly increased heterogeneity (suggested by the heterogeneity index calculated from the semiquantitative scores) may well impair tissue oxygenation more than the mere reduction of flow would suggest.

Some caution is warranted in comparing sublingual, ileal serosal and ileal mucosal sites [4]. For ileal mucosa, many fewer vessels were analyzed, and of those, a lower percentage were analyzable for red blood cell velocities; it appears that on average only 3–4 vessels in the ileal

Table 1 Blood flow and capillary density changes from the baseline

	Red blood cell velocity % of baseline			Blood flow % of baseline		Capillary density % of baseline		
	Sublingual mucosa (%)	Ileal serosa (%)	Ileal mucosa (%)	Cardiac output (%)	SMA (%)	Sublingual mucosa (%)	Ileal serosa (%)	Ileal mucosa (%)
5 ml/kg bleed	90	91	92	74	74	81	83	75
10 ml/kg bleed	88	84	92	63	62	67	73	57
15 ml/kg bleed	83	77	84	53	53	63	73	55

All values are based on the mean values reported in the original paper of Dubin et al. Some differences between these and mean values of individual changes can be expected. The red blood cell velocity and capillary densities have been estimated from the graphs using the "measure" tool of Adobe Acrobat Professional software version 7.1.0

SMA superior mesenteric artery

mucosa were available for velocities, versus 19–25 vessels in the serosa and 34–58 sublingually ($P < 0.0001$ ANOVA for between-site differences both before and after hemorrhage; derived from Table 1 in [4]). The small number of vessels analyzable at the ileal mucosa is a further indicator of the various difficulties in assessing microcirculation at the intestinal mucosa, recently also addressed by Bracht et al. [10]. The small number of vessels also makes any comparison of coefficient of variation between the ileal mucosa and the other territories meaningless.

Imaging in medicine has made giant steps in the last 30 years. In the late 1970s, computerized tomography could take 20–40 s for one slice; today, extremely sophisticated and precise three-dimensional and functional images of the various organs are available. Important advances in imaging of microcirculation have taken place in the last decades, and we can thank pioneers like Dr. Ince and colleagues for their efforts in developing devices to a stage where they can be applied for research purposes much more easily than in the past. Nevertheless, quantum leaps in the methodology, and especially in analysis, are needed before these devices can take their place in the bedside management of critically ill patients. Without such advancements, they will remain scientific tools, or as some would say, toys for the boys.

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