Metabolic alterations in sepsis and vasoactive drug–related metabolic effects

Karl Träger, MD,* Daniel DeBacker, MD,† and Peter Radermacher, MD, PhD*

The main clinical characteristics of sepsis and septic shock are derangements of cardiocirculatory and respiratory function. Additionally, profound alterations in metabolic pathways occur leading to hypermetabolism, enhanced energy expenditure, and insulin resistance. The clinical hallmarks are hyperglycemia, hyperlactatemia, and enhanced protein catabolism. These metabolic alterations are even more pronounced during sepsis as a result of cytokine release and subsequent induction of inflammatory pathways. Increased oxygen demands from mitochondrial oxygen utilization and oxygen consumption related to oxygen radical formation may contribute to hypermetabolism. In addition, mitochondrial dysfunction with impaired cellular respiration may be present. Mainstay therapeutic interventions for hemodynamic stabilization are adequate volume resuscitation and vasoactive agents, which, however, have additional impact on metabolic activity. Therefore, beyond hemodynamic effects, specific drug-related metabolic alterations need to be considered for optimal treatment during sepsis. This review gives an overview of the typical metabolic alterations during sepsis and septic shock and highlights the impact of vasoactive therapy on metabolism.

Keywords
glucose, lactate, catecholamines

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*Klinik für Anästhesiologie, Universitätsklinikum Ulm, Germany, †Department of Intensive Care, Erasme University Hospital, Brussels, Belgium.

Correspondence to Karl Träger, Klinik für Anästhesiologie, Universitätsklinikum Ulm, Steinhoevelstrasse 9, D-89075 Ulm, Germany; e-mail: karl.traeger@medizin.uni-ulm.de

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Abbreviation

Pco_2 partial pressure of carbon dioxide

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Consensus definitions of sepsis and septic shock are related to derangements of physiologic parameters as body temperature, cardiocirculation, respiration, and blood count parameters [1]. Therapeutic interventions in patients with sepsis primarily aim to restore hemodynamic and oxygen transport variables to warrant adequate organ perfusion and oxygen availability [2]. Sepsis, moreover, goes along with specific alterations in whole body and specific organ metabolism. These alterations indicate severity of critical illness, on the one hand, but also need to be considered for therapeutic concepts on the other. Therefore, the characteristic metabolic derangements with clinical relevance and typical laboratory signs are discussed, and the impact of vasoactive drug therapy on metabolic function and organ energy status is described.

Metabolic stress during critical illness

Hypermetabolism, enhanced energy expenditure, and insulin resistance are the main clinical features of stress and critical illness. Sepsis even aggravates these metabolic sequelae owing to cytokine-related effects. Oxygen demands from both mitochondrial oxygen utilization and oxygen radical formation, particularly in the liver [3], are increased. The predominant clinical and laboratory signs of metabolic alterations are hyperglycemia and hyperlactatemia despite increased oxygen uptake. Table 1 summarizes the most prominent metabolic alterations observed during sepsis.

During septic shock, impaired cellular energy metabolism associated with mitochondrial dysfunction may occur simultaneously [4,5,6••]. A triple-hormone infusion of catecholamines, cortisol, and glucagon reproduced typical metabolic alterations of sepsis [7]. Endotoxin administered to humans resulted in hyperglycemia, increased energy expenditure, hypoaminoacidemia, increased peripheral lactate, and free fatty acid output [8]. Moreover, the splanchnic bed was shown to be a major source of enhanced oxygen uptake, lactate, and glucose output, in parallel with a major splanchnic production of tumor necrosis factor-α. Briefly, humoral changes in combination with endotoxin and cytokine release mediate a major part of the observed metabolic alterations. Figure 1 depicts the humoral changes during sepsis and the effects on carbohydrate, protein, and lipid metabolism.

Table 1. Causes and sequelae of metabolic alterations during sepsis

Increased counterregulatory hormone concentrations
Cytokine-related metabolic stimulation
Hypermetabolism
Insulin resistance
Hyperglycemia
Hyperlactatemia without evidence of tissue ischemia
Impaired lactate clearance
Increased oxygen uptake
Increased oxygen demands from mitochondrial oxygen utilization
Increased oxygen radical formation in the liver

Hypermetabolism

Major injury and infection are associated with increased hepatic gluconeogenesis [9]. After severe injury or in patients with bacteremic complications, gluconeogenesis was even further enhanced and accompanied by increased hepatic amino acid uptake. However, when septic complications and organ failure occurred, hepatic glucose production and amino acid uptake decreased. These metabolic changes were paralleled by only minor alterations in splanchnic blood flow, oxygen utilization, and lactate uptake.

In patients after injury or during sepsis, the hepatosplanchnic area plays a crucial role in disturbances in oxygen transport and metabolic alterations. Splanchnic oxygen uptake and glucose output were found to be increased, together with increased albumin synthesis [4]. A nonlinear correlation between increased splanchnic oxygen uptake and increased splanchnic glucose output could be found, giving support for the concept that hepatic gluconeogenesis is a main determinant of hepatic energy and oxygen demand. Augmented oxygen consumption owing to enhanced reactive oxygen generation by respiratory-burst reaction in phagocytes additionally needs to be considered because reactive oxygen detoxification by cellular enzyme systems may lead to alterations in oxidative metabolism [3].

Glucose metabolism

Enhanced peripheral glucose uptake and utilization, increased glucose production, depressed glycogen synthesis, glucose intolerance, and insulin resistance are the key manifestations of altered glucose metabolism. These alterations are adaptive to provide adequate organ supply of glucose as an energy substrate [10]. Increased glucose uptake is mediated by effects of the counterregulatory hormones, by hyperglycemia itself, and by cytokine effects.

Gluconeogenesis is a main factor in the hyperglycemic response. As shown in Figure 2, increased gluconeogen-

Figure 1. Sepsis-related humoral changes and their metabolic effects

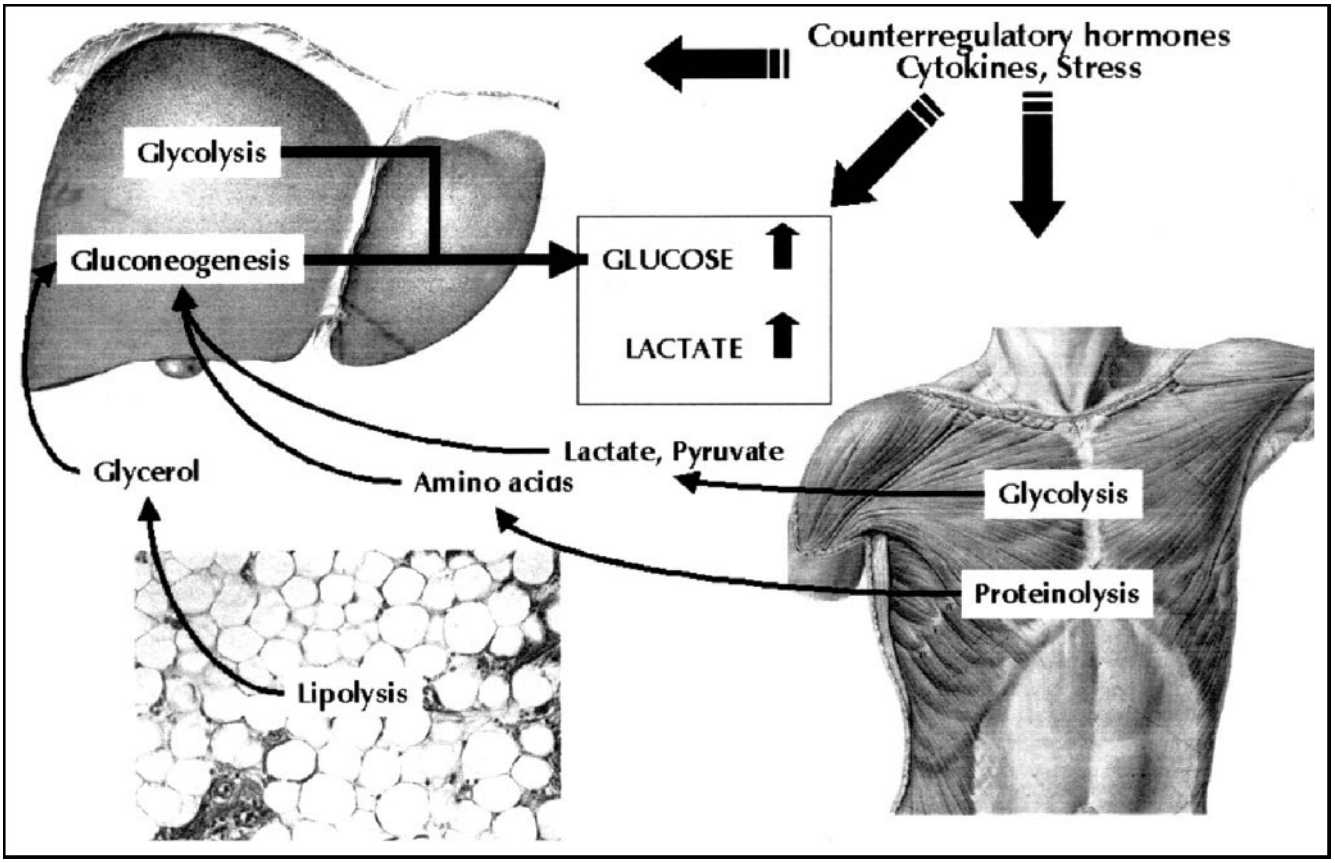
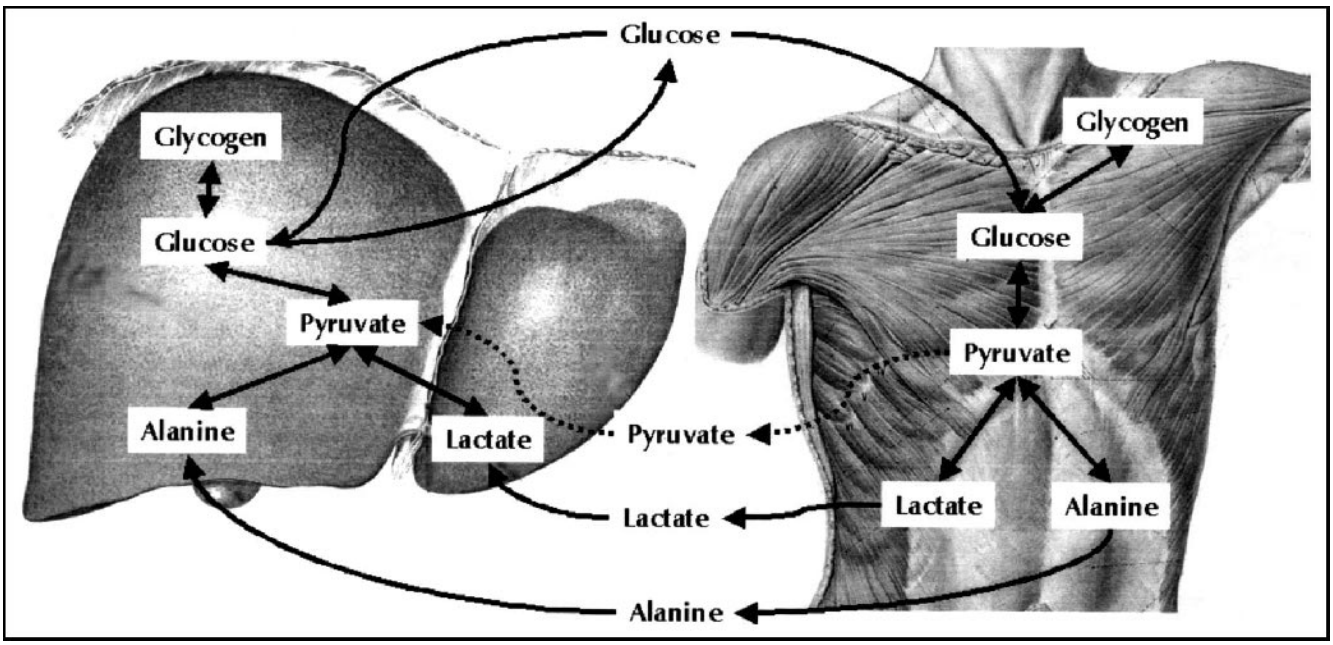


Figure 2. Interaction of liver and muscle compartments for glucose recycling via Cori and glucose–alanine cycles



esis is supplied by stimulated Cori cycle activity and enhanced glucose–alanine cycle turnover. Additional effectors of increased gluconeogenesis are counterregulatory hormones and direct cytokine stimulation [7,8]. Under these conditions, glucose production predominates glucose oxidation, indicating a substantial contribution of nonoxidative metabolic pathways for glucose (*ie*, mainly via the Cori cycle).

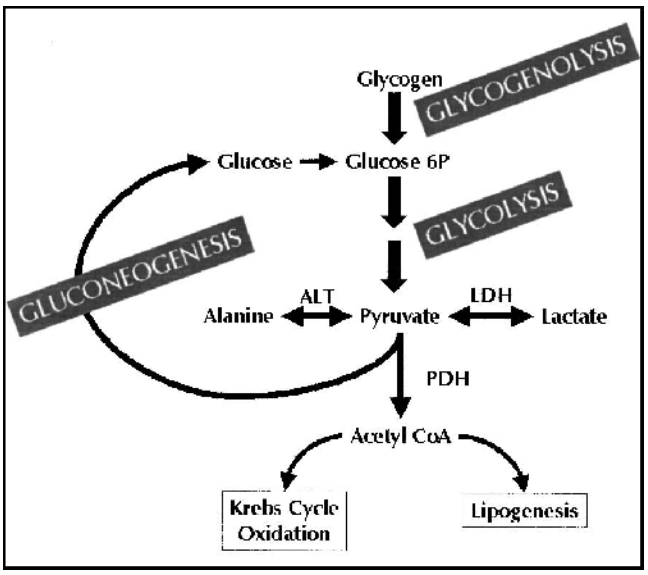
Whereas under normal conditions, glycemic control is achieved by the inhibitory effects of insulin and feedback control of gluconeogenesis, it is disturbed by insulin resistance and the loss of feedback control [11,12]. The mechanisms of insulin resistance have not been fully elucidated; a postreceptor defect involving the rate-limiting step for intracellular glucose disposal is hypothesized to be involved [10]. The importance of adequate glycemic control as a main metabolic goal was demonstrated by a clinical study from van den Berghe *et al.* [13••,14••]. Patients were allocated to either intensive glycemic control (blood glucose, 4.4–6.1 mmol/L) or to conventional glycemic control allowing blood glucose levels to increase to 11.9 mmol/L and keeping glucose levels between 10.0 and 11.1 mmol/L. Intensive glycemic control by insulin reduced mortality during intensive care. Reduction in mortality predominantly involved deaths owing to multiple organ failure with a proven septic focus. In-hospital mortality, incidence of bloodstream infections, and acute renal failure could be reduced. Because there has been debate about the differential contribution of either normoglycemia or the direct effects of insulin to decreases in morbidity and mortality, the investigators recently proposed that normoglycemic control of blood glucose levels rather than the infused insulin *per se* was linked to the protective effects of intensive insulin therapy [14••]. The mechanisms by which glucose may exert these detrimental effects are far from clear. There has been some recent work, however, that contributes to the understanding of glucose not only as an energetic substrate but also as a signaling molecule involved in the regulation of radical oxygen species formation [15••,16].

In conclusion, particularly during conditions with illness-induced hyperglycemia, a rigorous control of blood glucose should be implemented and derangements of blood glucose levels avoided [17••]. The bedside availability of blood glucose determinations, the use of insulin, and the regulation of exogenous glucose administration are the clinical tools to achieve these goals.

Lactate

Hyperlactatemia and even lactic acidosis may be associated with sepsis [18]. In patients with shock, lactate is known to be of prognostic value. The pathogenesis of sepsis-induced hyperlactatemia is owing to several mechanisms [19,20••]. Because formation of lactate typically occurs during anaerobic cellular metabolism, hyperlactatemia during sepsis was attributed to a hypoxia-related phenomenon. However, this often does not hold true during sepsis. An increase in glycolysis resulting in increased pyruvate and the conversion of pyruvate to lactate with a maintained lactate/pyruvate ratio (normal range, 10:1–15:1) contribute to increased lactate levels. As depicted in Figure 3, pyruvate may enter four different pathways: conversion to lactate, transamination to alanine, oxidation (Krebs cycle), and gluconeogenesis.

Figure 3. Metabolic pathways of pyruvate



Defective oxidative pyruvate metabolism by pyruvate dehydrogenase during sepsis has been hypothesized to cause increased pyruvate levels. However, clinical data are inconsistent, showing rather increased pyruvate dehydrogenase activity during sepsis [21].

To uncover the metabolism of lactate during sepsis, Levraut *et al.* [22] investigated the metabolic fate of lactate in hemodynamically stable patients with sepsis. Hyperlactatemia in patients with increased lactate levels was a result of lower lactate clearance compared with normolactatemic patients despite comparable lactate production. Reduced lactate utilization in stable patients with sepsis therefore may contribute to mild hyperlactatemia. By evaluating the prognostic meaning of lactate clearance and lactate production in patients with sepsis, they could indeed demonstrate that in patients with sepsis, normal or only mildly elevated lactate levels may occur despite profound pathologic alterations in lactate production and lactate clearance. These changes, however, were shown to be predictive of outcome independent of other known risk factors [23].

Lactate as a useful parameter for estimating cellular energy status is controversial. Lactate determinations are clinically easily available, and blood lactate concentration is one of the most often used parameters to judge adequacy of tissue oxygen availability. During severe cardiovascular failure, lactate levels help to estimate efficacy of resuscitation measures and prove to be a prognostic tool. The exclusive use of increased lactate levels in patients with sepsis as an indicator of tissue hypoxia, however, is certainly not justified [18,24–26]. Lactate levels result from the equilibrium between lactate production and utilization. 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 ATP deficit because other mechanisms such as the effects of insulin and activated Na^+, K^+-ATPase, may cause an increased glycolytic flux not necessarily linked with an energy deficit. Hyperlactatemia, hence, cannot be merely attributed to deficient oxygen supply and/or tissue hypoxia.

Redox state

Pyruvate determination and thereby calculation of the lactate/pyruvate ratio as a substitute of cytosolic nicotinamide adenine dinucleotide (oxidized form)/nicotinamide adenine dinucleotide (reduced form) ratio may be helpful in interpreting lactate values [18,27]. However, the lactate/pyruvate ratio could not be demonstrated to yield better prognostic evaluation than lactate levels alone [28].

Ketone body ratio as a surrogate of the mitochondrial redox state is supposed to provide a deeper insight into mitochondrial metabolism [29]. However, the technical difficulty of ketone body measurements excludes routine clinical availability and, moreover, yields relevant effects mainly during severe irreversible shock or severe cardiogenic shock [30,31]. During clinical sepsis and septic shock [31,32], ketone body ratio is much less sensitive to prove mitochondrial redox failure. There are only limited data from critically ill patient studies in which ketone body ratio provided a link with nitrite/nitrate levels as an indicator of sepsis-induced nitric oxide overproduction [33] and was related to prognostic evaluation [34]. For routine clinical use, arterial ketone body ratio not only lacks criteria of availability but also additional clear recommendations for therapeutic intervention.

Mitochondrial dysfunction

Recently, an additional concept has been proposed that provides a potential explanation for the disturbances in oxidative metabolism not necessarily linked to blood flow maldistribution or limited tissue oxygen availability. This concept is based on an acquired defect in cellular respiration, termed cytopathic hypoxia, as a mechanism for mitochondrial dysfunction [35••].

Among the mechanisms responsible for cytopathic hypoxia are disturbances of respiratory chain function. Brealey *et al.* [6••], using muscle specimens from critically ill patients, confirmed an interrelationship between severity of illness and reduced respiratory chain activity, mitochondrial dysfunction, decreased ATP concentration, antioxidant depletion, and nitric oxide overproduction. As a consequence of mitochondrial dysfunction, cell death may occur, and this may finally be linked to organ failure [36]. As a mediator of these functional defects,

nitric oxide is discussed as one of the suspects. In concert with its metabolite peroxynitrite, it is not only capable of inhibiting electron transport chain but may also induce other pathways of cellular injury such as activation of poly(ADP-ribose) synthase. Identification of etiologic factors for mitochondrial dysfunction might open some attractive future approaches to be tested in the treatment of organ failure [37,38•]

Metabolic modulation by vasoactive therapy

Vasoactive agents are one the main approaches in the hemodynamic management of the critically ill [39]. Various metabolic effects, both at the cellular and interorgan level, may be linked with these drugs. Because septic shock *per se* induces profound alterations of cellular energy metabolism, additional changes induced by adrenergic substances may be of particular importance. 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 [40].

Adrenoceptor agonists

Adrenoceptor agonists are the most common substances in the clinical setting, whereas nonadrenergic substances are far less established in clinical practice. Nonadrenergic vasoactive therapeutic approaches as an additional option for hemodynamic or metabolic modulation are mainly in clinical investigation. Various adrenoceptor activity properties of catecholamines are related to different adrenergic effects. Perfusion and myocardial function are modulated by α- and β-adrenoceptors; metabolic effects, however, are mainly mediated by β_2-adrenoceptors [41,42]. Changes in receptor density and efficacy as a consequence of critical illness may provoke additional metabolic modulation in the critically ill patient [43]. Under physiologic conditions, the main metabolic effects of adrenergic agents refer to increased glucose production, enhanced Cori cycle and glucose–alanine cycle activity, and hyperglycemia [44].

Under clinical circumstances, the relative effects on regional perfusion and metabolism and, thereby, a supply–demand relationship are crucial for the relevance of metabolic modulation. Data from critically ill patients may be equivocal owing to a variety of patient conditions that influence the metabolic response to adrenergic substances.

Physiologic catecholamines: epinephrine, norepinephrine, and dopamine

Epinephrine is most potent in affecting metabolism. VO_2 and glucose production are profoundly enhanced; hyperglycemia without adequate insulin response owing to suppression of insulin release and hyperlactatemia are predominant features. Under clinical conditions, epinephrine not only decreased hepatosplanchnic blood flow and oxygen exchange but also compromised hepatosplanchnic lactate clearance [45]. Epinephrine was associated with increased the lactate/pyruvate ratios as an indicator of disturbed cytosolic redox state [46–48]. In cardiac surgery patients, epinephrine led to an increase in lactate levels, a decrease in arterial pH, and higher blood glucose levels, without indicators of compromised tissue oxygenation [49]. Despite hemodynamic stabilization during septic shock, epinephrine may not only induce compromised regional hepatosplanchnic perfusion [45,46] but may also cause profound metabolic alterations as lactic acidosis [50]. Treatment of patients with septic shock should therefore not only aim at hemodynamic parameters but should also consider drug-induced metabolic alteration. In the case of epinephrine, potential metabolic drug-induced deteriorations caused by metabolic overstimulation uncompensated by blood flow distribution have to be considered. This led to limited recommended use of epinephrine for the treatment of septic shock [2].

Norepinephrine is the catecholamine primarily used to treat hemodynamic instability during septic shock, although even this may be a matter of discussion [51,52]. Metabolic effects in patients with sepsis are not completely known. Norepinephrine in a clinical study increased splanchnic blood flow and oxygen uptake, with unchanged hepatic venous oxygen saturation ($S_{hv}O_2$) and intramucosal pH [53]. Others found unchanged splanchnic blood flow, oxygen uptake, and increased $S_{hv}O_2$ during septic shock [54,55]. In contrast to epinephrine, norepinephrine is much less metabolically active. In a clinical study, DeBacker *et al.* [56•] investigated patients with moderate and severe septic shock in whom dopamine was withdrawn and successively replaced by epinephrine or norepinephrine, respectively, maintaining systemic blood pressure. Although for patients with moderate septic shock, no clear-cut hemodynamic or metabolic advantage or disadvantage for dopamine, norepinephrine, or epinephrine could be found, this was completely different for patients with severe septic shock. In a direct comparison of epinephrine and norepinephrine, this study confirms the potentially detrimental effect of epinephrine on hepatosplanchnic perfusion. In parallel with impaired perfusion, however, significant stimulation of glucose and lactate metabolic pathways and also limited hepatic indocyanine green clearance and increased gradient between mixed and hepatic venous oxygen saturation were found.

There are no clear data on the adverse effects of norepinephrine on adequately volume-resuscitated patients. For hemodynamic stabilization in patients with septic shock, norepinephrine, therefore, is one of the first-line catecholamines recommended [2].

Dopamine has been reported with different equivocal effects on splanchnic perfusion [57] but finally could not

be proven to beneficially affect regional P_{CO_2} equilibrium, given as either an intramucosal pH or P_{CO_2} gap [58]. When used in moderate doses, dopamine does not compromise regional hepatosplanchnic perfusion in postoperative cardiac and in patients with sepsis. However, in patients with sepsis, a reduction in hepatosplanchnic oxygen consumption was seen, suggesting impaired metabolic conditions [59]. Regarding metabolic actions, dopamine did not exert any measurable effect on monoethylglycine xylidide formation in patients with sepsis despite modulation of hepatosplanchnic blood flow [60]. Although dopamine has been widely used in the intensive care setting for purposes of renal and splanchnic perfusion benefits, it finally could not be proven to exert a positive effect on splanchnic perfusion or metabolism to justify ongoing routine use [61].

Synthetic catecholamines: dobutamine, dopexamine, and phenylephrine

The synthetic catecholamine dobutamine is effective in modulating systemic oxygen delivery and has been used to detect systemic and regional pathologic oxygen uptake/oxygen delivery relationships [62]. In patients with septic shock, dobutamine increased regional blood flow with parallel increases in oxygen delivery and $S_{hv}O_2$ but unchanged oxygen uptake and decreased endogenous glucose production [63].

Enhanced regional oxygen availability might be of importance for energy-consuming pathways because oxygen requirements resulting from the *de novo* formation of glucose were reduced. The effects of dobutamine on the arterial-gastric mucosal P_{CO_2} gap were shown to be useful for disclosing patients with splanchnic hypoperfusion [64]. Dobutamine added to norepinephrine in volume-resuscitated patients increased cardiac output and decreased the arterial-gastric mucosal P_{CO_2} gap concomitantly but failed to show an influence on hepatic metabolism as determined by indocyanine green elimination [65]. After cardiac surgery, dobutamine increased systemic and regional blood flow, without affecting splanchnic glucose production and lactate or amino acid balance [66]. Compared with epinephrine alone, dobutamine combined with norepinephrine may be equally effective in maintaining hemodynamic stability in patients with sepsis without deteriorating parameters of systemic and regional metabolism. Despite the limitations of an experimental animal study with a peritonitis model of sepsis, there is some evidence that combined administration of norepinephrine and dobutamine may result in the most favorable effects on hemodynamics, oxygen transport, and metabolic parameters in parallel with less anatomic injury in the lung, liver, and intestine [67•].

Dopexamine compared with dobutamine in patients with septic shock had no advantage regarding lactate/pyruvate ratios [68]. There is controversy about its beneficial effects on metabolism. Although proposed to "protect the hepatosplanchnic organs" [69] by microcirculatory blood flow modulation [70], this effect has been challenged. Neither the preferential rise of the hepatosplanchnic blood flow nor any beneficial effects on parameters of regional metabolism and energy balance could finally be confirmed in patients with septic shock [71,72]. The arterial-gastric mucosal P_{CO_2} gap even worsened, despite increased regional blood flow, when incremental infusion rates of dopexamine were administered to patients with concomitant dobutamine administration [73].

A prolonged infusion of dopexamine over 7 days in critically ill patients failed to result in any improvement of gastrointestinal barrier function or renal function or any improvement in organ dysfunction [74•].

Phenylephrine, when administered in norepinephrine-dependent patients, selectively reduced regional hepatosplanchnic blood flow and impaired hepatosplanchnic metabolic performance, as shown by a decreased splanchnic lactate uptake rate despite no change in systemic hemodynamics or gas exchange [75]. Although data about the metabolic effects of phenylephrine in patients with sepsis are very limited, administration of pure α-agonists may threaten the hepatosplanchnic metabolism and, therefore, should be avoided.

Nonadrenergic substances

Under clinical conditions, vasopressin, prostacyclin (and its analogue iloprost), and *N*-acetylcysteine have been investigated as nonadrenergic compounds in the treatment of patients with septic shock. Although vasopressin is used as an investigational approach for hemodynamic stabilization, there are no data available with respect to intermediate metabolism. The effects of *N*-acetylcysteine on hemodynamics and oxygen transport parameters have been studied, but only very limited information is available about their influence on metabolism.

Prostacyclin

Prostacyclin led to enhanced oxygen delivery and oxygen uptake and restored intramucosal pH [76,77]. In patients with sepsis not on vasopressor therapy, prostacyclin improved glucose oxidation [78]. Iloprost, when administered in patients with septic shock receiving norepinephrine, increased splanchnic blood flow and oxygen delivery and systemic oxygen uptake. Additionally, it decreased endogenous glucose production rate, which persisted even after drug withdrawal. Iloprost hypothetically might have been related to shifting oxygen utilization from *de novo* glucose production to other oxygen-demanding metabolic pathways. Continuous iloprost infusion improved plasma indocyanine green clearance with no detectable effects on systemic hemodynamics

[79]. The potential adverse effects of prostacyclin on hemodynamics and gas exchange, however, limit a recommendation for routine clinical use based on the currently available data.

Conclusions

Sepsis and septic shock induce profound metabolic alterations. One has to be aware of the additional impact of therapeutic measures, such as vasoactive therapy, on metabolism.

Hyperglycemia is a main consequence of sepsis, and aggravation of hyperglycemia as a consequence of therapeutic maneuvers should be avoided. Sufficient blood glucose control and avoidance of excessive hyperglycemia are recommended. For adequate blood glucose control, insulin administration is used in patients with sepsis. For vasoactive support of the patient with sepsis, epinephrine use should be limited because of its potential compromising effects on regional blood flow and highly stimulatory effects on energy metabolism. Conversely, pure α-adrenergic substances seem to have a negative impact on hepatosplanchnic metabolism and, therefore, should be avoided in patients with sepsis.

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