EDITORIAL

Could resuscitation be based on microcirculation data? Yes

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Dear Editor,

What is microcirculatory shock? The concept of shock has been central in the ideas governing resuscitation [1]. From a clinical macrocirculatory point of view, Weil and Henning described the four states of shock as including cardiogenic, obstructive, distributive, and hypovolemic shock [2]. Shock is defined as a condition whereby the circulation is unable to deliver adequate blood flow to meet the metabolic demands of the parenchymal cells needed to support organ function [1] and/or when cellular metabolism dysfunction occurs [3]. In the description of clinical shock the conceptual origin of shock has been emphasized as being of a cellular nature. From this latest perspective, shock concerns a cellular definition. The physiological interface compartment between macrocirculatory shock and cellular shock is therefore open to discussion and definition, i.e., the microcirculation [4]. How the target in resuscitation is achieved, however, is different in the three compartments (i.e., macro, micro, and cellular). For the macrocirculation, resuscitation mainly targets cardiac output, perfusion pressure achieved by heart filling, adjustment of cardiac contractility, and manipulation of vascular tone all with the aim of achieving adequate amounts of oxygen delivery to the circulation.

What makes the condition of shock complicated is that these three compartments are not coupled, especially in disease states, and that one compartment can be in shock in the presence of a relatively normal other compartment. Thus shock in one compartment does not necessarily mean there is shock in another compartment

(a condition especially prevalent in distributive shock). Such a discordance can occur between the macro- and microcirculation but also between different organs in shock [5]. Furthermore the cause as well as the resolution of the perspective types of shock can be very different. This condition has been well described at the bedside using handheld video microscopes to observe the sublingual microcirculation whereby a relatively normal systemic circulation has been found to persist in the presence of microcirculatory alterations or shock [6] and is also routinely identified at the bedside with persistent skin mottling, prolonged capillary refill time despite optimization of blood pressure and cardiac output [7]. Such a condition has been described as there being a loss of hemodynamic coherence and leads to the clinical manifestation of a reduced capacity of the tissue for oxygen extraction and utilization [8].

From this point of view we can consider the concept of microcirculatory shock as the interface compartment between the systemic circulation and the parenchymal cells, which drives cellular shock. Basically microcirculatory shock can be defined as the condition whereby its primary function of transporting oxygen to the tissue cells is no longer adequate to meet the metabolic and oxygen needs of the cells. Its causes, however, are many fold and thus need defining and refining. This is important because one needs to identify the type of microcirculatory shock before appropriate resuscitation is administered to fix the particular type of microcirculatory function. In this manner a drug meant to improve a parameter thought to be associated with macrocirculatory shock may not be effective in improving oxygen transport in the microcirculation [9, 10].

Essentially four types of microcirculatory states of shock can be identified each with a specific cause in need of specific resuscitation strategies: distributive, anemic, obstructive, and hypoperfused. Their causes can be

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macrocirculatory induced (e.g., reduction in cardiac output due to loss of contractility or volume) but can also be purely due to dysfunction of the constituent cell types of the microcirculation. This has to be kept in mind since resuscitation will have to target functional data relating to the microcirculation, since as mentioned simply correcting systemic hemodynamic variables does not always lead to a parallel improvement in the microcirculation. That is why an integrative and combined monitoring of the macro- and microcirculation is required. Since conditions of inflammation, hypoperfusion, anemia, and reperfusion injury can cause a loss in the oxygen carrying capacity of the microcirculation, resuscitation of this condition of microcirculatory shock requires different approaches than that of the macrocirculation. This is because left ventricular filling and vasoplegia requiring

fluids and vasoactive compounds used in resuscitation procedures directed at the macrocirculation level may not be beneficial in resuscitating the microcirculation. The pathophysiology of microcirculatory shock requires the cellular constituents of the microcirculation, e.g., red and white blood cells, endothelial cells, and the parenchymal cells, to be targeted.

Microcirculatory assessment using handheld vital microscopy can be used to identify the specific type of microcirculatory alteration which is dominant, thus providing an indication as to the most appropriate type of resuscitation for correcting microcirculatory shock. In addition an advantage of evaluating the microcirculation by direct visualization is that a normal microcirculation requires all participating cellular systems to be healthy. Any pathogenic alteration in any one of the participating

cell types of the microcirculation (e.g., red and white blood cells, endothelial cells, or parenchymal cells) will manifest itself as a dysfunctioning microcirculation.

Each type of microcirculatory shock has its own pathology and the intervention needs to be based on the understanding of what is wrong [11]. To this end, cells which are sick need to be identified and resuscitation focused on their well-being [12, 13]. If microcirculatory hypoperfusion is the cause then vasodilators can be considered [14]. Dysfunctioning endothelial cells or parenchymal cells may require tissue protective agents (TPA) such as anti-inflammatories, specific treatments [15], or even tissue regenerative compounds currently under development can be considered. On the other hand, if a low vascular density with normal flow (diffusion limitation) is observed, it would indicate hemodilution, requiring diuretics or red blood cell transfusion. Under such extreme conditions of course where true damage has been done to the parenchymal cells resulting in loss of organ function, mechanical assist devices can be considered and adjunct therapies administered to allow regeneration of damaged organs (Fig. 1). It must be underscored, however, that the subject matter presented in this paper regarding the clinical efficacy of the correction of a lack of microcirculation will have to be demonstrated in future clinical investigations. Targeting the microcirculation as a clinical end point at present lacks clinical data and should be regarded as a program for research for the near future where clinical studies will need to be carried out. It is clear that the future will require better phenotyping and tailored treatment for integratively treating conditions of macro, micro, and cellular shock present in our critically ill patients.

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Compliance with ethical standards

Conflicts of interest

Dr. Ince has no financial relationship of any sort with industry commercializing handheld vital microscopes. He runs an educational internet site <https://microcirculationacademy.org>

which offers services (training, courses, and analysis) related to clinical microcirculation. H. Ait-Oufella and M. Legrand have no conflict of interest to declare.

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