Metabolic failure

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Definitions

"Shock" is currently defined as a state of inadequate perfusion and oxygenation of the body's organs. This definition should probably be expanded to include ". . .and/or a cellular failure to utilize oxygen," as it is becoming increasingly apparent that the multiple organ dysfunction underlying severe sepsis and other extreme cardiorespiratory pathophysiologies also involves cellular respiration directly. The ensuing metabolic failure represents an inability of the cell to perform normal processes such as protein synthesis, DNA repair, and membrane pump activity. When this failure is sufficiently severe and widespread, organ function is compromised.

This metabolic failure may be occasionally related to significant amounts of cell death, as in irreversible brain injury after a prolonged cardiac arrest or myocardial infarction after a coronary thrombosis. However, in the majority of shock situations, the insult is not so severe and abrupt as to immediately compromise cell viability and thus cause necrotic or apoptotic cell death (1). Nevertheless, these affected (albeit normal-looking) organs still become dysfunctional and may fail to maintain an acceptable degree of homeostasis, both functionally and biochemically. An example is the anuria and azotemia seen with acute renal failure.

Any putative mechanism must therefore account for the development of organ dysfunction in the absence of cell death. It must also be compatible with the high likelihood of functional recovery, as witnessed in the majority of survivors of critical illness, even in those organs with poor regenerative capacity (2). One paradigm describes a metabolic shutdown resulting from an inadequate supply of energy to power the various cellular processes (3). Because >95% of adenosine triphosphate (ATP), the body's primary energy currency, is provided by mitochondrial respiration, pathologic mechanisms affecting these organelles can plausibly explain the development of organ failure after a severe systemic inflammatory insult (Fig. 1).

History of Discovery

Sepsis presents multiple paradoxes, many of which have been misconstrued or inadequately addressed. During the 1980s, recognition of an elevated mixed venous oxygen saturation and a concurrent lactic acidosis in septic patients spawned the concept of altered oxygen supply dependency and a heavily promoted strategy of driving the circulation with fluids and high-dose inotropes to achieve "supranormal" levels of oxygen delivery and consumption. Although this proved successful in high-risk surgical patients (4), outcomes were adverse when applied to critically ill patients in established organ failure (5).

We now appreciate that sepsis-induced lactic acidosis is related to increased activity of muscle Na^+ pumps rather than anaerobic metabolism secondary to inadequate tissue perfusion (6). Septic patients and laboratory models also demonstrate elevated tissue oxygen tensions in gut, bladder epithelium, and skeletal muscle (7–9). This is in marked contradistinction to other shock states induced by hemorrhage, hypoxemia, or heart failure in which tissue Po_2 is reduced (9–11). As this variable represents the balance between local oxygen supply and demand, the elevated values found in sepsis imply a pathologic process relating to abnormal cellular utilization of oxygen rather than microvascular shunting, thereby accounting for the elevation in mixed venous oxygen saturation. Of note, survivors were characterized by a subsequent decrease in tissue Po_2 to normal levels (9), suggesting an inherent cellular capacity to recommence normal metabolic activity in the right circumstances. Other findings provide further support for this "cytopathic dysoxia" theory. For example, sepsis is commonly considered a hypermetabolic condition because patients are often febrile with a high-output circulation. However, published data usually report the converse in both adults and children (12, 13). One study (12) demonstrated that an increasing severity of sepsis was associated with a progressive decrease in oxygen consumption such that septic shock patients had resting energy expenditure levels equivalent to healthy subjects, although an increase in resting energy expenditure was noted during recovery.

Mitochondrial activity is controlled by numerous extrinsic factors, including levels of ATP, local Po_2, and reactive oxygen species. Numerous hormonal influences (e.g., thyroid hormones, leptin, catecholamines, and corticosteroids) also mediate their actions partly through influencing mitochondrial respiration. Nitric oxide and its metabolite peroxynitrite are potent inhibitors of the electron transport chain, with variable duration effects depending on the levels produced (14). Sepsis is the classic condition in which large amounts of nitric oxide are generated systemically. Indeed, numerous studies have confirmed an inhibitory effect of nitric oxide on mitochondria in both septic patients and in laboratory models (15–17). Apart from respiratory complex inhibition, studies also describe physical damage to mitochondria that varies across organs and depends on sepsis severity (18).

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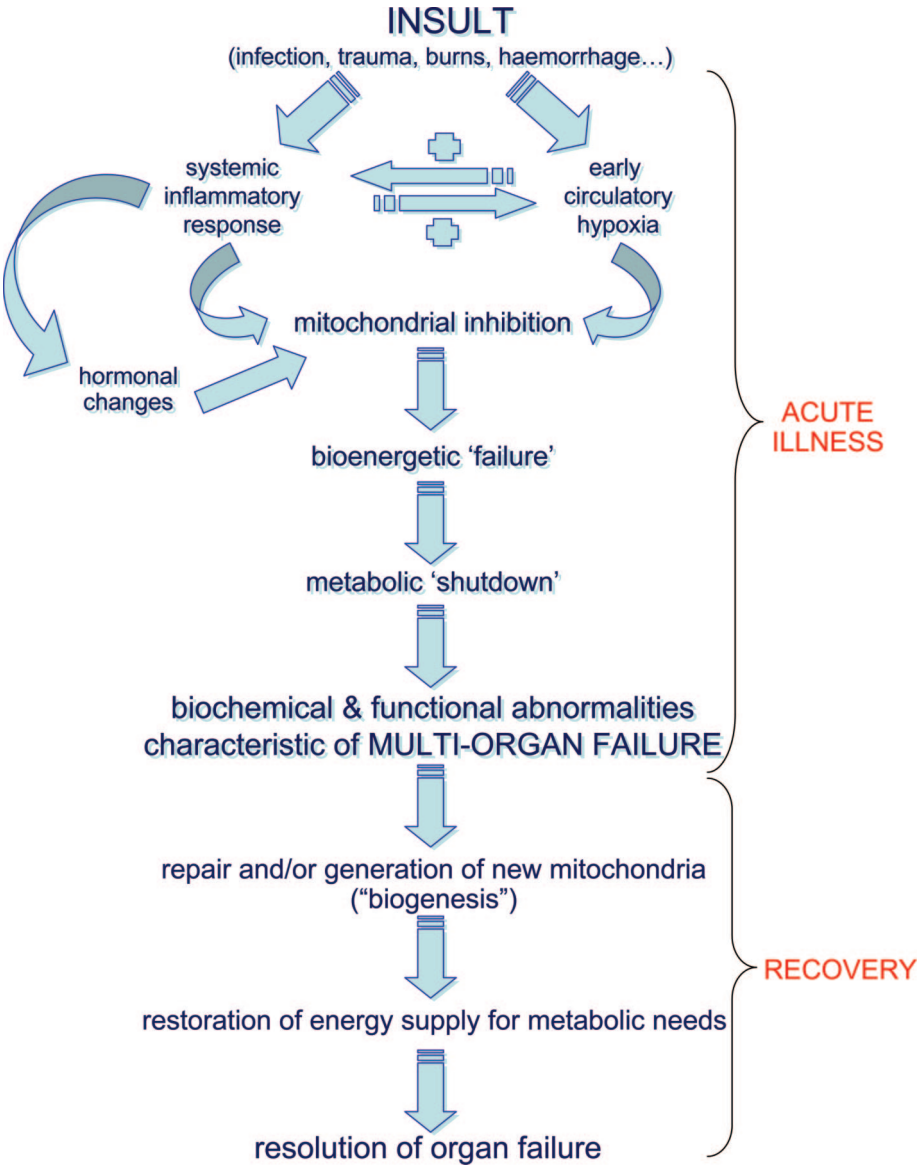

Figure 1. Suggested metabolic failure paradigm for organ failure development and recovery.

Why It Is Important in Health and Critical Illness

To function normally, cells need an adequate supply of oxygen and substrate to fuel aerobic respiration. In health, this is only limited at extremes of exercise or altitude, although adaptations occur with training and acclimatization to enable enhanced performance. Multiple physiologic and biochemical adjustments are recognized, including angiogenesis, changes in mitochondrial density and activity, increased glycolytic activity, altered substrate utilization, shifts in the oxyhemoglobin dissociation curve, erythropoiesis, and so forth.

In disease states in which supply is limited by critical decreases in cardiac output, hemoglobin concentration, or arterial oxygen saturation, continued functioning of the cell in the absence of sufficient energy to fuel metabolism will deplete ATP stores. Once a critical threshold of ATP is reached, cell-death pathways are triggered.

In sepsis, in which mitochondrial injury develops over hours rather than seconds, ATP levels are reduced in very severe cases although not, as described above, to the point at which cell death becomes a major characteristic (15). However, normal ATP levels are often reported in sepsis despite concurrent ultrastructural or biochemical evidence of mitochondrial damage and dysfunction (15, 18). Glycolytic (anaerobic) respiration can support shortfalls in aerobic ATP production, although only to a limited extent and over relatively short periods. The reduction in oxygen consumption and elevation in tissue P_{O_2}, with concurrent mitochondrial dysfunction and maintained ATP levels, thus suggests a decrease in ATP turnover during prolonged sepsis. This "energy failure" reduces cellular metabolic activity, leading to a dysfunctional state perceived as organ failure but perhaps better considered as an adaptive "programmed" metabolic shutdown to enable long-term survival in the face of a severe and prolonged insult (3). This is analogous to hibernation as found in wintering animals and in the human heart during prolonged ischemia. Although yet to be conclusively shown, this remains an attractive hypothesis.

Developing this theme further, resolution from organ failure will equate to cells emerging from this state of dormancy. If energy failure is the primary driver of the metabolic shutdown, repair or regeneration of mitochondria are fundamental to recovery. This process is known as mitochondrial biogenesis (19). An interesting aside is that antibiotics acting through inhibition of protein synthesis will affect biogenesis (20). This is not altogether surprising considering the evolutionary relationship between bacteria and mitochondria.

If proven, this concept of metabolic failure presents an important new therapeutic avenue whereby steps can be taken to prevent mitochondrial dysfunction by early resuscitation to abolish or minimize tissue hypoxia (21), by augmenting mitochondrial defense mechanisms (e.g., glutathione, manganese-superoxide dismutase) (22, 23), or by modifying substrates (24, 25). In established organ failure, techniques to stimulate mitochondrial regeneration, for example, by increasing expression of the biogenetic factor PGC-1α (26), may hasten resolution and recovery.

How It Is Measured

An abundance of research tools but, as yet, no routinely used bedside monitoring devices are available to assess mitochondrial function and metabolic failure *in vivo*. As mentioned earlier, the origins of hyperlactatemia in sepsis are not related to tissue hypoxia, so its utility as a marker of metabolic failure is questionable. Monitoring of oxygen consumption can be performed readily at the whole-

body level, but measuring individual organ utilization is much more invasive. Furthermore, $\dot{V}O_2$ measurements cannot ascertain what proportion is being used to generate ATP and what is consumed in other processes such as reactive oxygen species generation and mitochondrial uncoupling. Measurement of tissue PO_2 can be performed in muscle, bladder, and other tissues (7–11) in which an elevated level would be suggestive of decreased mitochondrial utilization. The redox status of mitochondrial respiratory enzymes can be assessed noninvasively in various tissues. Although absolute values cannot be determined, changes can be followed. Examples include nicotinamide adenine dinucleotide (NADH) fluoroscopy (10, 27) and near-infrared spectroscopy (28). NADH fluoroscopy assesses the redox state of complex I, the first enzyme in the electron transport chain and the one that seems most affected by sepsis. Near-infrared spectroscopy can noninvasively measure the redox status of cytochrome oxidase, the oxygen-consuming enzyme at the end of the chain. Phosphorus-31–magnetic resonance spectroscopy can measure nucleotide levels *in vivo*. Using the technique of saturation transfer, this can be further extended to assess ATP turnover (29).

Tissue samples can be taken allowing mitochondrial biochemical function and oxygen consumption to be assessed *ex vivo*. However, tissue sampling is generally limited for ethical and safety reasons in septic patients, and only muscle, fat, and blood cells are readily and safely accessible. The relevance of findings in blood cells to solid organs is still unknown. However, erythrocytes contain no mitochondria and are purely glycolytic. Neutrophils also produce a greater proportion of their ATP from glycolysis and consume a greater proportion of oxygen for their phagocytic respiratory burst.

Caveats

The major caveat is that although a clear association exists between mitochondrial dysfunction, metabolic failure, and multiple organ failure, causation has yet to be proved. All these findings could simply be epiphenomenal, although the degree of mitochondrial abnormality found across patients and laboratory models does imply at least some involvement in the pathologic process. I have yet to hear an alternative yet equally plausible hypothesis that satisfactorily explains how systemic inflammation produces organ failure, so it does seem to be worth pursuing at least a little further.

Example

In, say, 10 yrs' time, one could envisage a management plan whereby a sick patient admitted to the emergency room is resuscitated with fluids to an end point of cellular well-being as judged by tissue PO_2 and no further change in mitochondrial redox status. A mitochondrial protective strategy could be enacted at the same time, boosting substrate provision (e.g., with insulin/glucose, hypertonic lactate, or coenzyme Q) and antioxidant defences (e.g., with a manganese-superoxide dismutase mimetic). On the other hand, patients in established organ failure may benefit from a period of dormancy until the inflammatory phase has passed and then have their organ recovery accelerated by stimulating mitochondrial biogenesis (e.g., by leptin).

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