EDITORIAL

Advances in Microcirculatory Assessment: A Game Changer in Sepsis Management or the Latest Fad?

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Sepsis causes organ dysfunction by triggering multiple pathways, most of which converge to cause microcirculatory dysfunction, impaired oxygen utilization, and ultimately tissue dysoxia and dysfunction.[1] The degree of microcirculatory dysfunction has been found to correlate with the severity of sepsis, organ dysfunction, and mortality.[1–4] Sepsis definition has evolved over years to include organ dysfunction and excluding macrocirculatory hemodynamic parameters. Regional microcirculatory dysregulation, an important mechanism of sepsis-induced organ dysfunction may or may not be reflected by the global macrocirculation.[5]

The microcirculation begins from the arterioles less than 100–200 µm and continues in the capillaries to the venules. Smooth muscles in the arterioles regulate the regional blood flow and the peripheral vascular resistance. The capillary network allows gas and nutrient exchange to and from tissues. The venules act as the capacitance vessels of the circulation.

Macrocirculatory hemodynamics are easier to assess and interpret, but are not the true reflection of microcirculation and tissue oxygenation. Various clinical parameters like capillary refill time, mottling, and lactate levels have been extensively studied as surrogates for microcirculation and still are relevant bedside clinical tools for decision-making.[6,7] These have shown to correlate well with the severity of sepsis.[6,7] They are also used as markers of fluid responsiveness and peripheral perfusion following vasopressor administration.[7]

Technological advancements in medical care have found their way into microcirculatory assessment for four decades. However, none of the modalities studied have been able to replace the clinical parameters. Near-infrared spectroscopy once extensively studied is no longer in production. Handheld videomicroscopy (HVM), laser Doppler flowmetry, and tissue oxygen assessment electrodes are currently being researched for the assessment of microcirculation. Video microscopic assessment of microcirculation by providing direct visualization of capillaries and blood flow has become the latest reverie of intensivists with a potential for a breakthrough in sepsis management.

The technology itself has evolved greatly over the years from orthogonal polarization spectral imaging involving complex calculations to sidestream dark field (SDF) imaging and the latest being the Cytocam-incident dark field (Cytocam IDF) illumination with automated data processing. The SDF technology used in the study in this issue of the journal by Anshumali Panda et al.[8] involves analysis of the sublingual region whereby a magnified image is obtained showing red blood cells (RBCs) and white blood cells (WBCs) flowing through the capillaries. Sublingual microcirculation has been found to correlate with intestinal mucosal microcirculation and is presumed to be representative of whole-body microcirculation.[9] The image is then processed to obtain various markers for interpretation of robustness of microcirculation. In sepsis, the regional microcirculatory dysregulation is seen as an increased capillary density network albeit decreased perfusion. Increased capillary density (De Backer density [dBD]) with paradoxical decreased functional capillary density, proportion of perfused vessels, and proportion of perfused vessels (small) along with increased flow heterogeneity index and flow velocities and reduced microcirculatory flow index (MFI) have been observed.[10] Most of these parameters have been found to correlate with the severity of sepsis.[11] HVM has also been used for assessments of microcirculation for various therapeutic interventions like fluid resuscitation,[4,12] inotropes,[13] nitroglycerin,[14] hydrocortisone[15] in sepsis and also in other pathological states.

Tascon et al.[12] found that early-phase resuscitation in severe sepsis was associated with an improved total and small vessel density and increased proportion of perfused small vessels. These changes failed to correlate with initial mean arterial pressure (MAP), cardiac index, and pulse pressure variation. The changes in lactate levels following fluid resuscitation correlated with the proportion of perfused small vessels and their density, but not with MAP and cardiac output. Like lactate, venous-to-arterial carbon dioxide difference [P(v-a)CO_2] has been correlated closely with the microcirculatory abnormalities in sepsis.[16]

Tascon et al.[12] in their limited number of patients showed a clear dissociation between markers of macro- and microcirculation. Microcirculation was seen to improve with fluid independence of initial MAP or cardiac output. Trzeciak et al.[4] showed similar results with improvement in microcirculatory flow velocities following fluid resuscitation without changes in global hemodynamic markers.

Boerma et al.[14] Failed to demonstrate any improvement in microcirculation indices following nitroglycerin administration in sepsis. Dobutamine failed to restore capillary perfusion in sepsis as shown by De Backer et al.

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Jhanji et al.[17] compared most available modalities of microcirculatory assessment and arterial waveform analysis by LiDCO to analyze the effect of different MAP targets using norepinephrine in sixteen patients. They found an increased global oxygen delivery with improved cutaneous microvascular flow and tissue oxygenation without improvement in sublingual microvascular flow using SDF imaging. Similar to the findings by Jhanji et al., Dubin et al.[18] found no improvement in sublingual microcirculation with a higher MAP target.

Changes in global hemodynamic parameters like mean arterial pressure and cardiac index did not correlate with parameters of microcirculation in all these studies.[1,11–14,18] Whether the improvement in microcirculatory parameters translates into real survival benefit is yet to be established. Trzeciak et al.[4] did show a correlation between MFI improvement following early goal-directed therapy and Sequential Organ Failure Assessment (SOFA) score after 24 hours.

These inconsistent responses in microvascular circulatory assessment tools make us question the validation of sublingual region as a true representation of global microcirculation but also open an avenue for further research and development.

The findings of the study by Anshumali Panda et al. were consistent with the existing data on a sublingual assessment by SDF imaging. The strength of the study in discussion is the large sample size (249 overall: 124 with sepsis and 125 without sepsis) compared to existing literature. Sublingual microcirculation assessment began from day 1 of admission in patients with suspected infection irrespective of the severity. Proportion of perfused vessels (small) was reduced in patients with sepsis and was found to have an inverse correlation with mortality. Density of vessel (dBD) overall and of small vessels was higher in sepsis, but did not correlate with mortality.

HVM data were collected for three subsequent days, allowing serial observations in patients with sepsis. In patients who died, proportion of perfused vessels (PPV) small was consistently low with a higher mean dBD small and large. Clinical deterioration or improvement, new-onset organ dysfunction, or effects of any therapeutic intervention during the four serial assessments of microcirculation could have been incorporated in the study and would have enhanced our current understanding. Crosscomparison with existing surrogates for microcirculation like capillary refill time, mottling score, and lactate levels and global hemodynamic markers were not done. The heterogeneity index and microvascular flow index were not included in the protocol as accepted by the authors due to its nonavailability at the time of protocol inception.

Though the studies on HVMs are numerous, it is yet to move from research arena to the bedside. This is attributed to limited availability, cost-effectiveness, and acquisition of technical skills. Unlike the macrocirculation, which provide a discrete target for resuscitation and therapeutic intervention, no such targets are defined with videomicroscopy.

The scope of these tools, namely HVMs, at present may be limited to research, but are still at cusp of expanding our knowledge. This direct noninvasive visualization of microcirculation is already incorporated in many protocols to study the effects of various therapeutic interventions and other pathological states apart from sepsis. The third-generation Cytocam IDF simplifies image acquisition and interpretation. This might bring HVMs to the forefront of sepsis management and open new avenues for research.

Only time and further research on these advanced modalities will tell us whether they provide a better target of resuscitation as compared to simpler tools like lactate or $P(v\text{-}a)CO_2$ or capillary refill and whether resuscitation based on these targets translates into an improvement of mitochondrial dysoxia in sepsis.

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