Metabolic resuscitation in sepsis: a necessary step beyond the hemodynamic?

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Abstract: Despite the advances made in monitoring and treatment of sepsis and septic shock, many septic patients ultimately develop multiple organ dysfunction (MODS) and die, suggesting that other players are involved in the pathophysiology of this syndrome. Mitochondrial dysfunction occurs early in sepsis and has a central role in MODS development. MODS severity and recovery of mitochondrial function have been associated with survival. In recent clinical and experimental investigations, mitochondrion-target therapy for sepsis and septic shock has been suggested to reduce MODS severity and mortality. This intervention, which might be named "metabolic resuscitation", would lead to improved mitochondrial activity afforded by pharmacological and nutritional agents. Of particular interest in this therapeutic strategy is thiamine, a water-soluble vitamin that plays an essential role in cellular energy metabolism. Critical illness associated with hypermetabolic states may predispose susceptible individuals to the development of thiamine deficiency, which is not usually identified by clinicians as a source of lactic acidosis. The protective effects of thiamine on mitochondrial function may justify supplementation in septic patients at risk of deficiency. Perspectives of supplementation with other micronutrients (ascorbic acid, tocopherol, selenium and zinc) and potential metabolic resuscitators [coenzyme Q10 (CoQ10), cytochrome oxidase (CytOx), L-carnitine, melatonin] to target sepsis-induced mitochondrial dysfunction are also emerging. Metabolic resuscitation may probably be a safe and effective strategy in the treatment of septic shock in the future. However, until then, preliminary investigations should be replicated in further researches for confirmation. Better identification of groups of patients presumed to benefit clinically by a certain intervention directed to "mitochondrial resuscitation" are expected to increase driven by genomics and metabolomics.

Keywords: Mitochondria; sepsis; multiple organ failure; oxidative stress; thiamine; selenium

Early and appropriate hemodynamic resuscitation is of paramount importance for survival in septic shock patients. Mortality and morbidity severity are dependent on its adequacy (1,2). Despite of attainment of the resuscitation goals, many septic patients ultimately develop multiple organ dysfunction syndrome (MODS) and die, suggesting that other players are involved in the pathophysiology of the syndrome (3,4).

Mitochondria are the powerhouses of the cells. Approximately 98% of the available oxygen to the cells are used by these organelles, whose most important function is the generation of energy through the Krebs cycle. Besides energy generation, mitochondria are responsible for heat generation and thermoregulation, intracellular calcium homeostasis, production of reactive oxygen species (ROS) that are involved in immunity and signaling pathways, and biosynthesis (e.g., cortisol, hypoxia-inducible factors, vascular endothelium growth factor). They also regulate cell death mechanisms (necrosis and apoptosis) (5).

Mitochondrial dysfunction occurs early in sepsis and

has a central role in MODS development. MODS severity and recovery of mitochondrial function are associated with survival (6,7). Factors indirectly related to oxygen delivery (DO_2) seem to contribute to this dysfunction. It has been proposed that inflammatory signaling leads to oxidative phosphorylation impairment and abated mitochondrial activity (8). Minimal or absent ultrastructural and histopathologic alterations were observed in organs of patients with sepsis-associated MODS, suggesting that the abnormality is primarily functional rather than structural, and potentially reversible. In this way, MODS may represent an adaptive, protective and reactive response to overwhelming inflammation triggered by systemic infection (9). The activation of a "danger response" pathway in cells drives a reduction in cellular activity beyond the level of maintenance of basic cellular integrity. Under this condition, cells suppress some energy-dependent activities in favor of those that are essential for cell survival. Reduced cellular metabolism could increase the chances of cell survival, and thus organs, when confronted with such a devastating injury. Evidence of myocardial "hibernation" recently reported in experimental animal models of sepsis corroborates this theory (10). Acute kidney injury, reduced hepatic synthesis function and cholestasis, and reduced pulmonary Na-K ATPase activity frequently reported in septic patients may represent organ dysfunction consequent to this adaptive cellular response.

Adequate hemodynamic resuscitation is not enough for survival

In recent years, many improvements in hemodynamic optimization in sepsis and septic shock have been made. Early and aggressive, but not excessive fluid resuscitation has been recommended (11). The role of albumin in septic fluid resuscitation has been clarified (11-13). Data regarding the effects of the class and intensity of inotropes treatment on the hemodynamic and microcirculatory parameters are increasing (14,15). Extracorporeal life support for treatment of the refractory cases has been recommended and saved a significant number of lives (16).

In parallel, improvement in monitoring has allowed for a better adjustment of the therapy, minimizing the hazards of both over and under-treatment. Methods of non-invasive cardiac output monitoring, such as echocardiography and ultrasonic cardiac output monitor (USCOM) are available bedside and have their use incorporated in many intensive care units worldwide (17,18). Improvement in

microcirculatory monitoring has revealed that profound derangements may be present in septic patients; timely reversal of these abnormalities impacts positively on the outcomes (19). Central venous oxygen saturation, lactate clearance and arterial-venous CO_2 gradient has helped treatment (20,21).

Notwithstanding these notable advances, current sepsis mortality rates still remain high. The reported mortality rates from studies focusing on early resuscitation in septic shock in adults are in the range of 18.2% to 30.5% (22-25). For children, in-hospital mortality rate for severe sepsis was estimated at 10.3% (26). Mitochondrion-target therapy is being regarded as a reasonable and promising strategy to prevent, mitigate or reverse MODS and reduce sepsis mortality. This intervention might be named "metabolic resuscitation".

Metabolic resuscitation as a possible, safe and effective strategy

A few clinical trials and a larger number of experimental investigations have reported improved mitochondrial activity and positive effects on the outcome driven by pharmacological and nutritional management strategies. Although preliminary, the results point to the need of advances in research.

Micronutrients as metabolic resuscitators

Thiamine

Of particular interest in metabolic resuscitation is thiamine (vitamin B1), a water-soluble vitamin that plays an essential role in cellular energy metabolism. Thiamine is a cofactor for the multienzyme pyruvate dehydrogenase (PDH) complex and is essential for converting pyruvate from glucose into acetyl coenzyme A for entry to the Krebs cycle with subsequent oxidative phosphorylation and generation of ATP. If there is thiamine deficiency, pyruvate is converted to lactate rather than converted to acetyl-CoA by PDH to enter the Krebs cycle, resulting in cellular energy deficit and lactic acidosis (27). Thiamine serves also as a cofactor for alpha-ketoglutarate dehydrogenase, an enzyme of Krebs cycle and for transketolase, a key enzyme for the pentose phosphate pathway and the production of NADPH.

Critical illness associated with hypermetabolic states may predispose susceptible individuals to the development of thiamine deficiency. Conversely, clinicians do not usually

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identify thiamine deficiency as a source of lactic acidosis in severe sepsis/septic shock (28). In the majority of reports in the literature on lactic acidosis as a result of thiamine deficiency in critically ill patients, a dramatic improvement in clinical condition of patients has been shown after thiamine administration (29,30). Fatal cases have been reported, including one patient who died of refractory metabolic acidosis and shock and the diagnosis was reached post mortem (31,32).

Starting from the premise that a relative or absolute thiamine deficiency state could exist in patients with septic shock, Donnino *et al*. carried out a study to test the hypothesis that the administration of thiamine in such patients would lead to a reduction in lactate serum levels and that this effect would be greater in those with absolute thiamine deficiency. The authors measured baseline plasma thiamine concentrations in 79 patients with septic shock and increased serum lactate (>3 mmol/L). Of these, 28 (35%) were thiamine deficient (15 in the thiamine group and 13 in the placebo group). Thiamine and placebo groups did not differ regarding clinical outcome. However, among the 28 patients with thiamine deficiency, lactate was lower after 24 hours in the subgroup who received thiamine compared to placebo, and survival curves showed a difference in time to death between thiamine and placebo groups. The hypothesis that thiamine supplementation would be effective in decreasing serum lactate for the whole group was not confirmed; however, thiamine was effective in the subgroup of patients with thiamine deficiency (33). Among the limitations of this well conducted study is the small sample size for the thiamine deficient group. In addition, the impact of the analysis would have greater meaning if it had been controlled for inflammatory response (e.g., C-reactive protein). Plasma concentration represents only a small portion of the total body thiamine (less than 5% of the circulating thiamine diphosphate concentration), and systemic inflammatory response may result in transiently decreased micronutrient concentrations in plasma independent of tissue stores (34). Thiamine concentrations in whole blood or in red blood cells are likely to be more reliable indicators of body stores in the presence of systemic inflammation.

To our knowledge, the study by Donnino *et al*. was the first clinical trial designed to ascertain if the administration of intravenous thiamine in patients with septic shock would lead to a reduction in lactate (33). It will be important for future research to reproduce the results of this study by including larger samples of thiamine deficient patients or

stratifying based on that diagnosis. In practical terms, the key messages that can be drawn from this and other studies are: (I) we should be aware of the role played by thiamine deficiency in lactic acidosis in severe sepsis and septic shock states; (II) routine administration of intravenous thiamine would be justified during the acute phase of critical illness until full enteral intake is reached. Thiamine supplementation should be considered particularly for patients with risk factors for thiamine deficiency, which include malnutrition, alcoholism, chronic wasting diseases, renal replacement therapy, hyperemesis gravidarum, anorexia nervosa, gastric bypass surgery and refeeding. Lactic acidosis resulting from thiamine deficiency is an often overlooked but easily treated condition that should be suspected in patients of otherwise unexplained elevated serum lactate (29). Intravenous formulation of thiamine is cheap, extensively available and safe for administration. Considering that thiamine deficiency has shown a non-negligible prevalence in adult and critically ill children, we have recommended its supplementation in the presence of risk factors (35).

Ascorbic acid, tocopherol, selenium and zinc

Perspectives of supplementation with other micronutrients to target sepsis-induced mitochondrial dysfunction are emerging from experimental studies. Previous treatment of monocytes with dehydroascorbic acid, a bio-available isoform of vitamin C, induced an increased expression of superoxide dismutase and catalase resulting in a cytoprotective antioxidant effect after exposure to lipopolysaccharide. Such effect was not evidenced with the other isoform (ascorbic acid) (36).

The mitochondrial antioxidant system may be overwhelmed during sepsis. Antioxidants targeted to the matrix provide better protection than untargeted ones. Conjugation of one antioxidant to the lipophilic cation triphenylphosphonium (TPP) that concentrates in the matrix has been tested as a strategy to reach this goal. Mito-Vit-E, a TPP-conjugated form of tocopherol (vitamin E), protects mitochondria and whole cells from oxidative stress. In a septic animal model, it reduced myocardial injury, diminished apoptosis and ameliorated cardiac morphology. An inferior effect has been obtained for non-targeted vitamin E analog (37,38).

When incorporated to selenoproteins, selenium protects the organs and tissues from damage caused by oxidative stress (39). Zinc protects against oxidative stress through

the antioxidant metalloenzyme copper-zinc superoxide dismutase and by regulating metallothioneins that have roles in free radical scavenging and inflammatory processes. Mertens *et al.* reported combined suboptimal zinc and selenium plasma concentrations in critically ill patients that were associated with marked oxidative damage to proteins and lipids. In their clinical and experimental study, the authors have also shown that, in human cultured endothelial cells, higher zinc and selenium concentrations improve mitochondrial function in conditions mimicking sepsis (40). In critically ill pediatric patients, increasing selenium concentrations were associated with better outcomes during the ICU stay (41). Increased survival and reduced morbidity were associated to zinc supplementation in preterm (42). High-dose selenium has been shown to decrease mortality in adult patients with sepsis, but given the significant heterogeneity in the different trials, whether septic patients may benefit from selenium and zinc supplementation still deserves further investigation (43-45).

Other putative metabolic resuscitators

Several other potential interventions aimed at restoring the mitochondrial function in sepsis exist, but their clinical benefit still remains to be proven (38,46). Coenzyme Q10 (CoQ10) is a component of mitochondrial electron transport chain. It acts by carrying electrons from complex I and II to complex III. Low CoQ10 levels have been found in plasma of patients with septic shock. Oral or nasogastric administration of ubiquinol (a reduced form of CoQ10) resulted in improved levels of CoQ10 in these patients (47).

L-carnitine is essential for mitochondrial fatty acid -oxidation. Disruption of mitochondrial electron transport inhibits this process, resulting in accumulation of long chain acyl-CoA. Palmitoyl-CoA induces the mitochondrial inner membrane permeability transition and consequent dysfunction. In a pharmacometabolomic study enrolling vasopressor dependent septic shock patients, a subgroup of patients with favorable response to the treatment with L-carnitine (low-ketone group) was identified (48).

Cytochrome oxidase (CytOx), the terminal oxidase of the electron transport chain, is inhibited in the septic heart. In a sepsis animal model, caffeine injection restored myocardial CytCOx activity, improved cardiac function and increased survival of survival compared with saline injection (49).

Melatonin and its metabolites accumulate in the mitochondria and have potent antioxidant properties. In a phase I clinical trial melatonin was shown to reduce oxidative stress, inflammation and mitochondrial dysfunction in septic patients (50).

Now and the future

Regarding the protective effects on mitochondrial function, thiamine supplementation deserves a consideration in septic patients at risk of thiamine deficiency. Selenium and zinc should be given at the recommended doses from the first day of nutritional support, aiming to improve antioxidant function; doses around or below the tolerable upper intake level (UL) should be sufficient to correct previous deficiency. The other interventions seem far from clinical routine yet.

Better identification of groups of patients presumed to benefit clinically by a certain intervention directed to "mitochondrial resuscitation" are expected to increase driven by genomics and metabolomics. Like for other therapeutic interventions in septic patients, appropriateness will be strongly determined by the time of the intervention. Prevention or attenuation of mitochondrial dysfunction is preferable to reversing it and therapeutic interventions will probably be different according to the stage of the dysfunction. Future researches will open new perspectives in sepsis treatment that may result in positive clinical trials.

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Footnote

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