EDITORIAL

Mottling, Lactate, and the Microcirculation in Sepsis: Are We Back to Bedside Clinical Assessment after the Honeymoon with Technology?

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The microcirculation consists of arterioles, post-capillary venules, and capillaries, and their components play the most important role in exchange of gas, nutrients, and hormones. Hemodynamic resuscitation primarily focuses on parameters of macrocirculation, and the microcirculation is usually overlooked for multiple reasons. It is well known that sepsis and septic shock are associated profound disturbances of microcirculation. The postulated mechanism of this disturbance includes endothelial dysfunction, glycocalyx degradation, altered blood cell rheology (reduced RBC deformability), and imbalance between vasodilation and vasoconstriction.[1] Impaired microcirculation manifests clinically as a reduction in the oxygen extraction by the tissues, and it can occur in the presence of normalized systemic hemodynamic variables following resuscitation. This "loss of hemodynamic coherence" between the macrocirculation and microcirculation in sepsis is characterized by heterogeneity in capillary density, shunting blood flow, hemodilution, and use of high dose of vasopressors.[2] Persistent microcirculatory dysfunction is an independent predictor of organ dysfunction and morbidity, despite normalization of the macrocirculation. Thus, monitoring the microcirculation should become a quintessential part of hemodynamic monitoring. That's easier said than done! Unlike the macrocirculation, tools and methods to monitor the microcirculation have not been either well devised or calibrated or experimentally proven. Their availability is also an issue. Thus, certain clinical signs have classically been used as surrogate markers of impaired microcirculation, such as capillary refill time, skin mottling, core to toe temperature gradient, urine output, etc.

Skin examination provides important clues about tissue perfusion, and it has been known for many years. A cold skin is often considered to be associated with lowcardiac output state in a critically ill patient. More than 60 years ago, Altemeier et al. noted that a moist and cool skin on septic patients is a bad prognostic sign.[3] Mottling is a patchy skin discoloration and a relatively easy to access clinical sign (though not in dark skinned people!). It is due to heterogenic small vessel vasoconstriction and is thought to reflect abnormal skin microperfusion. Mottling score is based on the extension of mottling around the knee (ranging from 0 to 5) and a few recent studies found significant correlation between mottling and organ dysfunction and mortality in septic patients.[4,5] These studies have renewed our interest in these low-technology classical clinical signs to be used as markers of the adequacy of the microcirculation in sepsis and overall disease severity. The current Surviving Sepsis Guidelines emphasize monitoring the microcirculation and recommend measuring serum lactate which has been traditionally considered as a marker of tissue hypoperfusion.[6] Studies have been conducted to compare clinical parameters of hypoperfusion like capillary refilling time, mottling score with serum lactate.[7,8] The study in this issue of the journal, conducted by Ferraris et al., is one of the pioneering studies that assessed clinical utility of mottling in patient with sepsis and also explored if there is any correlation between appearance of mottling and high arterial lactate. Ferraris et al. prospectively observed hemodynamic parameters, lactate, and mottling in 43 patients. The median ages of the patients were 67 $\pm$ 4 years and mean sequential organ function scores were 11 $\pm$ 4. Patients were divided in two groups based on arterial lactate and study parameters that were recorded at admission and after 6 hours. The incidence of mottling was 75% in patient with lactate $\geq$2 mmol/L and 69% in patient with lactate <2 mmol/L. This difference did not reach statistical significance. After 6 hours of resuscitation, incidence of mottling was significantly higher in the high lactate group (86.2% vs 47.4%). However, incidence of mottling was not associated with increased morality.[8]

The authors attempted to explore an important aspect of hemodynamic resuscitation in sepsis and showed that presence of mottling was associated with high lactate levels. The importance of this finding lies on the fact that many a time occult sepsis is diagnosed by high arterial lactate in the absence other clinical sign. This study raises the possibility of mottling being a reliable sign of sepsis. Traditionally, lactate has been considered to be a result of tissue hypoxia. However, current research has shown there are many other causes of high arterial lactate. Hyperlactatemia may be due to deficit in oxygen delivery or impaired oxygen extraction, peripheral shunting, stress, increased adrenergic stimulation, and also due to a shift in metabolism to the glycolytic pathway from oxidative phosphorylation (OXPHOS) even in the presence of normal tissue

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oxygen levels. It is not clear which mechanism plays a major role in lactate production in sepsis. In a large analysis on 1,741 patients, after admission in ICU, it was found that only 35% of the patients had $ScvO_2 < 70\%$, while 65% had high lactate coexisting with normal or increased $ScvO_2$.[9] Since lactate is not produced in sepsis solely due to tissue hypoxia and impaired microcirculation, we need to find out whether there is also other mechanism apart from impaired microcirculation that explains the correlation between mottling and high lactate. In a previous study, Ferraris et al. showed that skin temperature measured with infrared thermography technology around the knee is lower when mottling sign is present, and cold periphery is an accepted sign of microcirculatory alterations.[10]

Mottling as an indicator of microcirculatory insufficiency has to be proved more convincingly by good-quality clinical studies. Videomicroscopy referred as Cytocam—Incident Dark Field (IDF) is considered to be the best technique at present for assessing the microcirculation at the bedside. It is computer-controlled high-resolution high-pixel density digital camera with an advanced computer-assisted software that allows automatic image analysis and almost immediate assessment of the microcirculation.[11] But evidence to support its clinical utility is yet to be found. Thus, assessing the utility of mottling to evaluate the adequacy of the microcirculation against a proven technology or methodology is a difficult task.

Although Ferraris et al. did not find mortality difference between patient with mottling and patients without it.[8] A large study of 259 septic patients observed that high mottling score is strongly associated with increased 14 days mortality.[4] In an observational study, mottling incidence was 29% in a non-selected cohort of 791 patients admitted to ICU and increased to 49% in patients with sepsis. Simplified acute physiologic score II" (SAPS II) was greater in mottled patients compared to those free of mottling.[12]

Mottling and mottling score are easily accessible bedside parameters. This study conveys an important message of interesting clinical utility—that mottling is associated with high arterial lactate and possibility that mottling is also a sign of sepsis. High levels of lactate have been associated with poorer outcomes in sepsis, but the evidence to suggest that targeting lactate levels to resuscitate patients of sepsis would improve outcome is still debated. The ANDROMEDA-SHOCK trial showed that using capillary refill time (CRT) to target resuscitation in sepsis may improve outcome.[7] Thus, bringing us back to the value of bedside clinical assessment, even in this age of high technology. In that context, would mottling scores and resuscitation targeting mottling be another bedside assessment tool to help resuscitation and outcomes in sepsis? This surely needs further evaluation and only time and further research will tell if we need to focus more on the basics of clinical assessment, rather than be seduced by technology.

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