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Catecholamines and Vasopressin During Critical Illness

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Life-threatening disease is a severe stress that induces a set of neuroendocrine responses, including the activation of the sympathetic nervous system and secretion of epinephrine from the adrenal medulla [1]. This response has an impact on blood pressure, vital organ perfusion, and supply of metabolic substrates, all of which affect survival [2]. Although most plasma norepinephrine is derived from synaptic nerve clefts, circulating epinephrine is produced largely in the adrenal gland. Unlike norepinephrine, which is a neurotransmitter of the sympathetic nervous system, epinephrine functions as a circulating hormone [2]. Interestingly, the enteric nervous system, which contains more than 100 million neurons, is capable of releasing a previously unrecognized proportion of total sympathetic outflow [3]. Mesenteric organs were shown to produce considerable amounts of norepinephrine [4] and dopamine [5], which accounts for 37% and >50%, respectively, of the total amount of these catecholamines formed in the body. Given this capability of the gut, the interaction of enteric bacteria and toxins

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with the enteric nervous system might gain a particular importance in critically ill patients.

Catecholamines in circulatory failure

Pathophysiology of circulatory failure: the many faces of hypotension

Sytemic hypotension is a medical emergency which often leads to end-organ failure and death if left untreated. The most frequent cause of severe hypotension in an ICU is systemic vasodilatation, referred to as vasodilatory shock [6]. Although sepsis is recognized as the main cause of this syndrome, vasodilatory shock is also the final common pathway for late-phase shock of any etiology [6]. The underlying mechanism of vasodilatory hypotension seems to be very complex and not yet completely understood. Nevertheless, the present evidence suggests that at least three—probably closely interacting—major pathways are involved in this loss of peripheral vascular tone.

First, several lines of evidence support the view that the overproduction of nitric oxide (NO) by inducible nitric oxide synthase (iNOS) contributes significantly to the circulatory shock [7]. Not only nitric oxide itself (by way of cyclic guanosine monophosphate [cGMP]-mediated smooth muscle relaxation), but also its downstream biological effects may play a role in vasodilatory hypotension. Peroxynitrite, a highly toxic reactive species formed from nitric oxide and superoxide, is capable of inducing endothelial dysfunction and vascular hyporeactivity [8]. Recent data also showed that peroxynitrite is implicated in the inactivation of α_1-adrenoreceptors [9] and norepinephrine [10], and that superoxide deactivates catecholamines resulting in loss of their vasopressor activity [11]. Moreover, administration of superoxide dismutase mimetic to a rat model of septic shock restored the vasopressor response to norepinephrine [11], and attenuated the sepsis-induced hypotension in pigs [12]. Finally, nitric oxide may also exert its vasodilatatory effects by activation of potassium channels in the plasma membrane of vascular smooth muscle cells [13].

Second, the membrane potential of vascular smooth muscle cells plays the key role in the regulation of vascular tone. Hyperpolarization closes calcium channels, thereby decreasing the cytosolic calcium concentration resulting in relaxation. ATP-sensitive potassium channels (K_{ATP} channels) markedly influence the membrane potential of vascular smooth muscle cells. The opening of K_{ATP} channels, triggered by decreased cellular ATP content or increased intracellular concentrations of lactate or hydrogen ion, promotes vasodilatation by hyperpolarizing the membrane and preventing the influx of calcium into the vascular cells [6,14]. The potency of sulfonylurea drugs in antagonising vasorelaxant actions of these K_{ATP} channels was experimentaly as well as clinically documented [15–17], although the potential negative impact on cellular energy metabolism might outweigh beneficial hemodynamic effects [18].

Third, vasopressin, a peptide hormone, is an essential component of cardiovascular homeostasis. Interestingly, later in the course of septic shock, the plasma levels of vasopressin are inappropriately low [19]. This relative deficiency of vasopressin seems to be another crucial player in the pathogenesis of vasodilatatory shock. Among other factors, nitric oxide plays an important inhibitory role in vasopressin release during endotoxemia, thereby underscoring the complexity of NO-mediated vascular effects [13,20].

Nevertheless, although restitution of vascular reactivity is undoubtedly an emerging approach for the treatment of vasodilatory shock, catecholamines still constitute the basic pharmacological armamentarium to re-establish an effective circulation in the current clinical practice.

Basic pharmacology of catecholamines

Schematically, adrenergic drugs are capable of restoring circulation through their effects on α-adrenergic receptors (vasoconstriction), β-adrenergic receptors (inotropy), or both [2]. Norepinephrine, epinephrine, and dopamine are the most commonly used naturally occurring catecholamines, and dobutamine, dopexamine, isoproterenol, and phenylephrine are synthetic sympathomimetic amines. These agents display different receptor selectivity and clinical effects. Phenylephrine is the only pure α-agonist, and isoproterenol and dopexamine are the only pure β-adrenergic agonists. Norepinephrine, epinephrine, and dopamine manifest vasopressor effects by way of their α_1-adrenergic agonist activity. All these catecholamines also exert some inotropic effect by their action on β_1 receptors. The most prominent are, in order of potency, in epinephrine, norepinephrine, and dopamine as assessed by their capacity to directly stimulate cyclic adenosine monophosphate production in human lymphocytes [21].

Choosing an agent and end-points

Choice of an agent must be based upon the underlying pathology and patient-specific responses. Although relatively straightforward principles apply for cardiogenic hypotension, the optimal selection of catecholamines is far less clear in septic shock when an altered adrenergic receptor function (desensitization), changes in receptor density, and responsiveness make the individual response to various catecholamines unpredictable [22,23].

Unfortunately, no large, prospective, randomized and well-conducted studies to guide the pharmacologic management of septic hypotension are available so far. In this context, only one observational study demonstrated a survival benefit of norepinephrine over other catecholamine therapy [24]. Nevertheless, a recently published evidence-based review recommends either norepinephrine or dopamine as first-line therapy to correct hypotension in septic shock [25], although norepinephrine is more potent to reverse hypotension in septic shock patients. The use of epinephrine should be limited to patients in whom volume resuscitation and either norepinephrine or dopamine failed to restore sufficient blood pressure [26],

although this view has recently been challenged [27]. Given the lack of high-quality data, a recent meta-analysis by the Cochrane Database concluded that no firm evidence can be given that any one catecholamine is more effective or safer than any other in the treatment of shock [28]. These questions are addressed in two ongoing multi-center trials that compare epinephrine to combined dobutamine and norepinephrine and dopamine versus norepinephrine. Comprehensive recommendations are provided by Surviving Sepsis Campaign guidelines [29] and by recently revised practice parameters for hemodynamic support of sepsis [26].

Although arterial pressure is one of the important end-points of vasopressor therapy, the exact goal for blood pressure maintenance in septic patients still remains a contentious issue. Two recent clinical studies indicated that increasing mean arterial pressure from 65 to 85 mmHg by using norepinephrine in patients who have septic shock, neither improved nor jeopardized global and organ perfusion variables and renal function [29,30]. These data suggest that it is usually not advisable to increase mean arterial pressure above 65–70 mmHg [26,29,31]. Nonetheless, an individualized approach should be considered, particularly in patients with atherosclerosis or severe hypertension, who may require higher blood pressure to maintain sufficient organ perfusion.

Catecholamines and regional circulation

Many experimental and clinical studies have attempted to determine which, if any, of the available vasoactive drugs has a specific action on enhancing regional perfusion. Given the recognized role of hepatosplanchnic region in the pathogenesis of multiple organ dysfunction [32], it is not surprising that the investigators targeted this area. Under physiological conditions, β-adrenergic stimulation has the potential to increase hepatosplanchnic perfusion and modulate cellular metabolism, whereas α-agonists manifest the opposite effect [33,34]. The impact of various vasoactive agents on the hepatosplanchnic region in patients who have sepsis and septic shock has been ambiguous [35,36]. The kidney is another organ in which the susceptibility to hypoperfusion is particularly high. Inadequate renal perfusion is recognized as an important factor that contributes to the pathogenesis of acute renal dysfunction, and hence, the preservation of renal perfusion is a vital part of renal protection. These issues have been summarized in recent comprehensive reviews [35,37].

Dopamine

In theory, low-dose dopamine (< 5μg/kg/min) may increase hepatosplanchnic blood flow through its effect on dopaminergic receptors. The evidence is, however, equivocal. Although some authors observed the increase in hepatosplanchnic blood flow [38,39], no effect on gastric mucosal pH or PCO_2 gap [38,40,41], or even decreased gut mucosal blood flow were reported [40]. The resulting effect of dopamine might, in part, be dependent on the initial fractional

splanchnic blood flow [38]. Likewise, the effect of higher doses of dopamine has also been mixed [42–44], ranging from increased, constant to decreased splanchnic blood flow [45]. By comparing the regional effects of dopamine, norepinephrine, and epinephrine, De Backer and colleagues showed recently that in patients who have moderate septic shock, dopamine exerted the most beneficial profile of effects (in terms of lower gradient between mixed venous and hepatic venous oxygen saturation) on hepatosplanchnic circulation [46]. In contrast to these apparently inconclusive results, there is a consensus that although low dose dopamine may increase diuresis, no data exist to support the use of low-dose dopamine for the purpose of renal protection [47,48].

Norepinephrine

Although systemic hemodynamic effects of norepinephrine are quite predictable, no such conclusion can be made regarding its impact on splanchnic circulation. Indeed, clinical studies reported increased [49], unchanged [42,44], or even variable [42] splanchnic blood flow or hepatic oxygen venous saturation in septic shock patients. Moreover, the interpretation of the available evidence is complicated by the fact that norepinephrine is often combined with dobutamine, which prohibits separating the effects of individual agents. This limitation has recently been treated by De Backer and coworkers, who compared the effects of norepinephrine, dopamine, and epinephrine in moderate and severe septic shock [46]. In patients with moderate shock, no marked differences in splanchnic blood flow and PCO_2 gap could be detected; the splanchnic blood flow was higher with norepinephrine than with epinephrine despite higher cardiac output in patients receiving epinephrine. In a crossover design, Guerin and coworkers recently demonstrated that despite a higher cardiac index, dopamine infusion resulted in lower splanchnic fractional blood flow compared with norepinephrine [36]. Concerns have been expressed about the potential of norepinephrine to impair renal perfusion. Although this might be true in patients who have hypotension and hypovolemia, recent experimental and clinical evidence suggest that norepienphrine can be used safely in vasodilatory, well-resuscitated shock states without jeopardizing the renal function [37,50] On the other hand, there is no clear-cut evidence to support higher targets for arterial blood pressure: two recent clinical studies showed that increasing mean arterial blood pressure from 65 to 85 mmHg with norepinephrine in patients with septic shock was not associated with improved renal function [30,51].

Epinephrine

Despite its potential to restore effective macrocirculation, even in refractory shock, epinephrine was shown to reduce splanchnic blood flow and, at least transiently, compromise gastric mucosal perfusion/metabolism [52,53]. As cited above, the potentially detrimental effect of epinephrine on hepatosplanchnic hemodynamics was also reported in patients who have severe septic shock [52].

Its renal effects in humans have not been documented. Apart from hemodynamic effects, particular metabolic properties of epinephrine have to be considered.

Dobutamin and dopexamine

Dobutamine is currently the preferred drug to increase cardiac output in critically ill patients and is recommended as the agent of choice in septic shock patients [25,26]. In this group of patients, dobutamine alone, as well as in combination with norepinephrine, quite consistently increased regional blood flow [54–56], although the preferential effect on splanchnic circulation was not found [54]. Similarly, PCO_2 gap could be beneficially affected by dobutamine [53,57], although this effect was not always related to an increased splanchnic blood flow [55,58]. Dopexamine was proposed to protect hepatosplanchnic microcirculation [59,60]; however, this view was seriously challenged because dopexamine failed to preferentially increase splanchnic blood flow [61] and even lowered gastric pH [62]. Moreover, dopexamine did not beneficially affect regional metabolic capacity [63] and did lack any potency to improve gastrointestinal barrier and renal function when studied over 7 days of its administration [64]. Hence, the exact role of dopexamine is as yet undefined.

Given the profound microcirculatory disturbances in critically ill patients [65], and because the alterations in microcirculatory functions may not be predicted from systemic or even regional circulation [66], exploring the microcirculatory effects of various vasoactive drugs would give us further important insights into the effects of these interventions. Unfortunately, such human data are still lacking [65].

Can the reported different physiologic effects of various catecholamines translate into relevant clinically important data? Studies evaluating the influence of different vasoactive treatments on the main outcome variables, such as mortality, are strongly needed.

Metabolic consequences of catecholamines: effects beyond perfusion

Multiple effectors must be considered when assessing effects of catecholamines. In fact, the final effect of any vasoactive drug depends on the relative contribution of multiple interrelated factors, including cellular and interorgan metabolic effects of such interventions [67,68]. Sepsis, shock, or trauma causes profound changes in cellular energy metabolism [67]. These changes might be further modified by any vasoactive drug that acts on adrenergic receptors, and influences the local relationship between oxygen and substrate supply and metabolic needs [69,70]. In this context, however, not all catecholamines are created equal.

Epinephrine exhibits the most pronounced capacity to influence metabolism. Epinephrine-induced hyperglycemia (by way of increased gluconeogenesis and

glycogenolysis concomitantly with α-mediated suppression of insulin secretion) and lactate production (via stimulated aerobic glycolysis) are well-known phenomena under physiologic conditions [27,34]. In critically ill patients, epinephrine infusion was associated with a myriad of metabolic changes, including decreased hepatosplanchnic lactate clearance [52], increased lactate/pyruvate (L/P) ratio [52,53], and lactic acidosis [71,72]. In two recent experimental studies, epinephrine, in contrast to norepinephrine, induced marked metabolic changes (systemic hyperlactatemia, acidosis, regional L/P ratios, and intraperitoneal lactate release) [73], and adversely affected organ function and survival [74]. Because hepatic gluconeogenesis is a main determinant of hepatic energy, and hence, oxygen demand, it is reasonable to conclude that additional drug-induced stimulation of this metabolic pathway might result in impaired hepatic oxygen and substrate supply and demand balance [34,67]. The potency of epinephrine, which can induce metabolic "overstimulation," and its ability to compromise hepatosplanchnic blood flow, formed the main arguments for its limited use in the treatment of septic shock [25–27]. However, the popular beliefs that these epinephrine-induced metabolic changes do harm to critically ill patients, and that elevated lactate levels during septic shock are linked to tissue hypoxia, have recently been challenged [27]. In fact, Levy and coworkers demonstrated in an experimental study that epinephrine infusion indeed increased lactate production but without disturbing lactate/pyruvate ratio and tissue ATP, which suggests that these effects were related to the direct effect of epinephrine on carbohydrate metabolism rather than cellular hypoxia [75]. More recently, these authors provided the evidence that skeletal muscles could be a leading source of lactate formation as a result of exaggerated aerobic glycolysis through Na,K-ATPase stimulation during septic shock [76]. Although this study did not directly address the link between increased Na,K-ATPase activity and epinephrine, the authors supported the evidence that the increased rate of lactate production (by way of aerobic glycolysis) under epinephrine stimulation might serve as the important metabolic substrate to sustain specific processes that need a high rate of cytoplasmic ATP [76,77]. The significance of this hypothesis warrants further evaluation.

Norepinephrine is less metabolically active that epinephrine, although the metabolic effects are not completely defined [78]. In the study by De Backer and colleagues, norepinephrine, in contrast to epinephrine, did not adversely affect various metabolic variables in volume-resuscitated patients with moderate and severe septic shock [46]. Similarly, in two recent clinical studies, increasing mean arterial pressure with norepinephrine did not exhibit any effect on systemic metabolic and oxygen exchange variables [30,51]. Finally, the above cited experimental studies also argue against significant adverse metabolic effects of norepinephrine in sepsis [73,74].

Few data on metabolic action of dopamine are available in critically ill patients. Dopamine was shown to decrease splanchnic oxygen consumption despite the increase in blood flow, which suggests impaired hepatosplanchnic metabolic capacity [39]. The same group of investigators reported that dopamine-

induced increase in splanchnic blood flow was not associated with a metabolic modulation assessed by monoethylglycine xylidine formation [79]. Most recently, Guerin and coworkers clearly documented that unlike norepinephrine, infusion of dopamine to vasoplegic septic patients was associated with lower liver lactate uptake and higher hepatic venous L/P ratio [36].

In healthy volunteers, dobutamine exerted only minor metabolic effects on carbohydrate and protein metabolism [78]. Both in septic [54,55] and cardiac surgery patients [80] dobutamine increases regional blood flow without decreasing splanchnic oxygen consumption. In stable patients, after cardiac surgery, dobutamine did not affect splanchnic glucose production, lactate and amino acid metabolism [80], however, endogenous glucose production decreased in dobutamine-treated septic shock patients [54]. Moreover, dobutamine combined with norepinephrine may be equally effective in restoring systemic hemodynamics when compared with epinephrine, but without compromising systemic and regional metabolism [53]. In a clinically relevant model of experimental sepsis, this combination exhibited the most favorable hemodynamic, oxygen kinetic, and metabolic profile with less lung, liver, and intestinal injury [81]. The potentially important role of exogenous β-adrenergic receptor stimulation for the resuscitation of gastrointestinal tract in patients with septic shock is also supported by the evidence that replacing noradrenaline by the pure α-agonist phenylephrine markedly reduced regional perfusion and compromised splanchnic metabolic capacity despite of comparable systemic hemodynamics [82].

Catecholamines and immune-endocrine interactions

Evidence is emerging that adrenergic agents may also have potent inflammatory and endocrine effects, which may change the way in which these agents are selected in the treatment of septic shock and other acute inflammatory states such as pancreatitis, trauma, or major surgery. Immunomodulatory actions of catecholamines are predominantly mediated by way of β_2-receptors; almost all immune cells express these adrenergic receptors on their surface [83,84]. The specific effects of catecholamines are not yet fully defined and they range from controlling the expression of cytokines, neutrophil function, and immune cell distribution to direct pro-apoptotic effects [85]. Dopamine, epinephrine, and norepinephrine have the potential to induce inhibition of cellular immune functions, mainly by down-regulating pro-inflammatory cytokine responses [86–88]. In this context, epinephrine but not norepinephrine showed a profound effect on the interleukine-6 response of splanchnic reticuloendothelial tissues [89]. Immunoregulatory potency of catecholamines might also be mediated by inhibiting the production of pro-inflammatory cytokines and promoting Th_2-cell differentiation in critically ill patients [90,91]. Moreover, catecholamines, in particular epinephrine, may supress oxygen radical production of neutrophills [92], and significantly enhance platelet-neutrophil adhesion [93]. There is also increasing

evidence for a pro-apoptotic role of catecholamines in immune cells [85], cardiomyocytes [94], and endothelial cells [95].

In addition to their direct effects on the immune system, catecholamines might also modulate the immune response indirectly, through their effect on neuroendocrine system. The typical example is dopamine, which is known to supress the secretion and function of a number of key anterior pituitary hormones [96]. Indeed, decreased levels of prolactin, an immunomodulatory hormone with receptors on T and B lymphocytes, with concomitant reduced T-cell responsiveness, were observed in critically ill patients after infusion of low- dose dopamine [97]. Furthermore, by supressing pulsatile secretion of the growth hormone [98], and thyroid-stimulating hormone [99], exogenously administered dopamine (particularly when given for more than a few days) might aggravate cellular immune dysfunction, catabolism, and central hypothyroidism. Although conceivable, the clinical relevance of these consequences has yet to be studied. In contrast to dopamine, dobutamine and dopexamin had a minimal effect on pituitary function in high-risk surgical patients [100].

In conclusion, catecholamines are important in the management of circulatory failure. However, given their complex action on cardiovascular, metabolic, immunological, and endocrine systems, a more rational approach to vasoactive therapy, based on precise recognition of its many effects beyond macrohemodynamics, may be the next frontier.

Vasopressin

Vasopressin and its analog terlipressin exert their effects by way of vascular V1a receptors and renal tubular V2 receptors. V1a receptor stimulation leads to arterial vasoconstriction and V2 stimulation increases renal free water reabsorption. Terlipressin has a higher vascular affinity for vascular receptors than vasopressin as assessed by a higher V1a/V2 receptor ratio compared with vasopressin (2.2 versus 1, respectively) [101].

Abolished responsiveness of vascular smooth muscle to catecholamines stimulation is one of the mechanisms leading to hypotension during endotoxic shock [102]. The vasoconstrictor response to other agents such as angiotensin and vasopressin is similarly abolished [103,104] despite an increased plasmatic level of vasopressin as shown in sepsis or hypodynamic models of septic shock in baboons and dogs [105,106]. The decreased vascular responsiveness during sepsis is mediated by pro-inflammatory cytokines, which exert a down-regulation of V1 receptors [107].

Conversely, Landry and coworkers reported a vasopressin deficiency and hypersensitivity [19,108] in human septic shock. Indeed they demonstrated that for a same level of mean arterial pressure in septic shock and in cardiogenic shock, the vasopressin blood levels were dramatically lower in the former state. In addition, vasopressin administration at low concentration in vasodilatory septic

shock [19] and in post bypass vasodilatory shock showed a beneficial hemodynamic effect in humans [109].

Hemodynamic effects of vasopressin in septic shock

Experimental studies

In hypodynamic endotoxic shock models, vasopressin infusion induces a decrease in cardiac output [106,110,111] and myocardial ischemia [112]. In hyperdynamic endotoxic models, the hemodynamic effects of V1 agonists were dependent on the infusion rate of vasopressin or terlipressin. In a study where the infusion rate of V1 agonist was targeted to increase mean arterial pressure above physiological values (+20 mmHg above baseline values) cardiac output decreased as well as oxygen consumption [113,114]. However, the use of low doses of V1 agonists in hyperdynamic endotoxic animals increased mean arterial pressure without detrimental effect on cardiac output [115,116], and Malay demonstrated the detrimental effects of higher infusion rate of vasopressin on blood flow in various organs [116] in a dose response study in endotoxemic pigs. In long-term hyperdynamic endotoxic shock in pigs, our group reported a decrease in cardiac output associated with a hyperlactatemia [117] that did not originate from splanchnic circulation, despite the use of low-dose terlipressin. In addition, low-dose V1 agonists were reported to improve survival in fluid-resuscitated endotoxic rats [115], and in live bacteria septic shock in sheep [118], as well as in dogs [74].

Clinical studies

In all published studies, V1 agonists increased mean arterial pressure and reduced noradrenaline requirements [19,108,119–125]. The effect of V1 agonists on cardiac output was more variable. Cardiac output decreased in three studies [125–127], remained stable in two [122,128], and even increased in one [124]. In a prospective, randomized study Dünser and coworkers [124] investigated 48 patients who had catecholamine resistant vasodilatory shock and who received either a combined infusion of vasopressin and norepinephrine or norepinephrine alone. Vasopressin-treated patients had significantly lower heart rate, norepinephrine requirements, and a lower incidence of new-onset tachyarrhythmias. Mean arterial pressure, cardiac index, and stroke volume were significantly higher and the gastric mucosal-arterial PCO_2 gradient was significantly lower in patients treated with the vasopressin and norepinephrine. However, these patients also exhibited a significant increase in plasmatic bilirubin concentrations which suggests an impaired liver blood flow or a direct effect on excretory hepatic function mediated by vasopressin. In this study, 18 patients in each group (vasopressin versus norepinephrine) were treated with additional milrinone to compensate for excessive vasoconstriction. Data regarding the impact of V1

agonists on microcirculation is limited and conflicting. Whereas vasopressin infusion did not worsen sublingual microcirculatory alterations (assessed by orthogonal polarization spectral technique) in a patient who had distributive shock following cardiac surgery [129], 1 mg bolus of terlipressin caused a dramatic sublingual microcirculatory shutdown in a patient with vasopressor-resistant septic shock [130].

Effects of V1 agonist on splanchnic circulation

Experimental studies

Schmid and coworkers have assessed incremental doses of vasopressin on mesenteric, renal and iliac blood flows in anesthetized dogs [131]. Vasopressin induced a decrease in blood flow in the three vascular beds associated with a decrease in portal pressure. However, mesenteric and renal blood flows, expressed as percentage of cardiac output, significantly increased; whereas, they decreased in the ileac vascular bed, which suggests a redistribution of blood flow toward splanchnic organs. In an ex-vivo study in rabbits, vasopressin had a vasoconstrictor effect on the renal artery but not on the mesenteric artery, and this vasoconstriction was inhibited by nitric oxide [132]. Hence, depending on the species and the experimental model, effects of V1 agonists on regional hemodynamics are potentially different.

V1 agonists jeopardize splanchnic hemodynamics because of their potent vasoconstrictor effects such as Laszló and colleagues reported in various models of gastric mucosal injury in rats [133] and by infusing a V1 receptor antagonist that ultimately reduced this gastric mucosal damage [134]. Recently, in endotoxic, non fluid-resuscitated rats, our group reported that infusion of terlipressin dramatically decreased splanchnic blood flow. Conversely, fluid-challenged endotoxic rats had well-maintained splanchnic macrocirculatory blood flow, as well as ileal microcirculation assessed by Doppler echocardiography [115]. Fluid challenge, seems to assume crucial importance for the hemodynamic response: when the experimental design led to a hypodynamic state, infusion of V1 agonists induced detrimental macro- or micro-circulatory effects on the splanchnic area [111]. By contrast, when animals were in a hyperdynamic circulatory state, studies did not report harmful effects on splanchnic hemodynamics [115,117,118]. In fluid-resuscitated endotoxic pigs, Malay and colleagues reported the effects of incremental doses of vasopressin on global and regional circulation [116]. A low dose of vasopressin, such as typically used in the clinical management of septic shock, raised arterial pressure without detrimental effect on mesenteric, renal, iliac, and carotid blood flows. By contrast, moderately greater doses of vasopressin induced ischemia in the mesenteric and renal circulation. The study of Westphal and coworkers also nicely illustrated the importance of the dose of V1 agonists. The authors analyzed effects of high doses of vasopressin in peritonitis rat models (0.006 UI/min/340g of body weight

approximately 1.23 UI/min for a human of 70 kgs) on the ileal villous perfusion using videomicroscopy. As expected vasopressin markedly increased mean arterial pressure compared with controls, but also reduced the blood flow of continuously perfused terminal arterioles. Plasma vasopressin concentrations decreased below baseline during shock, and infusion of vasopressin induced supra-physiologic concentration of the hormone, which in turn probably led to an excessive vasoconstriction [135].

Clinical studies

Few studies report the effects of V1 agonists on the splanchnic circulation in patients with septic shock. Among the studies related to the systemic effects of V1 agonists, none reported clinical detrimental renal or splanchnic side effect [19,119–125]. Nevertheless, Klinzing and coworkers reported an increased gastric mucosal-arterial PCO_2 gradient when norepinephrine was replaced by high-dose vasopressin to keep mean arterial blood pressure constant [126]. It should be stressed, however, that the simple clinical assessment seems insufficient to affirm the absence of harm of V1 agonists on splanchnic circulation.

In a prospective controlled study in 16 patients with septic shock refractory to catecholamines, Tsuneyoshi and coworkers [120] reported a significant increase in urinary output in 10 patients with vasopressin, which was associated with a decreased arterial lactate concentration in the surviving patients. In a double blinded study that compared a continuous 4-hour vasopressin infusion with norepinephrine in 24 patients who had septic shock, Patel and coworkers [122] reported a significant increase in diuresis affiliated with a significant improvement of creatinine clearance with vasopressin. The gastric mucosal-arterial PCO_2 gradient remained unaltered in both groups. More recently, in a randomized study, Dünser and coworkers compared the combination of vasopressin (4 UI/h) with norepinephrine versus norepinephrine alone in 48 patients in vasodilatory shock, refractory to catecholamines [124]. In this study, the gastric-arterial PCO_2 gradient rose after one hour and remained stable until the end of the study with norepinephrine alone; whereas, the combination of vasopressin and norepinephrine induced a progressive raise of the gastric-arterial PCO_2 gradient and reached the same values after 48 hours. By contrast, the combination of the two vasopressors was associated with increased bilirubin levels, which suggests either compromised liver blood flow or direct impairment in hepato-cellular function [124]. In a short-term study in 12 patients who had septic shock, Klinzing and coworkers [126] reported that switching from norepinephrine (0.18 to 1.1 μg/kg/min) to a relatively high-dose vasopressin (0.06 to 1.8 UI/min) significantly increased the gastric mucosal-arterial PCO_2 gradient from 18 ± 27 to 37 ± 27 mmHg. It should be noted, however, that variations of a tonometry reading do not always mirror splanchnic blood flow changes [136]. Indeed, splanchnic blood flow was invasively assessed with continuous indocyanine green dye infusion and hepatic venous catheterization in this study. Although vasopressin significantly decreased cardiac index and systemic oxygen consumption, splanch-

nic blood flow decreased non-significantly, which resulted in a rise of the fractional splanchnic blood flow, from 11 ± 8 to 26 ± 17%. Moreover, the potential detrimental effects of the V1 agonist terlipressin on the gastric mucosal-arterial PCO_2 gradient were not confirmed by Morelli and coworkers [127] who reported on the effect of a bolus of 1 mg of terlipressin in 15 patients who had septic shock and were treated with a combination of norepinephrine and dobutamine to maintain a high cardiac output. Terlipressin increased mean arterial pressure and mean pulmonary artery pressure but lowered cardiac output, oxygen delivery, and consumption as well as arterial lactate concentration. Terlipressin did not alter the gastric mucosal-arterial PCO_2 gradient and even increased gastric mucosal perfusion assessed by an ultrasound flowmeter. Finally, Leone and colleagues reported that one or two boluses of 1 mg of terlipressin administered to septic-shock patients who are not responsive to high-dose catecholamien vasopressor support, were found effective in restoring arterial blood pressure and renal function, but bilirubin, aspartate aminotransferase, and alanine aminotransferase were significantly increased during the study period [125]. Given these controversial data, the hemodynamic effects of low doses of V1 agonists on splanchnic circulation in patients who have septic shock are not fully understood and justify further invasive studies.

In conclusion, during hyperdynamic septic shock, evidence for the beneficial effect of low-dose V1 agonists on global hemodynamics is accumulating. However, there are no data regarding the superiority of V1 agonists in terms of mortality and morbidity. The hemodynamic effects of V1 agonists on splanchnic circulation are controversial, and the use of V1 agonists is recommended only in clinical investigation protocols.

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