Special review

Catecholamines in the Treatment of Septic Shock: Effects Beyond Perfusion

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ABSTRACT

Objective: *To review the metabolic effects of sympathomimetic agents in the septic patient.*

Data sources: *A review of articles reported on the metabolic effects of the commonly used sympathomimetic agents in the critically ill patient.*

Summary of review: *Sepsis and septic shock are clinically charcterised mainly by derangements of cardiocirculatory function. Mainstay therapeutic interventions for haemodynamic stabilisation are adequate volume resuscitation and vasoactive agents. These, however, may be linked with additional effects on energy balance and cell metabolism. As well as the haemodynamic effects, specific metabolic effects need to be considered for optimal vasopressor treatment during severe sepsis and septic shock. This review highlights the typical haemodynamic and metabolic alterations associated with the commonly used sympathomimetic drugs in these conditions.*

Conclusions: *Sepsis and septic shock are linked with profound metabolic alterations. An additional impact of vasoactive therapy on metabolism has to be taken into account when using these agents to treat severe sepsis and septic shock.* (**Critical Care and Resuscitation 2003; 5: 270-276**)

Key words: Catecholamines, critically ill, lactic acidosis, metabolism

Sepsis and septic shock are defined by derangements of physiologic parameters including temperature, cardiovascular, respiratory and blood count parameters.[1] Additionally, septic shock is characterised by profound pathophysiologic changes resulting in disturbed tissue perfusion, oxygen transport and metabolism. The hierarchy of priority among the various organs may be affected in this situation and it is not known if these changes are adaptive or deleterious. Therapeutic strategies aiming to counteract these disturbances, such as low blood pressure,[2] may affect the blood flow redistribution to the various organs differently causing specific metabolic consequences. Moreover, sepsis, *per se*, results in specific alterations in organ metabolism.

The impact of vasoactive drug therapy on metabolic function and organ energy status should be carefully considered in critically ill patients who may already have an underlying septic metabolic dysfunction.

Alterations in metabolism during critical illness

Critical illness is associated with hypermetabolism, enhanced energy expenditure and insulin resistance. During sepsis these metabolic changes are even more pronounced. Clinical and laboratory signs of metabolic alterations include hyperglycaemia and hyperlactataemia despite an increased oxygen uptake (VO_2). Mitochond-rial dysfunction, as a mechanism of impaired cellular energy metabolism, may also be present.[3-5] Enhanced peripheral glucose uptake and utilisation, increased glucose production, depressed glycogen synthesis, glucose intolerance and insulin resistance are the main causes of these adaptive changes

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and are established to provide adequate organ supply of glucose as the energy substrate.[6] Under normal conditions glycaemic control is warranted by inhibitory effects of insulin and a feedback control of gluconeogenesis. During critical illness insulin resistance and the loss of feedback control occurs,[7,8] yet adequate glycaemic control as a main metabolic goal is important, as was demonstrated by a clinical study by van den Berghe *et al*.[9,10]

The mechanisms by which glucose exerts its detrimental effects are far from clear. There has been some recent work, however, that contributes to the understanding of glucose, not only in the role as an energetic substrate, but also as a signalling molecule involved in the regulation of radical oxygen species formation.[11,12] Thus, particularly during illness-induced hyperglycaemia, the rigorous control of blood glucose should be pursued and derangements of blood glucose levels avoided.[13] In particular, therapeutic strategies that may additionally worsen hypergylcaemia should be critically appraised.

Sepsis may be linked with hyperlactataemia and even lactic acidosis.[14] Sepsis-induced hyperlactataemia is caused by several mechanisms.[15,16] As lactate is typically a product of anaerobic cellular metabolism, hyperlactat-aemia during sepsis was initially interpreted as a hypoxia-related phenomenon. However, this may not necessarily hold true during sepsis, as an increase in glycolysis with enhanced pyruvate and conversion of pyruvate to lactate with a maintained lactate/pyruvate ratio (normal range 10:1 – 15:1), contributes to increased lactate levels.

Pyruvate may enter four different pathways: conversion to lactate, transamination to alanine, oxidation via Krebs cycle and, finally, gluconeogenesis. It has been hypothesised that during sepsis defective oxidative pyruvate metabolism by pyruvate dehydrogenase (PDH) may cause increased pyruvate levels. However, clinical data are inconsistent, as an increase, rather than decrease, in PDH activity during sepsis has been reported.[17]

Levraut *et al*. investigated the metabolic fate of lactate in haemodynamically stable patients with sepsis and found that hyperlactataemia in patients with increased lactate levels was a result of lower lactate clearance.[18] Reduced lactate utilisation in stable septic patients therefore may contribute to mild hyperlactataemia. These authors demonstrated that in septic patients normal, or only mildly elevated, lactate levels may occur despite profound pathologic alterations in lactate production and lactate clearance. These changes were shown to be predictive of outcome independent from other known risk factors.[19]

What are the feasible parameters to judge the underlying metabolic function or cellular energy status during clinical conditions? The rapid and ready availability of blood lactate levels in clinical practice makes blood lactate levels one of the most widely used parameters to judge adequacy of tissue oxygen. Under conditions of severe cardiovascular failure, lactate levels have been shown to provide a useful measure of the effectiveness of resuscitation,[20] and also to be a useful prognostic tool.[21]

The exclusive use of increased lactate levels as an indicator of tissue hypoxia in septic patients, however, is certainly not justified.[18,22-28] Lactate levels result from the equilibrium between lactate production and utilisation. An increased lactate production may indeed result from cellular oxygen deficit, provided cells are sufficiently supplied with glucose. Increased lactate production, however, does not necessarily mirror an adenosine triphosphate (ATP) deficit, because other mechanisms, including effects of insulin, activated state of Na^+, K^+-ATPase etc, may cause an increased glycolytic flux not necessarily linked with an energy deficit. Therefore, hyperlactataemia, cannot merely be attributed to deficient oxygen supply and/or tissue hypoxia.

Determination of pyruvate and additional calculation of lactate/pyruvate ratio representing cytosolic NAD^+/NADH ratio is supposed to provide deeper information.[14,29] However, in one study the lactate/pyruvate ratio could not be demonstrated to yield a better prognostic evaluation than lactate levels alone.[30]

Changes in ketone body ratio, providing a measure of mitochondrial redox state,[31] may mirror tissue hypoxia as a cause of metabolic derangement. However, for clinical purposes ketone body determinations may not be helpful, being technically cumbersome, and the ketone body ratio may only provide useful information under severe conditions of irreversible shock,[32] or during severe cardiogenic shock.[33] During sepsis and septic shock,[33,34] the ketone body ratio does not seem to be sufficiently sensitive to diagnose mitochondrial redox failure. Nevertheless, at least from few studies in critically ill patients, it has been demonstrated that the ketone body ratio is closely linked with nitrite/nitrate levels, indicating sepsis-induced nitric oxide overproduction.[35] Accordingly, the development of a ketone body ratio was suggested as a useful prognostic measure in critically ill patients.[36] However, for routine clinical use, arterial ketone body ratio not only lacks ready availability, but also lacks data to provide clear determinants for therapeutic intervention.

This reveals the dilemma of interpreting enhanced lactate levels under clinical situations in terms of its relevance to tissue perfusion. This problem is aggravated by the fact that metabolic parameters are derived

from blood samples that may not necessarily reflect relevant changes in tissue and organ metabolism.[29,37] More recent concepts provide a potential explanation for the disturbances in oxidative metabolism which are not necessarily linked to blood flow maldistribution or limited tissue oxygen availability. These concepts are based on the idea of an acquired defect in cellular respiration termed "cytopathic hypoxia" as a mechanism for mitochondrial dysfunction.[38]

The mechanisms responsible for cytopathic hypoxia include a fundamental disturbance of respiratory chain function. Brealey *et al*,[5] confirmed, in critically ill patients, an interrelationship between severity of illness and reduced respiratory chain activity, mitochondrial dysfunction, decreased ATP concentration, antioxidant depletion and nitric oxide overproduction. Consequently, mitochondrial dysfunction and cell death may occur and may finally lead to organ failure.[39] Identificat-ion of the aetiologic factors causing mitochondrial dysfunction could provide a stimulus for future therapy in the management of multi organ failure.[40,41]

Metabolic alterations induced by adrenergic drugs

Vasopressors are the mainstay treatment for different shock states and catecholamines are the most widely used in these circumstances. During septic shock, various strategies are used in applying adrenergic agents, depending on the haemodynamic status of the patient and the specific adrenoceptor profile of the different catecholamines.[2] Vasoactive therapy not only influences systemic and regional perfusion and organ blood flow distribution, but also affects the balance between oxygen and substrate supply and metabolic needs.[42] Nevertheless, it must be remembered that catecholamines may be linked with metabolic effects independent of their haemodynamic effects.[43,44]

Changes in receptor density and efficacy due to critical illness may result in additional metabolic modulation in the critically ill patient.[45] Under various clinical conditions the relative effects on regional perfusion and metabolism, and thereby supply-demand relationship, are crucial for the relevance of metabolic modulation. Data from critically ill patients, however, is often equivocal, due to a variety of patient conditions that influence the metabolic response to adrenergic substances.[46-48]

Epinephrine (adrenaline), norepinephrine (noradrenaline), dopamine

The characteristic effects of epinephrine on metabolism are well known. For example, under control conditions epinephrine (in contrast to norepinehrine) increases glucose and lactate levels in animal models,[49-52] as well as in humans.[53-55] Oxygen uptake and glucose production are profoundly enhanced, and hyperglycaemia, without adequate insulin response, and hyperlactataemia occur. In clinical studies, epinephrine not only leads to a decrease in hepatosplanchnic perfusion and oxygen exchange, but also to a deterioration in hepatosplanchnic lactate clearance.[56] Epinephrine induces an increase in lactate/pyruvate ratios indicating a disturbed cytosolic redox state.[48,57,58]

In one study of cardiosurgical patients, epinephrine was associated with increased lactate levels, decreased arterial pH, and higher blood glucose levels, although compromised tissue oxygenation could not be shown.[59] During septic shock, epinephrine may not only result in compromised regional hepatosplanchnic perfusion,[48,56] but also in profound metabolic alterations such as lactic acidosis.[60] Potential metabolic drug-induced deteriorateions due to metabolic overstimulation by epinephrine, uncompensated by blood flow distribution, may jeopardise organ supply. Recommendations for epinephrine therapy in the treatment of septic shock are limited.[2]

Norepinephrine is used primarily for haemodynamic stabilisation during septic shock. However, its efficacy is still under debate.[61,62] The metabolic effects of norepinephrine in septic patients are not completely known. In one clinical study, norepinephrine induced an increase in splanchnic blood flow and VO_2, with no change in hepatic venous oxygen saturation ($S_{hv}O_2$) and intramucosal pH (pHi).[63] Other studies describe both unchanged splanchnic blood flow, VO_2 and increased $S_{hv}O_2$ during septic shock.[64,65]

Norepinephrine is much less metabolically active compared with epinephrine. DeBacker *et al*, investigated patients with moderate and severe septic shock, replacing dopamine with epinephrine or norepinephrine and maintaining the patient's systemic haemodynamic state. Comparing epinephrine with norepinephrine, in this study, confirmed the potentially detrimental effect of epinephrine on hepatosplanchnic perfusion. Impaired perfusion was paralleled by a significant stimulation of glucose and lactate metabolism, a deterioration in hepatic ICG clearance and increased gradient between mixed and hepatic venous O_2 saturation.[66] As norepinephrine has not been shown to adversely effect adequately volume-resuscitated patients, in patients with septic shock, it is often one of the first-line catechol-amines recommended.[2]

In several studies, dopamine led to different or equivocal effects on splanchnic perfusion,[67] although it was not proven to be beneficial to regional PCO_2 equilibrium.[68] In moderate doses, dopamine does not impair regional hepatosplanchnic perfusion in postoperative cardiosurgical patients. In septic patients, hepato-

splanchnic oxygen consumption appears to be reduced, suggesting impaired metabolic conditions.[69] In one study, dopamine failed to show any measurable effect on metabolism, as recorded by monoethylglycine xylidide (MEGX) formation, despite modulation of hepato-splanchnic blood flow.[70] Despite the wide use of dopamine in intensive care patients for renal and splanchnic perfusion, it is not effective in promoting splanchnic perfusion or metabolism.[71]

Dobutamine, dopexamine and phenylephrine

Dobutamine modulates systemic oxygen delivery (DO_2) and has been used to detect systemic and regional pathological VO_2/DO_2 relationships.[72] In patients with septic shock, dobutamine results in an increased regional blood flow, DO_2 and $S_{hv}O_2$, but does not change VO_2, and decreases endogenous glucose production.[73] In one study the effects of dobutamine on arterial-gastric mucosal PCO_2 gap were used to disclose patients with splanchnic hypoperfusion.[74] Combined with norepinephrine, in volume resuscitated patients, dobutamine increased cardiac output and decreased arterial-gastric mucosal PCO_2 gap. No effect on hepatic metabolism, as determined by ICG elimination, could be demonstrated.[75] In another study of postoperative cardiac surgical patients, dobutamine increased systemic and regional blood flow, but did not affect splanchnic glucose production, lactate or amino acid balance.[76]

Dobutamine combined with norepinephrine may be equally effective as epinephrine alone in maintaining haemodynamic stability in septic patients without induc-ing deteriorations of systemic and regional metabolism. In an experimental animal model of sepsis, a combined administration of both norepinephrine and dobutamine resulted in the most favourable effects on the haemody-namic status, oxygen transport and metabolic parameters as well as promoting less lung, liver and intestine injury.[77]

Dopexamine had no advantage regarding lactate/ pyruvate ratios in septic shock patient's when compared with dobutamine.[78] Controversy exists about its beneficial effects on metabolism. The "protective effect on the hepatosplanchnic organs"[79] by microcirculatory blood flow modulation[80] has been challenged as it has failed to show an increase in hepatosplanchnic blood flow or any other beneficial effect regional metabolism and energy balance in septic shock patients.[81,82] In one study the arterial-gastric mucosal PCO_2 gap worsened, although an increased regional blood flow with incremental doses of dopexamine during concomitant dobutamine administration was demonstrated.[83] In another study of critically ill patients, infusing dopexamine over 7 days did not result in any improvement of gastrointestinal barrier function, renal function or any improvement in organ dysfunction.[84]

When phenylephrine was administered to norepinephrine "dependent" patients, it induced a selective reduction in hepatosplanchnic blood flow and impairment of the hepatosplanchnic metabolic performance.[85] Although there are hardly any data about the metabolic effects of phenylephrine in septic patients, administration of pure α-agonists may threaten the hepatosplanchnic metabol-ism and probably should be avoided.

Conclusions

Sepsis and septic shock are linked with profound metabolic alterations and an additional impact of vasoactive therapy on metabolism has to be considered when using these agents. Hyperglycaemia, as one main consequence of sepsis, and aggravation of hyperglycaemia, due to metabolic stimulation should be avoided. As a consequence, the use of epinephrine in septic patients should be limited, due to its potential compromising effects on regional blood flow and highly stimulatory effects on energy metabolism. Pure α-adrenergic substances may jeopardise hepatosplanchnic metabolism and, therefore, should be avoided in septic patients.

As the clinical decision to use specific vasoactive treatment is based mainly on systemic as well as regional perfusion and oxygen transport, the clinician should remember that metabolic consequences, beyond perfusion, may compromise organ function by causing metabolic overstimulation.

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