Neuroanesthesia and Intensive Care

Review article: Organ perfusion/permeability-related effects of norepinephrine and vasopressin in sepsis

[Exposé de synthèse : Les effets reliés à la perfusion et à la perméabilité organique de la norépinéphrine et de la vasopressine durant le "sepsis"]

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Purpose: One invariable hallmark of severe sepsis is generalized tissue "malperfusion" and hyperpermeability secondary to microcirculatory/capillary leakage. This review focuses on direct and/or indirect influences of norepinephrine, as a standard of care, and vasopressin, as an alternative vasoactive drug, on organ and tissue perfusion/permeability in severe sepsis.

Source: English and French language articles and books published between 1966 and 2005 were identified through a computerized Medline search using the terms "sepsis, permeability, norepinephrine and vasopressin". Relevant publications were retrieved and scanned for additional sources.

Principal findings: There are few randomized clinical trials comparing different vasopressors in sepsis; most available literature consists of clinical reports, animal experiments and occasional reviews. Based on the best current evidence from these sources, we describe the status of major organ perfusion/permeability in sepsis (i.e., the lung, the kidney, the heart, the intestine/gut) in the context of sepsis-induced organ dysfunction/failure. Potential and differential therapeutic effects of the vasopressors norepinephrine and arginine-vasopressin, in the setting of sepsis, are identified.

Conclusions: In the treatment of sepsis, arginine-vasopressin exhibits organ-specific heterogeneity in vascular responsiveness, compared to norepinephrine. While norepinephrine is a current standard of care in sepsis, arginine-vasopressin shows promise for the treatment of septic shock.

***Objectif** : Un signe invariable du "sepsis" sévère est la «malperfusion» généralisée et l'hyperperméabilité secondaire à une fuite microcirculatoire ou capillaire. Le présent exposé insiste sur les influences directes ou indirectes de la norépinéphrine, comme norme de soin, et de la vasopressine, comme médicament vasoactif de remplacement, sur la perfusion et la perméabilité organiques et tissulaires durant le "sepsis".*

***Source** : Des articles de langue anglaise et française et des livres publiés entre 1966 et 2005 ont été repérés dans Medline sous les termes «sepsis, permeability, norepinephrine, vasopressin». Les publications pertinentes ont été extraites et examinées à la recherche d'autres sources.*

***Constatations principales** : Peu d'études cliniques randomisées comparent les effets des différents vasopresseurs durant le "sepsis" ; la documentation consiste surtout en résumés cliniques, expériences sur des animaux et revues occasionnelles. À partir de la meilleure preuve courante relevant de ces sources, nous décrivons l'état de la perfusion et de la perméabilité des organes principaux, c'est-à-dire le poumon, le rein, le cœur, l'intestin/le tube digestif, dans le contexte d'une dysfonction ou d'une défaillance organiques induites par le sepsis. Les effets thérapeutiques potentiels et différentiels de la norépinéphrine et de l'arginine-vasopressine sur le "sepsis" sont établis.*

***Conclusion** : Dans le traitement du "sepsis", l'arginine-vasopressine, comparée à la norépinéphrine, présente une hétérogénéité de la réactivité vasculaire qui est spécifique à l'organe traité. La norépinéphrine est le médicament couramment utilisé, mais l'arginine-vasopressine semble prometteuse pour traiter le choc septique.*

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Fluid distribution to endothelial/epithelial cells in sepsis

One of the invariable hallmarks of severe sepsis is overall tissue hyperpermeability secondary to microcirculatory/capillary leakage. This condition is promoted by early, severe and acute alterations of several components of the Starling equation.[1] Consequently, there is frequently a drop in oncotic pressure initiated by dilution of circulatory volume, protein breakdown (hypercatabolism) and extravascular leakage. The first hours of resuscitation in severe sepsis and septic shock comprise large infusions of fluid, often leading to rapid soft tissue swelling and potentially to organ edema. Not surprisingly, organ damage and dysfunction are frequently accompanied by changes in fluid and protein extravasation, although no causal relationship has been established. For instance, acute respiratory distress syndrome (ARDS) patients exhibited a 78% mortality rate when gaining weight (mean 4 kg) vs a 50% mortality when losing weight (mean 6 kg)[2] at day 14. Thus, control of body fluids is an essential process that is altered in sepsis, with potential consequences on patient outcome.

Over 50% of total body weight represents fluid, the absolute and relative distribution of which varies according to species and age.[3] In pathological situations such as sepsis, absolute and relative body fluid distribution between the various anatomical compartments varies considerably, and may ultimately contribute to a variety of reversible and/or irreversible target organ damage. Vascular and interstitial compartments of the extracellular fluid volume represent approximately 5 and 15% of total body weight, respectively, in normal adult humans. The vascular volume is divided into three major functional segments, the large delivery and resistance arteries (high pressure system), followed by numerous microcirculatory networks, and finally, by small and large collecting veins (low pressure system). Microcirculatory networks constitute the largest fraction, in which major and vital exchanges between vessels and adjacent interstitial compartments occur,[4] and the one most affected during sepsis. Indeed, pre- and postcapillary resistances represent the physiological basis of fluid and solute movement across the vascular barrier. Thus the permeability properties of capillaries and postcapillary venules to macromolecules (tenfold variation) may explain the particular location of target organ damage in a variety of diseases[5] including, most likely, sepsis.

Next to microcirculatory networks, interstitial fluid compartments occupy a strategic position between blood vessels and all cellular volumes, the latter representing the largest fluid compartment, roughly 40% of total body weight overall. Moreover, the respective vascular, interstitial and cellular volumes between the various organs also vary considerably.[6] The lymphatic system in the interstitial space is essential for returning excess fluid/proteins to the circulation, playing a key role in maintaining capillary/interstitial equilibrium. Lymphatic flow can significantly increase with increases in interstitial fluid pressure, but becomes quickly saturated.[7,8] In addition to distinctive fluid volume properties, the chemical composition of interstitial fluid differs markedly between organs, notably with regard to collagen, elastin, fibronectin and proteoglycan content[8,9] and has recently been proposed to explain unusual physical and chemical phenomena such as the albumin exclusion space. The latter appears to play a critical role in the transfer of vital substrates (including albumin-transported hormones and drugs) from blood vessels to the cell mass of all organs, as well as traffic of waste products in the opposite direction, a key process in target organ damage.[5] This concept of target organ damage, summarized in Figure 1, is clearly related to the traditional parameters of the Starling equation.[1,6] Next to vascular and interstitial compartments, intracellular body fluid compartments are less heterogeneous, but have important clinical implications. Since movement of fluid and the highly selective passage of solutes across cellular compartments have a major impact on adjacent interstitial fluid volumes and henceforth on the entire vasculature, the active and/or passive modulation of these movements becomes critical in health, as well as in sepsis.

Endothelial cell dysfunction is a well-established concept in severe sepsis.[9,10] Because the endothelium, as a vascular semi-permeable barrier, is critical in maintaining the balance between vasodilatation and vasoconstriction; inflammatory cell adherence and non-adherence; anti- and pro-coagulation as well as permeability and tightness, its dysfunction may be instrumental in the occurrence of multiple organ failure. Once stressed endothelial cells are exposed, tissue factor, thrombin or plasmin, all contribute to sepsis-induced microvascular coagulation and disseminated intravascular coagulation, and in synergy with pro-inflammatory cytokines, increase endothelial permeability. In contrast, antagonists such as activated protein C, antithrombin III; tissue factor pathway inhibitor and thrombomodulin deactivate this process. Lipopolysaccharides also induce an increase in paracellular permeability along with a selectively-elevated filtration capacity.[11] In addition, the shedding of apoptotic endothelial cells in the bloodstream of septic patients occurs in a rate-dependent relationship with outcome/mortality[12,13] and represents another per-

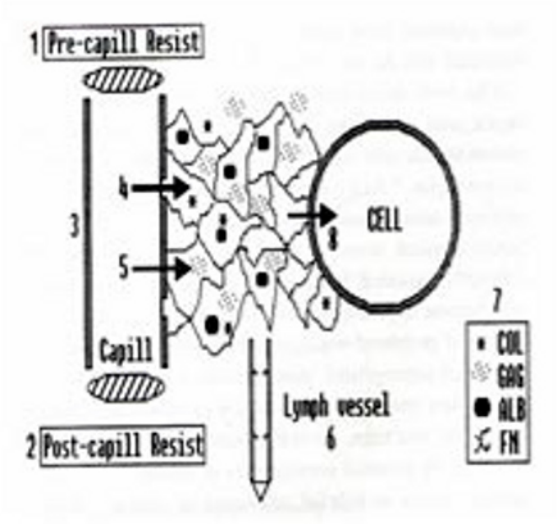

FIGURE 1 Vascular (3) pre- and postcapillary resistances (1, 2) and interstitial events (7) responsible for target organ damage/failure (8), following endothelial cell alteration/dysfunction. Alteration in endothelial (3) permeability to albumin (4, 5) is associated with extravasation of plasma into the interstital compartment. Changes in collagen (COL), albumin (ALB), fibronectin (FN) and glycoaminoglycans (GAG) arise and can affect size and physicochemical properties of this strategic fluid compartment, depending on the limited capacity of the lymphatic flow to adapt (6). Reproduced with permission from Elsevier: *Plante GE.* Vascular response to stress in health and disease. Metabolism 2002; 51: 25–30 (reference 8).

missive factor to permeability, as observed in capillary leak syndromes.[14] Epithelial dysfunction, although a less popular concept in sepsis, can nevertheless be involved, either as a very impermeable barrier, in the course of pro-inflammatory, pro-coagulatory and hyperpermeable phenotype as well,[15–17] or behave altogether differentially from the endothelium.[18]

The following sections will focus on the status of major organ perfusion/permeability in sepsis in the context of sepsis-induced organ failure, which is an archetype of body fluid intercompartmental shift (at least at the vascular-interstitial level). In addition to discussing four of the main target organs involved in sepsis, potential and differential influences of the vasopressors norepinephrine (NE) and arginine vasopressin (AVP), two molecules that target different receptors as well as different signaling pathways (Table), will be also considered.

Currently, it is unknown whether the use of a particular catecholamine or another vasopressive drug is able to influence outcome in septic patients, and most current observations are predominantly physiological. Outcome differences between NE and AVP in management of septic shock are difficult to demonstrate, and investigations addressing this issue are ongoing. While exogenous AVP is first and foremost indicated for vasopressive activity in resistant redistributive shock, one must bear in mind that AVP serves a major role in the neuroendocrine control of body fluid metabolism.

The lung in sepsis

Sepsis-induced organ hyperpermeability can be a life-threatening and outcome-related condition. The lung as an oxygen-provider/discloser can be quickly affected and septic patients with ARDS share lower survival rates compared to other etiologies such as urosepsis.[19] Indeed, increased extravascular lung water (EVLW) in critically-ill patients affects mortality rates, especially in septic ARDS patients.[2,20] Concomitantly, management of EVLW can reduce duration of mechanical ventilation,[21] whereas increased lung edema and EVLW in extra-pulmonary sepsis can provoke alteration of gas exchange along with hypoxemia, as well as enhance work of breathing and oxygen consumption.[20] Such situations often compel attending intensive care unit teams to place the patient at rest on mechanical ventilation in order to slow down this sepsis-induced metabolic storm. Unfortunately, the tracheal intubation procedure *per se* is neither easy nor always safe to perform in context of septic shock instability, not to mention that mechanical ventilation can impact outcome by duration of mechanical support and potential side effects (e.g., superinfection, volutrauma, etc.). Thus, addressing sepsis-induced lung permeability is clearly a relevant and evidence-based process. Concomitant to increased lung permeability, pulmonary arterial hypertension is almost constantly associated with septic ARDS,[22] further increasing hydrostatic pressure-directed fluid leakage. Some of these ARDS-associated high pulmonary arterial pressures are sensitive to inhaled nitric oxide (NO) therapy.[23] Strong arguments for sepsis-induced lung hyperpermeability to fluids and proteins not only stem from experimental endotoxic models which produce both functional and structural alterations of the alveolar-capillary barrier[24] but also from bedside clinical assessment.[20] Systemic response with recruitment of activated polymorphonuclear neutrophils releasing reactive oxygen species and proteases (including edemagenic serine protease and coagulation cascade-activator thrombin), together with multiple bloodstream inflammatory mediators (lipids, cytokines, etc.), are significant components of

TABLE Signal transduction pathways, distribution and tissue responses of AVP and catecholamines

Receptor type	*G protein*	*Biochemical effectors*	*Distribution*	*Tissue responses*
V_1 receptors	G_q	↑ phospholipase C-ß	Smooth muscle cells	Contraction
		↑ phospholipase D	Adrenal gland	Secretion of cortisol
		↑ phospholipase A_2	Brain	Secretion of aldosterone
			Liver, spleen, kidney, bladder	Secretion of CRF
V_2 receptors	G_s	↑ adenylyl cyclase	Renal collecting duct system	Conservation of water
			Platelets, endothelium	Aggregation
V_3 receptors			Adenohypophysis	Secretion ACTH
			Adrenal gland (medulla)	Secretion catecholamines
$\alpha_{1A, 1B, 1D}$ receptors*	G_q	↑ phospholipase C	Vascular smooth muscle	Contraction
	G_q	↑ phospholipase D		Contraction
	G_q, G_i/G_o	↑ phospholipase A_2	Genitourinary smooth muscle	Glycogenolysis
			Liver	Gluconeogenesis
				Hyperpolarization
				Relaxation
			Intestinal smooth muscle	↑ contractile force
			Heart	Arrhythmias
$\alpha_{2A, 2B, 2C}$ receptors*	$G_{i\ 1,2\ or\ 3}$	↑ adenylyl cyclase	Pancreatic islets (ß cells)	↓ insulin secretion
	G_i (ßγ subunits)	↑ K^+ channels		Aggregation
		↓ L- and N-type	Platelets	↓ release of NE
	G_o	Ca^{2+} channels	Nerve terminals	Contraction
			Vascular smooth muscle	
ß$_1$ receptors	G_s	↑ adenylyl cyclase	Heart	↑ force of contraction
		↑ L-type Ca^{2+} channels	Juxtaglomerular cells	↑ rate of contraction
				↑ AV nodal conduction
				↑ renin secretion
ß$_2$ receptors	G_s	↑ adenylyl cyclase	Smooth muscle	Relaxation
			Skeletal muscle	Glycogenolysis
				Uptake of K^+
			Liver	Glycogenolysis
				Gluconeogenesis
ß$_3$ receptors	G_s	↑ adenylyl cyclase	Adipose tissue	Lipolysis

CRF = cerebrospinal fluid; ACTH = adrenocorticotrophic hormone; NE = norepinephrine; AV = atrioventricular. * There are some differences in tissue localization for each subtype of α_1 and α_2 receptors, but the distinction in mechanisms of action and tissue responses are not sufficiently defined to be presented here. Rearrangement of Tables VI-III and VI-IV from: Reproduced with permission from McGraw-Hill Company. *Hoffman BB, Taylor P.* Neurotransmission: the autonomic and somatic motor nervous system. *In*: Hardman JG, Limbird LE (Eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill; 2001: 137–8; and of the Table reproduced with permission from Elsevier. *Lauzier F, Lamarre P, Lesur O.* Vasopressin in the treatment of septic shock. Reanimation 2004; 13: 147–53.

lung inflammation and hyperpermeability in sepsis, their blockage being ultimately effective in decreasing pulmonary vascular permeability.[25]

Impact of NE and AVP on pulmonary function and vascular permeability in sepsis

High infusion rates of exogenous catecholamines (mainly NE as standard of care in septic shock) can induce lung edema by increasing filtration and microvascular pressure, as well as by other mechanisms.[26] It therefore seems logical that the combination of sepsis and related permeability disorders (i.e., protein breakdown/hypercatabolism and extravascular leakage) with aggressive supportive treatments such as large volume crystalloid infusion and high levels of NE infusion, are plausible cornerstone contributors to sepsis-induced lung edema, acute lung injury and ARDS. By comparison, AVP used either solely or as a catecholamine-sparing drug appears to be relatively safe for the alveolar-capillary barrier. In fact, hemodynamic

effects of AVP on lung circulation are distinct from those observed with catecholamines. High doses of NE (1–2.5 $\mu g \cdot min^{-1}$), often used in refractory shock, can induce (or contribute to) increased pulmonary arterial pressures/resistances, whereas AVP does not, unless given in unusually high doses (above 1.0 to 1.5 $U \cdot min^{-1}$). In some cases, AVP may even decrease these circulatory parameters.[27] The use of AVP remains controversial however, especially for terlipressin, a synthetic analogue of AVP.[28] In an experimental setting, a rising pulmonary arterial pressure is an early initial event followed by right ventricular failure; hence control of associated pulmonary hypertension can protect against edema.[24,29] In the clinical setting, lowered pulmonary arterial pressure and improved right ventricular function is a distinctive pattern in septic shock survivors.[30] Thus, addition of pressure-supporting drugs sharing different pharmacological and physiological targets and pathways could influence the "physiological low-pressure pulmonary circulation". Remarkably, in a retrospective study of more than 600 patients, Hall *et al.*[31] denoted an increased incidence of ARDS (34%) in patients treated for septic shock with exogenous catecholamines (dopamine, NE) compared to those treated with AVP (18%). There was, however, no tentative pathophysiological explanation proposed for this striking epidemiological observation. Subsequent analysis excluding most of the patients (over 70%), failed to reproduce this differential trend of ARDS association with vasopressor selection.[32]

In contrast to the human experience, several experimentally-based studies relevant to this question have been reported. In a pig model of ventricular fibrillation, the use of epinephrine instead of AVP was associated with a deterioration in gas exchange (as assessed by ventilation/perfusion ratio and oxygen arterial partial pressures) in the first 30 min following cardiopulmonary resuscitation.[33] In an acute resuscitated model of rat endotoxemia, Evans Blue (sharing high affinity to albumin) was found to leak more heavily outside of the lung circulation when using NE instead of AVP after two hours of monitoring (Figure 2).[34] In a chronic ovine model of endotoxemia, there was pathological evidence of increased pulmonary edema and alveolar hemorrhaging in NE-treated animals compared to animals treated with AVP or a combination of AVP plus lower doses of NE.[35]

In the above-cited reports, AVP may not necessarily be pro-active per se in clearing or preventing lung edema/permeability, but rather simply distinctive to NE. In order to be proactive, AVP should strongly target expressed vasopressin-1 receptor (V1R) and vasopressin-2 receptor; the latter making the AVP-dependent aquaporin-2 (AQP-2) water pump useful for fluid clearance. Unfortunately, AQP-2 is neither visibly expressed nor inducible in the lung. On the other hand, other presently unidentified or lesser known AVP-dependent receptors (i.e., vasopressin-activated calcium-mobilizing receptor) may eventually be discovered or better characterized.[36] In addition, AVP could function with the salt pump sodium epithelial channel whose expression is enhanced in the lung of AVP-sustained exposed rats.[37] Other mechanisms by which AVP can be protective may possibly include AVP-induced atrial natriuretic peptide secretion, via the vasopressin-3 receptor, which can attenuate lung permeability. However, short-term infusion of atrial natriuretic peptide had no impact on EVLW or altered pulmonary gas exchange in a small cohort of ARDS patients.[38]

Effects of ß-adrenergic agonists on pulmonary permeability in vascular barrier-enhancing conditions are also a matter of debate. On the one hand, catecholamines: 1) contribute to the maintenance of vascular integrity; 2) exhibit overall anti-inflammatory activity by supporting quiescent states of polymorphonuclear neutrophils and monocytes; and 3) improve (with cyclic adenosine monophosphate agonists) lung alveolar fluid clearance.[39–42] However, NE increases

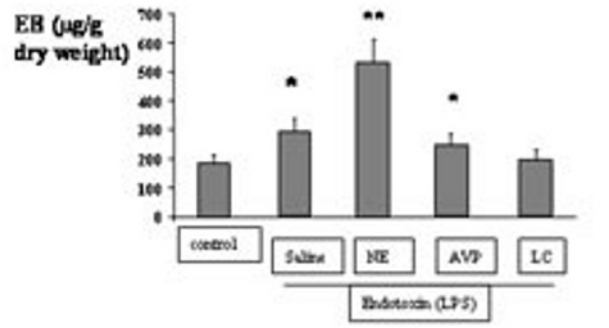

FIGURE 2 End-experimentation Evans Blue lung content in rats challenged with LPS (E coli O127:B28, 10 $mg \cdot kg^{-1}$ iv) or saline (control) and pressure supported by saline, NE, AVP or L-canavanin (LC). Reproduced with permission from the American Physiological Society. Levy et al. Comparative effects of vasopressin, norepinephrine and L-canavanine, a selective inhibitor of inducible nitric oxide synthase, in endotoxic shock. Am J Physiol 2004; 287: H209–15 (reference 34). LPS = lipopolysaccharides; NE = norepinephrine; AVP = arginine-vasopressin.

pulmonary microvascular pressure through greater constriction of postcapillary vessels,[26,42] while fever as well as acidosis, which are frequently observed in severe sepsis, can alter NE-induced barrier-improving functions.[43]

In summarizing pulmonary responses, selection of NE, especially at high infusion rates, may have deleterious effects on lung function/permeability in sepsis, whereas AVP may potentially have catecholamine- and lung leakage-sparing capabilities.

The kidney in sepsis

Severe sepsis is commonly associated with kidney dysfunction and oliguria and accounts for more than 50% of intensive care unit admissions for acute renal failure (ARF).[44,45] Mortality rates in these patients remain very high.[44,45] Septic shock can lead to reduced renal blood flow and to afferent arteriolar vasoconstriction, resulting in ischemic kidneys, although this is still under debate. Recent data obtained from hyperdynamic septic shock animal models reveal increased renal blood flow with a reduction in vascular resistance, reflecting systemic vasodilatation.[46] Endotoxemia *per se* causes alteration in intrarenal blood flow distribution, inducing an imbalance between "dilator" (NO, prostaglandins) and "constrictor" (endothelin, angiotensin II, NE) circulatory molecules.[46] Overproduction of NO, via the triggering of inducible NO synthase, as well as sepsis-induced endothelial NO synthase attenuation have been singled out in the redistribution of renal flow.[46,47] In this respect, specific inhibitors of inducible NO synthase preserve renal function whereas the endothelial NO synthase knockout approach further induces renal dysfunction by altering glomerular filtration rate in endotoxemic rats and mice.[48] Indeed, glomerular filtration rate is disproportionally reduced comparatively to renal blood flow, highlighting the fact that hemodynamic factors are only some of the mechanisms responsible for renal function alteration in sepsis. Furthermore, systemic and local inflammatory mediators can provoke renal dysfunction even in the absence of any obvious hemodynamic perturbation, possibly through endothelial dysfunction. Hence, acute renal failure can at times be the first clinical manifestation of sepsis. While neutralization of platelet activating factor, endothelin and tumour necrosis factor alpha (TNF-α) can prevent renal damage as well as adverse hemodynamic effects and glomerular filtration rate alteration in animal endotoxic models, it failed to show survival benefits in advanced phase trials.[49,50]

Microalbuminuria is a sensitive marker of increased permeability of glomerular endothelium correlating with systemic permeability in several conditions which precede organ dysfunction. Postoperative patients exhibiting sepsis often have increased microalbuminuria associated with organ dysfunction (sequential organ failure assessment score).[51] In addition, a rising microalbuminuria during the first 48 hr of intensive care unit stay is a good predictor of acute respiratory and multiple organ failures.[51] Tubular function can also be affected in addition to glomerular function in sepsis. At the outset, acute renal failure is associated with low sodium excretion fraction, while later on, sepsis causes tubular damage/necrosis and a fall in sodium reabsorption. One proposed hypothesis is an increased leakiness of the proximal tubular epithelium resulting in sodium back-flow towards the tubular lumen as well as equal work for less sodium reabsorption.[52]

Impact of NE and AVP on renal function in the septic patient

Norepinephrine, as a standard of care in septic shock resistant to fluid resuscitation, was originally thought to deteriorate renal function by extreme renal vascular constriction, combining both afferent and efferent effects. It is still debated as to whether "relevant dosing" of NE, by restoring blood pressure and vascular tone, can help maintain renal blood perfusion, glomerular filtration rate and urine output.[53,54] Like other ß-adrenergic agonists, NE is antinatriuretic;[55] however, whether this can influence kidney permeability/leakiness has not been extensively studied until just recently in an acute model of endotoxemia (Figure 3).[34]

Exogenous AVP, as an alternative to NE, can induce systemic vasoconstriction through V1R binding, and increases systemic blood pressure in septic shock. Arginine-vasopressin preferentially induces vasoconstriction of efferent arterioles over afferent arterioles in isolated human kidney vessel preparations *in vitro*, as well as inhibiting lipopolysaccharides- and interleukin-(IL) 1ß-stimulated NO (inducible NO synthase) in cultured rat glomerular mesangial cells.[56,57] Therefore, AVP can restore renal blood flow (particularly cortical blood flow) and glomerular filtration pressure in septic/endotoxic conditions.[58] Consequently, urine output as well as creatinine clearance can be substantially improved in patients exhibiting severe septic shock and treated with AVP.[59] This effect was also observed in two short-term animal models of endotoxemia (Figure 3) but not in a third model using viable E coli intraperitoneal implantation.[60] In addition to increasing glomerular filtration pressure, two other mechanisms have also been proposed to explain the increase in urine output observed

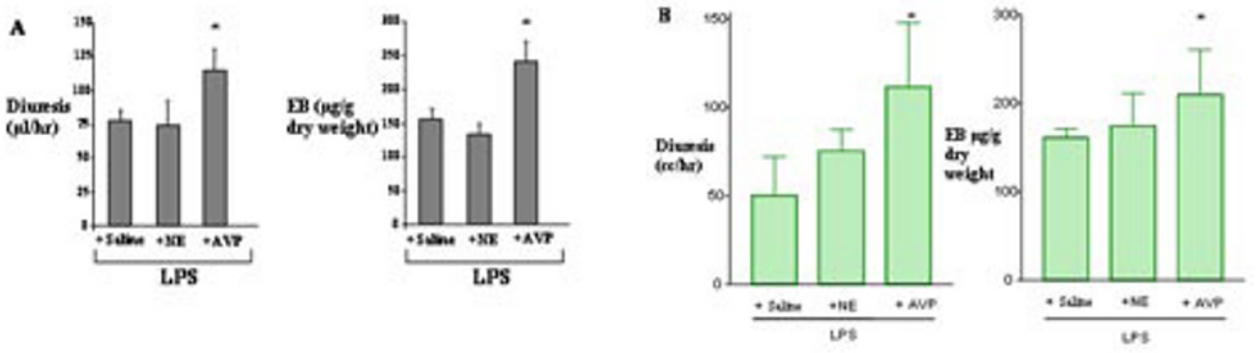

FIGURE 3 Effect of endotoxin (E coli O127:B5) on urine output and whole kidney EB permeability in anesthetized, mechanically ventilated animals: (A) adult rats, LPS 10 mg·kg^{-1} *iv*, two hours of experiments (reproduced with permission from the American Physiological Society. Levy *et al.* Comparative effects of vasopressin, norepinephrine and L-canavanine, a selective inhibitor of inducible nitric oxide synthase, in endotoxic shock. Am J Physiol 2004; 287: H209–15 (reference 34); and (B) ewes LPS: ~ 80–100 nanog·kg^{-1}·min^{-1} *iv*, three hours of experiments (unpublished). Support of blood pressure by saline; NE or AVP is aimed at maintaining MAP ≥ 65 mmHg. * $P < 0.05$ *vs* saline group. EB = Evans Blue; LPS = lipopolysaccharides; NE = norepinephrine; AVP = arginine-vasopressin; MAP = mean arterial pressure.

in AVP-treated patients with septic shock: 1) activation of oxytocin receptors; and 2) release of atrial natriuretic peptide, causing natriuresis. Interestingly, AVP-induced diuresis is paralleled by an increase in renal permeability in two animal models of endotoxemia (Figure 3). The benefit *vs* possible downside of this AVP-induced increased permeability on kidney function remains to be clarified. On the other hand, an enhanced renal interstitial hydrostatic pressure has already been reported to induce pressure-diuretic and a natriuretic response in non-endotoxic conditions.[61]

Finally, AVP exhibits a well known physiological antidiuretic property through activation of vasopressin-2 receptor and subsequently of the AQP-2 shuttle system, leading to increased water permeability in collecting ducts. In this respect, AQP-2 expression in animal kidney medulla was shown to be modulated after endotoxin challenge, downregulated in a subacute model[62] but upregulated in a short-term acute model.[63] In the latter instance, exogenous AVP further enhanced AQP-2 epithelial membrane translocation, but suppressed pump release in urine.[63] Finally, AVP also stimulates sodium reabsorption by activating sodium channels in collecting ducts.[37]

In summarizing effects on the kidney, sepsis-affected renal function does not appear to be adversely affected, but rather, is potentially improved by AVP as well as by NE therapy. The influence of AVP infusion on sepsis-induced altered AQP-2 expression and kidney permeability remains to be determined.

The heart in sepsis

Endotoxic experimental models have demonstrated evidence of acute and subacute remodelling alterations in the heart (e.g., increased collagen content, myocardial edema, etc.),[64] observations also confirmed by postmortem studies of deceased septic shock patients. However, these alterations are not necessarily specific to septic conditions, and can be observed in other states of shock requiring catecholamine support.[65] Hence, it is not clear whether myocardial edema, although possibly responsible for alterations in heart compliance by pressure/volume curve displacement, can actually affect organ function. On the other hand, indirect impact of myocardial permeability/edema can be readily observed by a permissive effect on polymorphonuclear neutrophil migration into the myocardium.[66] More specifically, the increase in myocardial permeability observed in sepsis could be explained by several mechanisms including: 1) alteration of the endocardial surface layer; 2) myocardial cellular apoptosis; 3) myocardial dysfunction induced by inflammatory mediators [platelet activating factor, TNF–α, NO, IL-6, macrophage migration inhibitory factor][67,68] and; 4) sepsis-induced microcirculatory malperfusion/ redistribution.

The endothelial surface layer which contains mostly proteoglycans, TNF-α[69] as well as platelet activating factor,[70] alters its composition and function in sepsis. It is also known that destroying the endothelial surface layer by hyaluronidase treatment can lead to irrevers-

ible myocardial tissue edema.[71] Consequently, endothelial surface layer alterations may partly explain the presence of cardiac tissue edema observed in sepsis.

Apoptosis associated with intramural hemorrhagic areas has also been observed in autopsies of septic patients.[72] This apoptotic process may be partly responsible for decreased heart function in sepsis. Inflammatory cytokines such as TNF-α and IL-1ß[73] are some of the many factors suspected of inducing cardiomyocyte apoptosis in sepsis as well.

Coronary arterial flow is usually considered to be increased in human septic shock[73] (although several animal models have reported a decreased arterial flow) together with a general occurrence of microcirculatory dysfunction.[73] Increased but dysregulated coronary blood flow with secondary hyperemia may be induced by local NO production.[74] On the other hand, myocardial ischemia in susceptible areas is induced by NO inhibition, hence reducing coronary blood flow.[75] Overall, any mismatch of perfusion to oxygen consumption ratio occurring in septic patients is liable to induce patchy microareas of myocardial damage with troponin I release,[76] because of the limited available myocardial oxygen extraction reserve.

Impact of NE and AVP on myocardial function and ischemia in sepsis

Vasopressors in general can have a potentially deleterious role on the endotoxic/septic heart. In experimental settings, ß-agonist isoproterenol infusion is associated with cardiac edema and tissue injury.[77] High doses of catecholamines increase cardiac output and rate, oxygen consumption, cardiomyocyte apoptosis, as well as inducing coronary vasoconstriction.[77,78] In contrast, high infusion rates of AVP as well as terlipressin (an analogue of AVP) have been shown to reduce cardiac output and rate, both of which are secondary to increased vagal and decreased sympathetic tones, associated with a decrease in coronary blood flow. Such observations have been confirmed in a model of isolated rabbit hearts without vasodilatory shock.[79] On the other hand, it is unlikely that AVP moderates excess edema in cardiac tissue, since V1R are the only subtype receptors expressed in the heart (along with oxytocin receptors), with no evidence of vasopressin-2 receptor or AQP-2 expression.

In summarizing the cardiac response of these pharmacological strategies, although the effects of AVP and NE on the heart are distinctive, both drugs have the potential to be harmful by enhancing ischemia in susceptible myocardium. Their impact on sepsis-induced cardiac permeability is still unknown, although AVP may prove to be an interesting substitute to NE by preserving catecholamine-induced myocardial dysfunction. However, the functional relevance of this myocardial permeability observed during sepsis remains equivocal.

The intestine in sepsis

Splanchnic hypoperfusion is generally associated with poor outcome in sepsis.[80] In addition, by enhancing intestinal mucosal and microcirculatory permeability, sepsis can lead to bacterial translocation, which in turn is related to the onset of multiple organ failure.[81] Hypoperfusion *per se* contributes, but is not indepedently sufficient to account for all mesenteric permeability mechanisms.[82] However, hypoperfusion as well as pro-inflammatory cytokines are triggers for epithelial cellular apoptosis, all of which are putative incriminating agents/events in sepsis-induced gut hyperpermeability. Intestinal epithelial apoptosis in human sepsis[83] can in fact compromise mucosal integrity whereas Bcl-2 intestinal overexpression is partially protective in mice challenged with *Pseudomonas aeruginosa* pneumonia.[84] In addition, apoptosis mediated by Fas (a cell-surface protein) causes an increased flux of small molecules in human intestinal cells while the caspase inhibitor z-VAD prevents gut apoptosis with improved barrier dysfunction.[85] Mechanisms leading to intestinal apoptosis involve several inflammatory molecules, including IL-1ß and IL-6.[86] Interleukin-6, by inducing intra-cellular actin rearrangement, as well as vascular endothelial growth factor, released by inflammatory and structural cells in response to endotoxin stress; both increase vascular permeability.[87,88] In this respect, IL-6 knockout mice are hence protected from sepsis-induced gut hyperpermeability.[89]

Impact of NE and AVP on intestinal function in the septic patient

Norepinephrine leads to local endothelium-derived IL-6 production[90] which can ultimately contribute to bacterial translocation, while AVP is a recognized vascular endothelial growth factor secretagogue[91] and therefore may be implicated in sepsis-induced gut hyperpermeability. In a rodent endotoxin model, both NE- and AVP-treated rats demonstrated better preservation of gut permeability in comparison to control animals, as measured by Evans Blue tissue concentration.[35] Sun *et al.*[36] also reported that sheep undergoing cecal perforation exhibit less small intestinal edema and congestion when exposed to combined AVP and NE in lieu of NE alone.

Furthermore, AVP and NE exhibit distinctive hemodynamic properties on splanchnic circulation. Arginine vasopressin induces vasoconstriction of endo-

toxin-stressed human gastroepiploic arteries[92] while potentiating vasoreactivity of catecholamine-exposed vessels *in vitro*.[93] Arginine-vasopressin also upregulates V1R messenger ribonucleic acids in mesenteric arteries, in contrast to kidney and brain arteries of animals with septic shock, and should contribute to direct flow away from the gut to other organs.[94] However, AVP-induced splanchnic hypoperfusion, as measured by either continuous dye dilution technique, ultrasonic microcirculatory flow probes or gut-arterial carbon dioxide partial pressures gradient modulations, has not been clearly demonstrated in septic shock. Two small short-term studies (two to four hours observation time and less than 25 patients overall) found that AVP infusion was associated with an increase in gut-arterial carbon dioxide partial pressures gradient. However, in the first study, NE was not titrated in order to maintain a threshold mean arterial pressure[95] while in the second study, AVP was infused up to very high concentrations but still increased absolute and fractional splanchnic blood flow.[96] In contrast, two other studies did not observe AVP-associated splanchnic hypoperfusion.[75,97] Furthermore, perfusion of terlipressin or AVP showed no detrimental effect on hepatosplanchnic perfusion in a porcine model of endotoxemia, as well as no impact on mesenteric flow with a further tendency of attenuating lactate content in endotoxin-challenged gut tissues.[35,98] Mechanisms potentially related to the beneficial effects of low-dose terlipressin and AVP have been linked to inducible NO synthase inhibition.[35] As in the case of AVP and analogs, there is no evidence that NE is deleterious to the gut during septic shock. Norepinephrine appears to be safe when used alone in septic shock.[99]

In summarizing effects on the intestine, sepsis-induced splanchnic hypoperfusion and gut epithelial apoptosis lead to bidirectional intestinal permeability, and therefore could be affected by vasopressor use. However, there are no known human studies which have clearly demonstrated any superiority or, alternatively, any distinctive deleterious effect of NE over AVP on gut perfusion/ permeability in sepsis. Fears regarding the use of high dosages of AVP and splanchnic perfusion remain to be evaluated in large scale human studies.

Conclusions

Sepsis-induced tissue and organ hyperpermeability is a clinical evidence-based phenomenon observed daily by critical care physicians at the bedside, although its contribution to patient outcome is still not clear. From a bench perspective, tissue hyperpermeability is both multifactorial and complex. In addition, a majority of studies presented herein stem from animal models of endotoxemia, and caution must be exercised not only in context of species model variability, but also in translating data obtained from animal settings to humans. At a time when knowledge on sepsis pathophysiology is still growing, together with the advent of novel and efficient therapies, critical care physicians must remain vigilant of both "old" and emerging issues such as the unrecognized impact of a standard treatment (NE) and a novel indication for AVP in sepsis on vital organ perfusion/permeability. In this respect, AVP exhibits organ-specific heterogeneity in vascular responsiveness, compared to NE.

Last but not least, one should bear in mind that NE is currently the standard of care in the treatment of septic shock, whereas AVP is still under evaluation.[100] Although infusion rates of AVP as high as ~ 2 to 6 $U \cdot hr^{-1}$ (0.03–0.1 $U \cdot mL^{-1}$ for a 70 kg-adult) were suggested in vasodilatory shock,[101] it has been recently recommended to select a range of 0.01–0.04 $U \cdot min^{-1}$ as a "physiological replacement dose" in patients with septic shock.[100] Other potential clinical uses of AVP still under evaluation, and not the focus of this review, include weaning from extracorporeal circulation, out of hospital cardiac arrest, and pulseless ventricular arrhythmia.[102–104]

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