Ageing Population

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Microtools to Identify and Resuscitate Microcirculatory Dysfunction in Critically Ill Patients

An overview of real-time digital assessment of microcirculation and quantification of tissue perfusion and the physiological and technical considerations that may, in the near future, change the way we look at circulatory shock in critically ill patients.

The Challenges of Detecting Circulatory Shock

Despite recent advances in the timely restoration of impairments in the oxygen supply chain to the tissue (Yealy et al. 2014; Peake et al. 2014; Mouncey et al. 2015), circulatory shock remains a major contributor to mortality in critically ill patients. The lung and pulmonary circulation, the right and left heart, and the systemic circulation consisting of arteries, veins, and microvessels, provide oxygen to the target cells by perfusing the tissue with red blood cells saturated with oxygen (Guven et al. 2020). In the systemic circulation, two overarching categories of circulatory shock may be differentiated by the primary mechanism of circulatory failure. On one hand, tissue red blood cell hypoperfusion may be secondary to a reduction of blood flow within the large arteries and veins, or a reduction of the oxygen-carrying capacity of the blood. Such dysfunction of the macrocirculation may be caused by primary pump failure in the form of forward or backward failure of the heart, hypovolemia as the cause of a reduction in cardiac output, or haemodilution which

may reduce tissue red blood cell perfusion even in the presence of otherwise sufficient cardiac output. These types of shock result in tissue hypoxia through insufficient delivery of oxygen by the macrocirculation and – if present long enough – in cell death and damage to the microvasculature, the interstitium and the parenchymatous cells within the tissue. Treatment aims at restoring cardiac output and tissue red blood cell perfusion before such irreversible damage ensues. On the other hand, circulatory shock may primarily manifest as dysfunction of the microvasculature within the tissue. In septic and inflammatory shock, the precipitation of an infectious or inflammatory agent has been demonstrated to directly cause dysfunction of red blood cells and the endothelial cells and induce disseminated intravascular coagulation, which together result in functional heterogeneity of the microcirculation and a deficit in the capacity of the tissue to extract oxygen culminating mainly through microcirculatory shunting and consecutive regional tissue hypoxia (Ince and Mik 2015; Ince 2015). In such a case, the timely restoration of oxygen

delivery to the tissues and elimination of the precipitating infectious or inflammatory agents may limit the additional damage caused by tissue hypoxia.

Both categories of circulatory shock, if allowed to progress, can result in a state of permanent microcirculatory damage and malfunction. The enabling step for the successful treatment of patients in circulatory shock is therefore the achievement of timely diagnosis and understanding of the underlying pathophysiology to identify and administer effective treatment strategies. However, the detection of circulatory shock is often challenging, especially in patients with effective compensatory mechanisms of the macrocirculation where parameters such as arterial blood pressure, blood haemoglobin concentration or even advanced haemodynamic measurements such as cardiac index may remain within the normal range despite the presence of severe tissue hypoxia. Direct insight into the function of the microcirculation in patients, on the other hand, may reveal deficiencies in tissue red blood cell perfusion and abnormal leukocyte kinetics from the onset. Such insights have been

achieved by the introduction of handheld vital microscopes for direct observation of sublingual microcirculatory alterations in critically ill patients (Ince et al. 2018). Even though the technological and methodological prerequisites to measure and interpret sublingual microcirculatory function have been demonstrated in a growing body of evidence (Ince 2015; Aykut et al. 2015; Ince 2014; Legrand et al. 2018), the applicability in clinical settings has been limited by complex and time-consuming data analysis processes (De Backer et al. 2007). Recent developments in advanced computer vision software such as realised in MicroTools are for the first time enabling the application of these technologies at the bedside (Hilty et al. 2020; Hilty et al. 2019; Hilty and Ince 2020).

The Microtools Advanced Computer Vision Algorithm Enables Quantification of Microcirculatory Function and Tissue Red Blood Cell Perfusion

The convective and diffusive capacity of the microcirculation are important determinants of the ability to deliver adequate amounts of oxygen to the tissue, through the movement of oxygen carrying red blood cells through the capillaries and the distance between the oxygen carriers and the parenchymatous cells (Guven et al. 2020). While surrogate parameters for both properties can be directly or indirectly measured using methods such as laser Doppler or near-infrared spectroscopy (Li et al. 2015), these only provide a partial insight. With the advent of handheld vital microscopy employing side stream or incident dark field microscopy, the imaging of individual red blood cell movement through the capillaries was made possible. Based on the principle that when observed for a long enough period, the total locus of moving red blood cells over time approximates the location of the capillary walls involved in

red blood cell transport, parameters such as the total length of capillaries divided by the field of view (total vessel density, TVD) and the total length of actively perfused capillaries divided by the field of view (functional capillary density, FCD) were formerly extracted from these images using manual analysis, providing insight into the microcirculatory diffusion capacity (De Backer et al. 2007). The quantification of red blood cell movement had initially relied on subjective scores in the absence of automated analysis algorithms (Naumann et al. 2016; Boerma et al. 2005). Early attempts at automatic analysis of HVM image sequences were not further developed to provide reliable measurements of such parameters and not validated in clinical settings (Eden et al. 2005; Bunyak et al. 2008; Bezemer et al. 2011; Behnke et al. 2012; Demir et al. 2012; Chao et al. 2015).

The development and validation of MicroTools using advanced computer vision algorithms utilising principal curvature-based region detection on equalised time-based mean images allowed automatic measurement of TVD and FCD (Hilty et al. 2020). In addition MicroTools allowed generation of space-time diagrams of the red blood cells moving through the detected capillaries (Ince et al. 2018), from which red blood cell velocity (RBCv) could be calculated to provide a reliable parameter reflecting the microcirculatory convection capacity in HVM image sequences (Hilty et al. 2019). MicroTools was further developed to compute capillary haematocrit (cHct), which next to FCD is a second major factor determining the diffusive capacity of the microcirculation (Hilty et al. 2019). With these quantitative parameters, HVM image sequences now provide a full overview of the parameters determining the perfusion of the tissue by red blood cells, which may thus be quantified as the displacement of red blood cell volume divided by the observed tissue volume which we have termed tissue red

blood cell perfusion (tRBCp) (Hilty and Ince 2020). Of major significance it that MicroTools allows the automatic calculation of these functional parameters of the microcirculation including tRBCp at the bedside in real-time and independent of the operator.

Automatic Analysis of the Sublingual Microcirculation Using Microtools Allows Systematic Analysis of Large Datasets

While the quantification of the determinants of oxygen delivery to the tissue provides the prerequisites for early recognition of circulatory shock and to guide resuscitation in critically ill patients at the bedside, algorithm-based analysis of HVM image sequences using MicroTools also for the first time opens large datasets of such measurements to the systematic analysis of the movement of red blood cells. In the first such use an analysis of a multicentral database consisting of 1525 measurements of the sublingual microcirculation, evaluating information on multiple trillion discrete red blood cell positions using the MicroTools algorithm was accomplished (Hilty et al. 2020). Such a systematic analysis marks the transition of the in-vivo examination of microcirculatory function to a data-driven realm and may, for example, provide the basis for identifying the defining characteristics of circulatory failure in the setting of different diseases in critically ill patients. Hypotheses generated from such analyses will serve to prospectively test the diagnostic power of HVM measurements and the possibility to assess the effect of therapeutic measures using real-time analysis of the sublingual microcirculation. Further, it enables the application of more complex methods such as latent cluster analysis or the training of neuronal networks using the parameters derived from red blood cell tracking within HVM image sequences using MicroTools.

Alterations in Sublingual Microcirculatory Diffusion and Convection Capacity Correspond to the Presence Of Circulatory Shock and the Success of Resuscitation

In the population of the above mentioned systematic, algorithm-based study in a multicentral microcirculation database, the combination of RBCv and FCD as measures of the microcirculatory convection and diffusion capacity were found to indicate the presence of circulatory failure in patients with septic, cardiogenic and obstructive shock, hypovolemia and haemodilution (Hilty et al. 2020). The sublingual microcirculatory measurements included in that database were collected from 145 patients hospitalised in an intensive care unit, 82 perioperative patients and 40 healthy volunteers, and the observed conditions represent the main causes of a failure to deliver oxygen to the tissues. At the same time, longitudinal analysis in subgroups of the database encompassing those patients that underwent interventions to potentially recruit the microcirculation demonstrated that an increase in cardiac output mainly recruited the microcirculatory convection capacity as represented by RBCv, while systemic vasodilation favored the recruitment of the microcirculatory diffusion capacity by increasing the density of the perfused capillary network. These results thus not only establish that the early diagnosis of circulatory shock may be aided by the assessment of the sublingual microcirculation at the bedside in critically ill patients, but they also confirm the hypothesis that the effects of resuscitation procedures result in changes in microcirculatory function that are detectable by the algorithm-derived parameters of microcirculatory convection and diffusion capacity.

In the future, the hypothesis may be tested that different interventions steer the microcirculatory function in specific ways, for example, that certain vasopressors may primarily increase the precapillary arteriolar tone while others could prioritise action on the postcapillary venules, resulting in capillary perfusion recruitment instead of de-recruitment. Similarly, volume resuscitation may recruit microcirculatory delivery of oxygen through an increase in convection capacity, but may be associated with capillary de-recruitment through haemodilution even when macrocirculatory parameters such as stroke volume are still volume responsive (Hilty and Ince 2020).

Conclusion

Automatic, algorithm-based analysis of HVM image sequences using Software such as MicroTools has been made possible by the rapid evolution of advanced computer vision libraries and processing hardware, has been validated in large clinical datasets and provides real-time insight into the microcirculatory function at the bedside. Mathematical models allow the calculation of tRBCp in the sublingual microcirculation as a quantitative measure of microcirculatory delivery of oxygen, providing a novel treatment target for resuscitation in circulatory shock. Patterns in the parameters of microcirculatory convection and diffusion capacity and red blood cell movement within the capillary system may provide insight into the presence of circulatory shock before it manifests in organ dysfunction or in macrocirculatory aberrations, and reveal information on the underlying pathophysiological processes.

Conflicts of interest

Can Ince (CI) has developed SDF imaging, which is a hand-held vital microscope, and is listed as the inventor on related patents commercialised by MicroVision Medical (MVM) under a license from the Academic Medical Center (AMC). He receives no royalties or benefits from this license. He has been a consultant for MVM in the past but has not been involved with this company for more than five years now and holds no shares or stock. Braedius Medi-cal, a company owned by a relative of CI, has developed and designed a handheld microscope called CytoCam-IDF imaging. CI has no financial relationship with Braedius Medical of any sort, i.e., never owned shares, or received consultancy or speaker fees from Braedius Medical. The MicroTools software is being developed by Mathias P. Hilty (MPH) and owned by Active Medical BV of which CI and MPH are shareholders. Active Medical runs an internet site called microcirculationacademy. org which offers educational courses and services related to clinical microcirculation and provides more information regarding MicroTools. ∎

Key Points

- Circulatory shock remains a major contributor to mortality in critically ill patients.
- The enabling step for the successful treatment of patients in circulatory shock is timely diagnosis and understanding of the underlying pathophysiology.
- Direct insight into the function of the microcirculation in patients may reveal deficiencies in tissue red blood cell perfusion and abnormal leukocyte kinetics from the onset.
- Recent developments in advanced computer vision software such as realised in MicroTools are, for the first time, enabling the application of these technologies at the bedside.

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