Editorial

The post-cardiac arrest microcirculation: More than meets the eye?

The microcirculation with its endothelial lining is estimated to represent an area of 4000–7000 m² and is thus best viewed as the body’s largest integrated functional organ system. The individual microcirculatory unit composed of arteriole, capillary bed, and postcapillary venule is designed to ensure the delivery of oxygen and other nutrients to tissues as well as to remove products of metabolism. The endothelial lining of the microcirculation itself representing some 10^13 cells is a major target of exploration in critical care. Complicating its understanding in health and disease is the fact that there is no universal phenotype for the endothelium and that this phenotypic heterogeneity is likely to simply be a core property as it is with parenchymal cells of other organ systems.

For example, arteriole endothelium plays a major role in regulating vascular tone through a number of mechanisms such as signal transduction to vascular smooth muscle via blood cell to endothelial cell shear stress, while the postcapillary venular endothelium plays a role in leukocyte trafficking in response to various injuries. Both of the above functions are likely in part mediated by the endothelium’s glycocalyx structure where a dynamic equilibrium exists between it and plasma, which normally resist erythrocyte, leukocyte, platelet interaction.

In this issue of Resuscitation, Omar and colleagues examine the sublingual microcirculation in 30 post-cardiac arrest patients at 6 and 24h post arrest and hypothesize that improved outcomes would be associated with better microcirculatory flow. An interesting twist to this study is that the authors hypothesized that any microcirculatory dysfunction observed would be similar to that seen in severe sepsis and septic shock and so the microcirculation of a cohort of patients with severe sepsis and septic shock as well as healthy controls were also recorded and analyzed during the study period. They further attempted to demonstrate that any microcirculatory dysfunction observed in post-arrest patients would also be associated with systemic inflammatory markers found to be elevated in sepsis.

The authors report that, similar to previous limited reports, the microcirculatory flow index (MFI) in the post-arrest state was impaired compared to controls and improved overtime. Furthermore, this impairment in flow was similar to that observed in sepsis. Interestingly, subgroup analysis demonstrated that MFI did not significantly differ whether patients received therapeutic hypothermia, heparin, or vasopressors. MFI was found to be significantly higher at 24h in patients who survived with good neurologic outcome. The authors found the MFI was similarly impaired in patients with sepsis although no outcomes are provided. Lastly, the authors found no correlation between MFI and any of the systemic inflammatory markers measured. In addition, no correlations were found between MFI in post-arrest patients and lactate levels.

This study, while providing some interesting insights really raises more questions than it answers as well providing insight into how future studies should be performed. The authors correctly point out several important limitations such as the small number of subjects, lack of more global and central oxygen transport measures (such as central or mixed venous hemoglobin oxygen saturation values), and no inflammatory marker data collected on the sepsis cohort. These issues prevent us from proper matching of groups in an attempt to connect changes in the microcirculation of a local site with that occurring at a central and wider systemic level and its potential effect on acute inflammation across global systemic insults such as cardiac arrest and sepsis which may share significant pathophysiologic overlap. Examination of the paper’s figure and Table 2 demonstrate the wide overlap of MFI values between groups and subgroups, which underscore the complexities of using microcirculatory indices such as MFI to gain definitive pathophysiological insights.

Several challenges exist before intravital microscopy of the human microcirculation can reach its full potential either as a research or clinical tool. These challenges are a combination of technology and knowledge gaps. On the technology side, as the authors point out, routine video quality still poses a tremendous hurdle and this is in large part may be user dependent. Significant motion artifact can be produced either by the user or the patient. Low flow and capillary density artifacts resulting from too much pressure remain a concern. A normal microcirculation can appear to be changed into one of severe shock by simply applying too much pressure to the probe. This is compounded by the unknown degree of functional heterogeneity of the microcirculation even at various sites in the sublingual region, remembering that the field of view provided by the probe is less than 1 mm². Do different shock states (sepsis, hemorrhage, post-arrest) produce a difference in the heterogeneity and if so, how many sites should be sampled and averaged? The analysis of the videos also provides users a tremendous challenge. The authors and others have previously gone to great lengths to develop and report on a video quality review system which will be helpful in the field. They have used MFI to quantitate and infer function of the microcirculation but even then the MFI metric used is semi quantitative. Others who use functional capillary density face even greater challenges in their analytics. While both flow and geometric indices have proved to be of value,
each is time consuming in its analysis. Improvements in technology for example that could provide continuous monitoring in a larger field of view and that would also mitigate against motion and pressure artifacts would be a boon for the this technique from both a research and clinical perspective. Development of robust automated software techniques to analyze videos at the bedside would also greatly assist in standardizing measures as well as helping to eventually make the information actionable from a clinical decision assist tool.12,13 As it stands now, the technique simply allows us a snap shot as opposed to the more valuable dynamic picture that may be needed to capture data that will help us answer important questions as it relates to the microcirculation and critical care.

However, even if all of the technology gaps described above were filled, intravital microscopy of the sublingual microcirculation still requires more research to clearly determine its usefulness as either a research or a point-of-care clinical decision making tool. Similar to most studies, the current study seems to make some assumptions that changes in the microcirculation reflect global changes including those in other organ systems such as the splanchnic bed and perhaps even the brain. While there is some evidence that the sublingual microcirculation is a reflection of small vessel disease in chronic condition such as cerebrovascular disease (in humans), evidence is a bit mixed between animal models of sepsis and humans as it relates to correlating early and late changes in the sublingual microcirculation to that of the splanchnic bed.14–16 In animal models of cardiogenic shock and hemorrhage, the brain’s microcirculation appears to be preserved despite significant decreases in the oral microcirculation.17,18 Confounding this are the potential effects of treatment protocols such as hypothermia, vasopressor use, and other treatments, which might further differentially affect the microcirculation and its function across organ systems.

In addition to this knowledge gap, are the gaps in understanding if visually observable changes in the microcirculation provide enough key insights into whether they will correlate with inflammatory changes that can be attributed to microcirculatory or endothelial injury? As mentioned earlier, the ultrastructure of the endothelium in the form of its glycocalyx is now the topic of great study in critical care. The current dark-field and related orthogonal polarization spectroscopy used is the current and similar studies are not capable of visualizing the glycocalyx.19,20 Thus, in terms of comparing the microcirculation and its function in post-cardiac arrest patients and those of sepsis patients, perhaps examining markers of endothelial cell injury such as the shedding of syndecan-1 (the major cell membrane protein of the glycocalyx) might be better than examining more generalized makers of inflammation.21–25 In fact, as many believe there is overlap in pathophysiology between global tissue hypoxia of cardiac arrest and that of sepsis and multisystem trauma, examining viscoelastic properties of blood coagulation might provide improved functional insight into microvascular injury since it can be argued that the inflammatory and coagulation systems cannot be separated form one another and that there common nexus occurs at the endothelium.26–33 It is not unreasonable to assume that in cardiac arrest, given the massive ischemic burden that it produces coupled with the complex post-resuscitation care it many times required, that an endotheliopathy is produced.

So while much emphasis (and rightly so) has been placed on achieving consensus on how to visually examine and score the sublingual microcirculation, perhaps more consensus is required to determine what co-variables of endothelial cell injury and function should be examined. This would allow an approach to the microcirculation in critical illness and injury reflective of the complex organ system that it really is.

Conflict of interest

Dr. Ward holds intellectual property through Virginia Commonwealth University on techniques used to evaluate the microcirculation.

References


Kevin R. Ward (MD)∗
Department of Emergency Medicine, Michigan Center for Integrative Research in Critical Care, University of Michigan, USA

∗Tel.: +1 734 764 6706.
E-mail address: keward@umich.edu

30 September 2013
30 September 2013