



The Microcirculatory and Mitochondrial Distress Syndrome (MMDS): A New Look at Sepsis

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Regional tissue dysoxia caused by microcirculatory dysfunction leading to mitochondrial depression underlie the condition in sepsis and shock where despite correction of systemic oxygen delivery variables, regional dysoxia and a deficit in oxygen extraction persist. This condition we have termed the Microcirculatory and Mitochondrial Distress Syndrome (MMDS) to identify the compartments and pathophysiology of this condition (1). In this view, MMDS is defined by the initiating condition leading to sepsis and genetic profile of the patient and also by the time the condition has persisted, and the treatment regime being followed. It has been shown in recent clinical studies that persistence of microcirculatory and mitochondrial distress indeed occurs in the presence of corrected systemic hemodynamics (2-7). It can also be considered that sepsis being treated with steroids, for example, has a substantial different pathophysiology than sepsis without steroids, underscoring the importance of the defining role of therapy in terms of its pathophysiology. The Rivers study has highlighted the importance of time as a pathogenic factor, a finding supported by recent sub-lingual microcirculation measurements (6). In a recent study we investigated how time defines the nature of microcirculatory alterations in MMDS. Here we investigated the nature of microcirculatory alterations in the sub-lingual area and in the intestines of patients who have undergone surgery for placement of a stoma and who subsequently developed abdominal sepsis. Comparison of the microcirculatory alteration in day 1 to day 3 of sepsis showed that in early sepsis microcirculatory alterations were regional in nature with no correlation between sublingual and intestinal microcirculatory alterations. In day three however microcirculatory alteration had become systemic in nature with correlation between sublingual and intestinal microcirculatory alterations (16). The difficulty in diagnosing MMDS lies in the lack of sensitivity of systemic hemodynamic parameters to detect microcirculatory dysfunction at the bedside and the lack of adequate techniques to monitor the microcirculation. This can lead to microcirculatory perfusion deficits persisting for extended periods of time and leading to lack of tissue oxygenation, organ failure and death. Microcirculatory dysfunction in MMDS is hidden from the systemic circulation due to the shunting of weak microcirculatory units in various organs (8). Here oxygen transport goes

straight from the arterial to the venous compartment leaving the regional microcirculatory units hypoxic. This has been demonstrated in many studies using clinically relevant large animal models of shock, sepsis and resuscitation. Using OPS imaging for monitoring sublingual microcirculation, de Backer and co-workers showed a correlation between the severity of microcirculatory alterations and outcome in septic patients, whereas no such relation existing with conventional systemic hemodynamic and oxygen derived parameters (2). In a more detailed study, Sakr et al. showed that unresponsive sublingual microcirculatory capillary flow not corrected within 24 hours after on-set of septic shock predicted outcome whereas systemic hemodynamic and oxygen derived variables as well as the type and amount of drugs administered was not related to survival from sepsis (5).

Based on the idea that active recruitment of the microcirculation is needed for adequate resuscitation from sepsis we hypothesized and confirmed in a clinical study by direct observation of sublingual microcirculation using OPS imaging, that vasodilator therapy effectively recruited obstructed microcirculation in pressure resuscitated septic patients (4). DeBacker and co-workers recently showed in septic patients that dobutamine (6) and activated protein C (9), while showing marginal effects on systemic hemodynamics, showed significant improvement of microcirculatory perfusion. Thrombolysis therapy using a recombinant tissue plasminogen activator in fulminant purpura was effective in recruiting sublingual microcirculation with little systemic effects (10). In a case study Boerma showed that potent vasoconstrictors while improving systemic hemodynamics can immobilize the microcirculation and lead to bad outcome (12). These considerations led us to define Microcirculatory Recruitment Maneuvers as interventions aimed at vasodilatation, inotropic improvement, control of coagulation, control of iNOS expression and improving endothelial cell function by anti-inflammatory measures (15).

Diagnosis and treatment of MMDS requires reliable tools aimed at monitoring the physiology of the microcirculation. These clinical microcirculatory investigations described above were mainly made with OPS imaging and its recent



improved version of SDF imaging (1,11,15). These devices are hand-held microscopes for video observation of the microcirculation at the bed side mostly applied sub-lingually. Quantification of the images can be accomplished by a scoring system aimed at quantification of the flow in the various order microvessels are used (14). A classification of the types of microcirculatory alterations observed in various disease states found 5 basic categories of abnormalities (15). These abnormalities were defined according to the disease state as well as to the therapy being applied. improved techniques and methods will allow a more detailed insight into the cellular components of the microcirculation. Future clinical investigations aimed at the response of the microcirculation to disease and therapy, in relation to organ function and outcome will be needed to optimally diagnose MDDS and guide therapy. Whether resuscitation procedures aimed at correcting microcirculatory distress will result in improved outcome, will need to be determined in future investigation. it is possible that following microcirculatory recruitment manoeuvres mitochondrial dysfunction may persist and that further resuscitation maneuvers may be needed directed at the mitochondria. For this purpose however new clinical techniques will need to be directed at measurement of mitochondrial function at the bed-side. We indeed recently developed such a techniques which has the potential to measure mitochondrial pO₂ in vivo (17). it is expected that combination of this technique with microcirculatory measurements will provide new insights into sepsis and its treatment and possibility new resuscitation end points.

Declared interests: Can ince is Chief Scientific Officer of Microvision Medical, an Academic Medical Center based company dedicated to the production of devices for microcirculatory imaging.

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