Vasoactive drugs and acute kidney injury

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The use of norepinephrine, and probably vasopressor therapy in general, in intensive care patients with hypotensive vasodilatation despite fluid resuscitation and evidence of acute kidney injury remains the subject of much debate and controversy. Although there is concern about the use of these drugs, these concerns are unfounded. At this time, the experimental and human data strongly suggest that, in these patients, vasopressor therapy is safe and probably beneficial from a renal, and probably general, point of view. On the basis of currently available evidence, in hypotensive vasodilated patients with acute kidney injury, restoration of blood pressure within autoregulatory values should occur promptly with noradrenaline and be sustained until such vasodilatation dissipates. The additional role of other vasopressors in these situations remains unclear. The addition of vasopressin may be helpful in individual patients, but widespread use is not supported by evidence. α-Dose dopamine has no advantages over noradrenaline and is not as reliably effective in restoring blood pressure and urine output. Its widespread use cannot be supported in patients with vasodilatation and acute kidney injury. Other vasopressor drugs such as epinephrine and phenylephrine may be similar in efficacy to noradrenaline. However, experience and available data with their use is vastly less than with noradrenaline. Adrenaline, in addition, is associated with hyperglycemia, hyperlactatemia, acidosis, and hypokalemia. Terlipressin appears useful in patients with acute kidney injury secondary to hepatorenal syndrome. Whether it is superior to noradrenaline in this setting remains uncertain, and more studies are needed before recommendations can be made. (Crit Care Med 2008; 36[Suppl.]:S179–S186)

KEY WORDS: norepinephrine; endotoxin; organ blood flow; sepsis; resuscitation; vasopressors; septic shock; critical illness; kidney; phosphodiesterase inhibitors

Septic shock, systemic inflammation (trauma, major surgery, cardiopulmonary bypass, and the like), or pharmacologic vasodilatation (phosphodiesterase inhibitors, sedative drugs, epidural or spinal block) often cause systemic hypotension despite a normal or increased cardiac output (1). Under these circumstances, hypotension may persist despite vigorous volume expansion. Potent systemic vasopressor agents—such as noradrenaline (norepinephrine in North America), so-called high-dose dopamine or adrenaline (epinephrine in North America), phenylephrine, or low-dose vasopressin or terlipressin—can then be used to restore an acceptable mean arterial blood pressure (2–5).

In the above clinical setting, acute kidney injury (AKI) is common. When AKI is present, the use of vasopressors is typically fraught with controversy because of a belief that renal vasoconstriction is responsible for AKI and because of the belief that such drugs will make renal vasoconstriction worse and induce more AKI. In this article, we will review the evidence on the renal effects of such drugs in critically ill patients with systemic vasodilatation. However, we will not discuss vasoactive drugs that induce vasodilatation (nitroprusside, glyceryl trinitrate) or drugs that, although vasodilating, are predominantly inotropic in nature (phosphodiesterase inhibitors or dobutamine). We also will not discuss the issue of so-called low-dose dopamine, as this agent typically does not have systemic vasopressor effects unless given at higher doses.

The Rationale for Using Vasopressors in AKI

The rationale for vasopressor therapy in hypotensive states is based on the physiologic knowledge that, in all regional circulations—including the renal, splanchnic, cerebral, and coronary beds—blood flow is pressure-dependent outside of levels of pressure that remain within autoregulation values for a given regional circulation. This means that, if cardiac output is preserved, as long as blood pressure is maintained at a sufficient value, organ blood flow also is preserved. However, when blood pressure falls below a given value (autoregulatory threshold), the ability of autoregulation to maintain vital organ blood flow is lost. Then, as blood pressure falls, organ blood flow also decreases in an almost linear fashion. Decreased blood flow may induce organ ischemia, which in turn may contribute to organ failure. This decrease in blood flow may be particularly marked in those patients with critical renal, mesenteric, carotid, or coronary lesions (atheroma, fibroplasia, and the like). Furthermore, this fall in renal blood flow is likely to occur at a higher blood pressure value in these patients, as well as in those with long-standing hypertension. It also is important to note that different vascular beds will lose autoregulation at different blood pressure values. For example, the mammalian kidney appears to do so at a mean arterial pressure (MAP) of about 80 mm Hg, while the brain and coronary circulation require a MAP of somewhere between 30 and 50 mm Hg, instead (Fig. 1). In addition, the pressure–flow relationship for the kidney appears to follow a relatively steeper slope than that of other regional beds. Thus, for a given fall in blood pressure, the proportional fall in blood flow
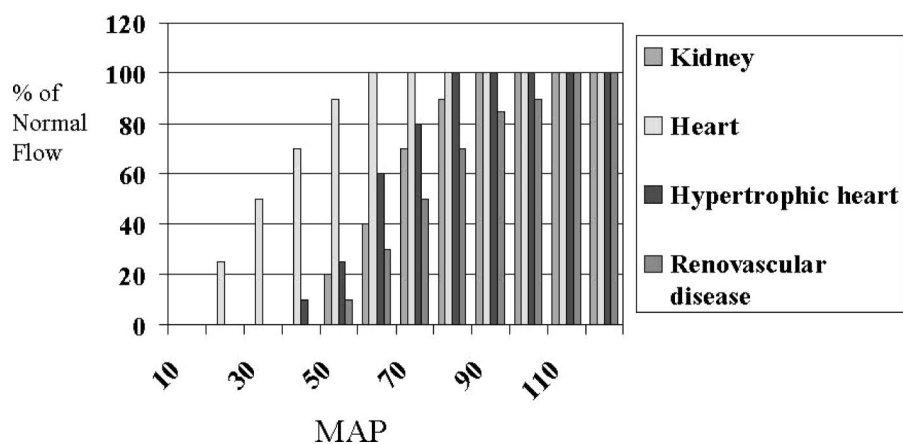
Figure 1. Graph illustrating the pressure flow relationship for the kidney and heart under normal and pathophysiologic conditions. The flow is expressed as percentage of normal and the mean arterial pressure (*MAP*) in mm Hg.

would be expected to be particularly sharp for the kidney.

These physiologic observations suggest that the restoration of blood pressure is a logical and desirable therapeutic goal in the pursuit of renal protection, particularly if a patient remains hypotensive and oliguric after adequate fluid resuscitation. Unfortunately, the drugs necessary to restore a higher MAP have properties that raise concerns about their use.

Norepinephrine

Norepinephrine is very effective in raising arterial blood pressure and, under almost all circumstances, can be titrated to achieve the desired MAP in a given patient. However, because norepinephrine is believed to induce vasoconstriction via α-adrenergic stimulation, there is concern it also may decrease vital organ blood flow, if regional vascular beds constrict in excess. In such a scenario, intraorgan vascular resistance would increase proportionately more than perfusion pressure and overall blood flow would decrease, particularly for the kidney.

In fact, norepinephrine infusion has been reported to decrease splanchnic (6, 7) and renal blood flow (8–10) under normal circulatory conditions, as well as during essential hypertension and hypovolemic hypotension. These reports have significantly inhibited the clinical use of norepinephrine.

The above studies that suggest norepinephrine may induce splanchnic or renal ischemia, however, are open to several criticisms. Importantly, they do not address the effects of norepinephrine in va-

sodilated, hypotensive states and may not even accurately reflect the longer-term effect of norepinephrine infusion in normal subjects. On the other hand, if norepinephrine infusion induces visceral organ hypoperfusion in the vasodilated patient, then it could induce multiple organ dysfunction, loss of gut mucosal integrity (11), renal ischemia, and the development of greater AKI. In light of such considerations, concern continues to exist as to the advisability of sustained vasopressor infusions in the hypotensive patient.

It is not at all clear, however, that the hypothetical scenario of vasopressor-induced renal hypoperfusion actually occurs in sepsis or other vasodilated states. Such clinical states are characterized by profound alterations in vascular tone. Down-regulation of vascular smooth muscle α-adrenergic receptor responsiveness (12) and active vasodilatation occur due to nitric oxide release (13). In addition, microvascular obstruction by aggregation of platelets and white blood cells, formed by adhesion to the activated vascular endothelium, can disrupt local blood flow distribution independent of α-adrenergic tone (14). Finally, increased cyclic adenosine monophosphate concentrations in the smooth muscle cells of blood vessels, induced by the administration of phosphodiesterase inhibitors, also will decrease vessel tone, as would the loss of sympathetic outflow from epidural blockade.

Under circumstances of marked vasodilatation, it makes physiologic sense to think that the restoration of normal or near normal vascular tone and adequate

renal perfusion pressure should improve renal blood flow and glomerular filtration rate. It is controversial, however, whether norepinephrine can achieve these goals safely. Given that these measurements typically require invasive monitoring, animal experimentation is needed to provide initial information on what may happen in the mammalian circulation when norepinephrine is infused in the setting of vasodilatation.

Experimental Data

Norepinephrine can be used to induce a reversible model of AKI (15, 16) when infused into the renal artery at very large doses. Such AKI is induced by marked renal vasoconstriction. Once again, such observations make the physician wary of using norepinephrine in the clinical setting of renal dysfunction, in case it may induce or contribute to AKI. However, a more accurate analysis of the available data is warranted. Norepinephrine-induced intense vasoconstriction only has been seen to occur with the infusion of the drug directly into the renal artery, not via the systemic route at clinically relevant doses (15, 16). In addition, the dose of drug used in models of norepinephrine-induced acute renal failure was twice to three times that used in appropriate animal studies and well beyond the mean dose usually administered in clinical practice. The relevance of these investigations to clinical practice is, at best, negligible.

Dr. Schaer and colleagues (17) also have reported the renal effects of norepinephrine infusion at different doses with or without the addition of low-dose dopamine. They measured renal blood flow with the technique of regional thermodilution (an unvalidated approach). They found that, although renal vascular resistance appeared to increase from baseline (there was no placebo arm), total renal blood flow progressively increased with increasing doses of intravenous norepinephrine up to 1.6 μg/kg/min. In their study, any adverse effects of norepinephrine infusion on renal vascular resistance (please note that total renal blood flow actually increased) were seen in animals with a baseline MAP of 151 mm Hg. No sane clinician would prescribe norepinephrine to a patient with a mean arterial blood pressure of 150 mm Hg!

On the other hand, a study by Dr. Anderson and colleagues (18) appears to mimic clinical practice more closely.
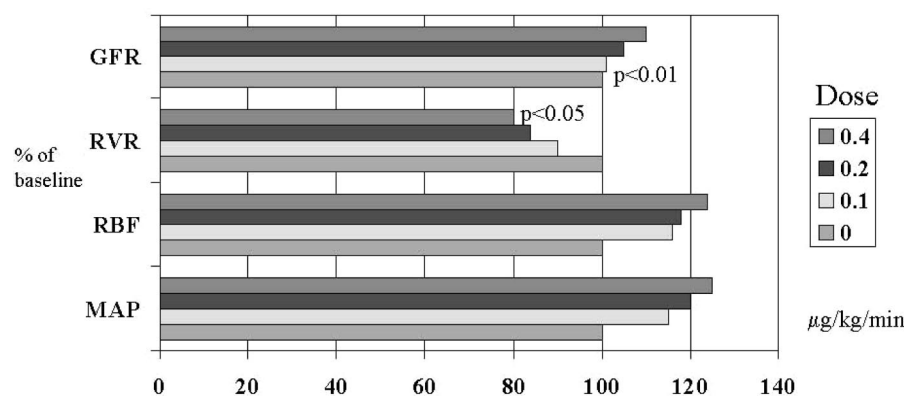
Figure 2. Histogram illustrating the effect of different doses (0–0.4 μg/kg/min) of norepinephrine on mean arterial pressure (*MAP*), renal blood flow (*RBF*), renal vascular resistance (*RVR*), and glomerular filtration rate (*GFR*) in the conscious dog. Flow is presented as a percentage, with 100% being flow in control dogs receiving placebo. Both MAP and GFR are significantly increased by norepinephrine at clinically relevant doses.

These investigators infused norepinephrine intravenously at 0.2 to 0.4 μg/kg/min (a clinically relevant dose) in conscious dogs and, using an electromagnetic flow probe, studied renal blood flow, renal vascular resistance, and glomerular filtration rate. They found that renal blood flow increased and renal vascular resistance decreased in response to short-term norepinephrine infusion (Fig. 2). Such norepinephrine-induced renal vasodilatation was unaffected by pretreatment with indomethacin, propranolol, or angiotensin-converting enzyme inhibition. Therefore, renal vasodilatation was not prostaglandin-mediated and was independent of β-receptor stimulation or of angiotensin-derived changes in vascular tone. However, efferent autonomic sympathetic nerve blockade with pentolinium before the administration of norepinephrine completely abrogated norepinephrine-induced renal vasodilatation. These investigators logically concluded that, in keeping with previous experimental data (19), most of the renal vasodilating effect of intravenous norepinephrine could be attributed to an increase in systemic blood pressure, which decreased renal sympathetic tone through a baroreceptor response. The important point here is that norepinephrine, when given at clinically relevant doses by an intravenous route, is not a significant renal vasoconstrictor. The effect of norepinephrine infusion on regional blood flow in the dog also has been recently explored by Dr. Zhang and colleagues (20). These investigators demonstrated that, in the endotoxemic dog, norepinephrine did not induce any decrease in renal or hepatic blood flow.

The effects of norepinephrine infusion on renal blood flow may not be unique to this vasopressor, but representative of the effects of a group of potent vasoconstrictor agents. For example, Dr. Bersten and colleagues (21, 22) recently have studied the renal effects of epinephrine, another potent vasopressor agent, with a strong mixed β- and α-adrenergic effect. These investigators administered epinephrine by continuous infusion at clinically relevant doses in the normal and septic sheep. After a short-lived (minutes) and small decrease in renal blood flow at the highest doses tested (0.4–0.8 μg/kg/min), renal blood flow progressively increased. It remained elevated for up to 6 hrs of norepinephrine infusion. A similar increase in renal blood flow occurred in septic animals. There are no controlled experimental data or controlled human data on the use of high-dose (α-dose) dopamine or phenylephrine, but it is likely that, in vasodilated states, they also have a beneficial effect on renal perfusion. The data on low-dose vasopressin (23) and terlipressin in liver failure (24) also support a potentially beneficial effect of vasopressors in general on renal perfusion and function.

All of the above studies support the notion that mixed β- and α-adrenergic agents (norepinephrine affects both receptors), when given to restore blood pressure during vasodilatation and hypotension, can be expected to generally improve renal blood flow. However, the physiologic question persists concerning the effect of norepinephrine *per se* on the tone of the renal vasculature. Such analysis demands that pressor effects of this agent should be removed from consideration by statistical methods and that issues of preload also should be eliminated by experimental methods. To address this issue, Dr. Bellomo and colleagues (25) recently have conducted a complex and highly invasive physiologic study in the dog using the vascular occlusion technique to study the effect of norepinephrine (norepineprhine) on vascular tone. While a discussion of the methodology is not warranted here, a few points should be emphasized. First, the vascular occlusion technique for the inferior vena cava was used. Such occlusion induces a fall in preload that allows differences in preload between different hemodynamic states to be essentially eliminated from the assessment of the effect of the drug itself on the renal vasculature. Second, both the pressure-to-cardiac index (dynamic resistance) and the point of zero flow were defined. The point of zero flow represents precapillary sphincter tone. Third, these investigators studied animals in the septic and normal state with repeated control observations and a crossover design.

Norepinephrine infusion, at clinically relevant dosages, affected renal blood flow differentially during basal and acute endotoxemic conditions. When normal circulatory controls existed in the otherwise unstressed circulation, norepinephrine infusion failed to proportionally increase dynamic renal blood flow despite increasing arterial pressure. By contrast, once the circulation had been perturbed by the insult of acute endotoxemia (and probably any other state inducing a major degree of vasodilatation), identical dosages of norepinephrine increased both dynamic renal blood flow and perfusion pressure. Importantly, the methodology used allowed the investigators to isolate the effect of the intravenous infusion of norepinephrine on the determinants of steady state renal blood flow independent of perfusion pressure. Under normal conditions, norepinephrine, infused intravenously at a rate capable of increasing MAP by approximately 15 mm Hg, induced a decrease in renal vascular ohmic resistance but an increase in vascular critical closing pressure. This change was such that, in the aggregate, these combined renal vasoactive effects reduced renal blood flow for a constant perfusion pressure. However, during acute endotoxemic conditions, the initial state of the renal vasculature became altered, reflecting the profound effects that endotoxemia has on vascular smooth muscle tone and vascular responsiveness. Under these conditions, the addition of norepinephrine infusion further decreased renal vascular ohmic resistance. It also decreased

the vascular critical closing pressure, such that in the aggregate these combined renal vascular effects served to increase renal blood flow for a constant perfusion pressure. Thus, norepinephrine infusion in acute endotoxemia appears to reverse systemic hypotension and improve renal blood flow independent of perfusion pressure. These findings, in association with other literature cited, provide a physiologic basis for the administration of norepinephrine during septic shock and other vasodilated states. They also strongly suggest that the paradigm that norepinephrine can or will induce renal ischemia or hypoperfusion in hypotensive vasodilatation is flawed, not evidence-based, contradicted by the available observations, and misleading.

Which Vasopressor?

Studies that directly measure renal blood flow and calculate renal vascular resistance in man are not available. Many clinical reports, however, support the notion that the continuous infusion of norepinephrine may increase urine output and improve creatinine clearance in hyperdynamic septic shock (26–31). Of particular interest is a study by Dr. Martin and colleagues (31) because it is the only randomized controlled study available. These investigators randomized 32 patients with hyperdynamic and hypotensive septic shock to either receive high-dose dopamine (up to 50 μg/kg/min) or norepinephrine (up to 1 μg/kg/min) to achieve a predetermined arterial blood pressure (>80 mm Hg). They studied the overall hemodynamic response of these patients as well as lactate and urinary output after 1 and 6 hrs of therapy. They found that high-dose dopamine failed to restore the target blood pressure in one third of patients while norepinephrine succeeded in all patients. In addition, in those patients whose hypotension could not be corrected with dopamine, norepinephrine restored a MAP of >80 mm Hg. Urinary output was significantly and markedly improved from baseline once blood pressure was increased. These effects also are seen in experimental sepsis in conscious sheep (Fig. 3). The controlled study by Dr. Martin and colleagues clearly suggests that norepinephrine is superior to α-dose dopamine in restoring blood pressure in septic vasodilated patients and that such correction of blood pressure induces an improvement in urine output. More recently, Dr. Martin and colleagues (31) also

reported on the outcome of 97 adult patients with septic shock, of whom 57 were treated with norepinephrine. Patients treated with norepinephrine had a lower mortality than those treated with other pressor drugs and norepinephrine use was identified as a predictor of survival on multivariate logistic regression analysis. These findings support the argument that norepinephrine is safe and effective in hypotensive vasodilated states, and that its renal effects under such circumstances are likely to be beneficial. There are no controlled studies to directly compare other vasopressor drugs such as phenylephrine or epinephrine to norepinephrine. However, phenylephrine and epinephrine are not recommended as first-line agents (32) because of concern regarding unbalanced α vasoconstriction with phenylephrine and lack of sufficient human data and, in the case of epinephrine, concern about its greater tendency to induce hyperlactatemia, acidosis, hyperglycemia, and tachycardia. On the other hand, low-dose vasopressin (10 IU/hr) has been proposed as an adjunct to norepinephrine to decrease its dose in the treatment of septic shock (33).

Low-Dose Vasopressin

Arginine vasopressin (AVP) is an antidiuretic and vasopressor hormone, which, at high doses, induces marked mesenteric vasoconstriction (32). Because of these properties, AVP has been used for the treatment of patients with diabetes insipidus and variceal hemorrhage due to hepatic failure (32).

More recently, some studies have shown that a relative AVP deficiency may exist in patients with septic shock

(35) and that such deficiency may contribute to the diminished vessel tone seen in this setting (35–37). These observations have established a biological rationale for AVP as a possible effective vasopressor in septic shock patients (38, 39) when administered at low doses (0.02–0.04 IU/min). Its ability to improve blood pressure at such low doses has been demonstrated in several small clinical studies (38–45). It has been assumed that, at such low doses, AVP should have limited adverse effects on regional blood flows. In spite of the increasing reports of its use in human sepsis, little is known about the effects of low-dose AVP infusion on vital organ flows in the normal and septic mammalian circulation in the conscious animal.

We recently reported the finding of a controlled study in normal and septic conscious sheep in which regional blood flows were continuously monitored with transit time flow probes (23). In this study, we demonstrated that infusion of a low-dose of AVP infusion (0.02 units/min in sheep of approximately 40 kg) had no significant effect on systemic hemodynamics, but induced significant mesenteric vasoconstriction with decreased mesenteric blood flow in normal sheep. The same AVP infusion, when given to septic sheep, decreased cardiac output (CO) as well as mesenteric blood flow through significant mesenteric vasoconstriction. Furthermore, in normal sheep, AVP infusion was associated with a nonsignificant increase in urine output. This increase was more marked during sepsis and became statistically significant, in
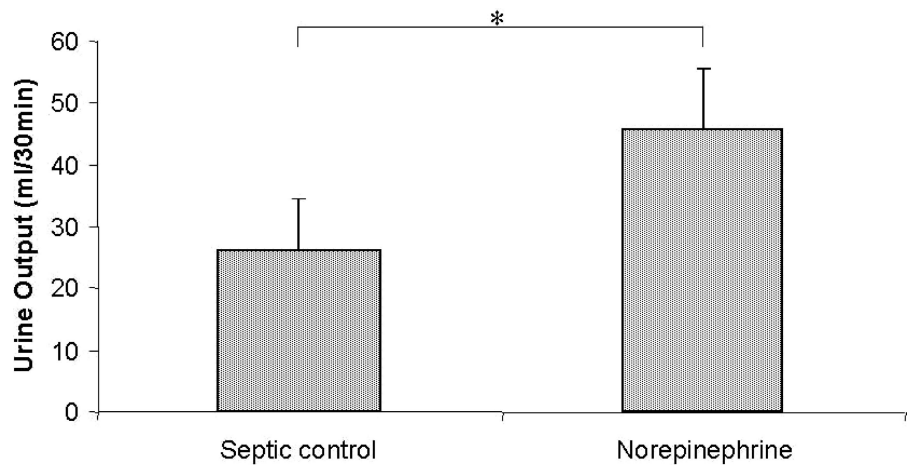

Figure 3. Histogram showing the effect of norepinephrine infusion on urine output in septic sheep compared with placebo (*septic control*). Norepinephrine infusion nearly doubled urine output.

combination with a significant increase in creatinine clearance.

In terms of central hemodynamic variables, we found no significant changes in MAP with AVP infusion at a rate of 0.02 units/min in either normal or septic sheep. In normal human subjects, it is known that AVP has little effect on MAP, whereas more recent studies showed that AVP could increase MAP in clinical septic shock (40–45). It has been suggested that these different responses of MAP to AVP infusion are secondary to the low concentrations of AVP in septic shock. However, many of the studies showing an effect of AVP in MAP have combined AVP with another vasopressor agent. These observations suggest that AVP may potentiate the effect of other vasopressors but that, when used alone, it may have only a limited pressor effect. To our knowledge, there has not been any controlled trial comparing isolated low-dose AVP infusion to placebo in human septic shock. In a recent study in humans, Dr. Klinzing and colleagues (45) needed to infuse an average of 0.47 IU/min of AVP to maintain blood pressure in septic shock. This is >20 times the dose we administered to our sheep. In animals, fixed low-dose AVP infusion at a dose equal to ours has been studied recently in a lethal model of sepsis in anesthetized sheep (43). AVP was found to extend survival time and delay the onset of progressive hypotension. In this study and in our report, low-dose AVP clearly could be shown to induce vasoconstriction.

In our study, low-dose AVP infusion significantly decreased CO in septic animals and showed a trend toward decreasing CO in normal sheep. In both normal and septic sheep, these decreases in CO were associated with bradycardia and a reduction in total peripheral conductance. These observations are not physiologically surprising. AVP is known to act on the area postrema to enhance baroreflex activity and, compared with other vasopressor agents, causes a greater fall in CO and heart rate for a given rise in pressure. In a clinical study, AVP infusion decreased CO by 14%. Our findings also are consistent with previous studies using higher doses of AVP (46–49). Although we cannot speculate whether this decreased CO would be clinically detrimental or not, our results strongly suggest that low-dose AVP infusion can decrease CO through decreased heart rate and peripheral vasoconstriction. These observations suggest that it may be undesirable to administer low-dose AVP in hypodynamic septic shock.

Low-dose AVP infusion also significantly decreased mesenteric blood flow in both normal and septic sheep. These findings are indirectly supported by studies in other clinical situations, such as cardiopulmonary resuscitation and portal hypertension (50, 51), in which AVP has been used at higher doses. They demonstrate that, even at low doses, AVP reduces global mesenteric blood flow. The observation that even low-dose AVP remains a powerful mesenteric vasoconstrictor is supported by several recent studies in humans and animals (52, 53). The clinical implications of such global mesenteric vasoconstriction and decreased gut blood flow are unknown. However, they raise concerns about the physiologic safety of low-dose AVP infusion. Given the lack of major mesenteric vasoconstriction with other vasopressor agents (54, 55), they invite caution with its prescription. Low-dose AVP was associated with a consistent trend toward coronary vasoconstriction and a decrease in coronary flow in septic sheep, which failed to achieve statistical significance. It is probable that the tendency of AVP to decrease coronary blood flow reflects changes in myocardial oxygen demand induced by decreased heart rate and CO.

Low-dose AVP did not significantly affect renal blood flow but showed a slight trend toward an increased flow in septic animals. However, AVP increased urine output and creatinine clearance in the septic sheep and was associated with similar trends in normal animals. Previous studies have demonstrated that AVP infusion increased urine output and creatinine clearance (40) but, to our knowledge, this is the first study to measure directly the effect of low-dose AVP infusion on renal blood flow. Our findings suggest that, at a low dose, AVP may slightly increase renal blood flow and may have only a limited effect on the V_2 receptors responsible for antidiuresis such that other effects on intrarenal hemodynamics (56) may overcome its normal antidiuretic effect. Our observations also confirm that, during the infusion of vasoactive drugs, urine output and creatinine clearance do not reliably reflect changes in renal blood flow. In conclusion, it appears that low-dose AVP infusion induces a significant increase in mesenteric vascular resistance (decreased conductance) with an associated decrease in mesenteric blood flow. It also decreases heart rate and cardiac output, while it significantly increases urine output and creatinine clearance in septic animals. It would appear unlikely that these systemic and regional hemodynamic effects could add up to clinically important benefits in septic man. The international, multicenter Vasopressin in Septic Shock Trial sought to address the issue of vasopressin support in intensive care units by comparing low-dose vasopressin and norepinephrine to norepinephrine alone in the vasopressor treatment of septic shock. It found no significant overall difference in clinical outcomes. Thus, the addition of low-dose vasopressin to norepinephrine, while not detrimental, does not appear to be of clinical benefit.

Epinephrine

There are no controlled studies of epinephrine in septic man, even though epinephrine (EPI) is the agent of choice for anaphylactic shock. Only case series have been reported in which this agent has been used for the treatment of fluid-refractory hypotension in severe sepsis/septic shock (57, 58). The major reasons for epinephrine not being more extensively used in the vasopressor treatment of septic shock are related to its metabolic effects—which include hyperglycemia, increased lactate levels, and acidosis—and its tendency to induce a greater degree of tachycardia than other agents (34). However, little information exists in relation to its effects on regional blood flows and on the kidney (22). Accordingly, we used a model of hyperdynamic septic shock to investigate the effects of EPI infusion (0.4 µg/kg/min) over a prolonged period (6 hrs) on global and regional hemodynamics, on several metabolic variables, and on some indicators of organ function. Our investigation of the regional flow and functional and metabolic effects of EPI in hyperdynamic sepsis revealed several clinically relevant findings. First, we confirmed that EPI infusion at 0.4 µg/kg/min has strong positive inotropic actions, which act to increase contractility, stroke volume, and CO. Second, we confirmed that EPI significantly increases MAP. Third, in this clinical setting, which reproduces the central hemodynamic effects of EPI seen in resuscitated human sepsis, we found that EPI had important and variable effects on the four vital regional circulations under study.

We found that EPI significantly reduced renal blood flow and decreased renal conductance (renal vasoconstriction), increased overall urine output, and did not affect creatinine clearance. These observations are very similar to those of Dr. Day and colleagues (59) in patients with severe hyperdynamic human sepsis. These investigators found an increase in renal vascular resistance, a decreased renal blood flow/CO ratio, and no detectable effect on urine output and creatinine clearance. Dr. Bersten and colleagues (22) infused EPI at approximately 0.8 μg/kg/min in septic sheep (intraperitoneal sepsis) and found that EPI had no effect on renal blood flow and induced a short-lived decrease in creatinine clearance. However, this model of sepsis was normotensive and normodynamic. No other such studies exist.

Mesenteric blood flow was increased during hyperdynamic sepsis and remained unchanged during EPI infusion. However, mesenteric conductance fell (mesenteric vasoconstriction). Coronary blood flow was increased during hyperdynamic sepsis. EPI did not significantly decrease global coronary flow but, as was the case for the renal and mesenteric circulations, it induced a significant degree of local vasoconstriction. No other studies of the effect of EPI on coronary blood flow and conductance in sepsis have been performed. We measured sagittal sinus flow, which in the sheep has been validated as a reliable surrogate for cerebral blood flow. We found that severe sepsis did not alter sagittal sinus flow and that the administration of EPI also failed to induce a significant change. Our study found that infusion of EPI resulted in a significant increase in serum glucose concentration, a significant reduction in serum potassium, and hyperlactatemia. In conclusion, EPI infusion at 0.4 μg/kg/min in septic, hyperdynamic animals resulted, as in humans, in a significant increase in MAP, CO, heart rate, and myocardial contractility. However, these seemingly positive systemic effects induced vasoconstriction in most regional circulations, decreased renal blood flow, and led to severe metabolic derangements. The clinical meaning of the changes and their significance in relation to AKI remain uncertain. A double-blind randomized controlled trial comparing norepinephrine to epinephrine has been recently completed in Australia

and its publication will address some of these issues.

Terlipressin

Glycine vasopressin (terlipressin) is a modification of the vasopressin molecule that confers somewhat different properties to this vasopressor, the most important one being its long half-life and ability to be given intermittently at dosages between 1 and 2 mg every 6 hrs. This vasopressor agent has been used for the adjunctive treatment of sepsis in experimental studies (60) and several case reports (61). However, the available evidence is insufficient to come to any conclusion about its possible role in this setting. More interestingly, its most frequent use is in the treatment of hepatorenal syndrome. This use is, of course, particularly relevant to AKI.

In patients with hepatorenal syndrome, systemic vasodilatation, which has been attributed mainly to splanchnic vasodilatation, is believed to play a critical role in the activation of endogenous renal vasoconstrictor pathways. These pathways, in turn, are believed to induce functional AKI. According to this logic, vasoconstrictors such as terlipressin may improve renal function by reducing splanchnic vasodilation and increasing central circulating blood volume and reducing endogenous renal vasoconstriction (62). In fact, although more studies have been performed with terlipressin than with other agents, other vasoconstrictors, such as norepinephrine, may be equally effective (63). The effect of terlipressin on the circulation of patients with cirrhotic ascites has been studied in detail in six patients (64). In these patients, terlipressin reduced the heart rate, increased mean arterial pressure by approximately 15 mm Hg, and reduced cardiac output. However, it failed to affect renal blood flow and hepatic venous pressure gradient. These observations highlight our very limited understanding of how terlipressin may affect renal function in cirrhotic patients. The Cochrane meta-analysis group recently reviewed the clinical efficacy of terlipressin for hepatorenal syndrome (65). As of 2006, there had been only six randomized clinical trials of which three were still ongoing. The three available trials had only studied 51 patients and, in such trials, other significant treatments also were given, such as fresh frozen plasma, albumin, and cimetidine. Only one trial had appropriate blinding and randomization. However,

within the confines of these significant limitations, terlipressin therapy was associated with a significant improvement in creatinine clearance, a lowering of serum creatinine, increase in urine output, and a decrease in short-term mortality (65). These observations suggest that terlipressin has a potential for benefit but also that more rigorous multicenter blinded assessment of its renal and systemic effects is needed.

CONCLUSIONS

The use of norepinephrine (and probably vasopressor therapy in general) in ICU patients with hypotensive vasodilatation despite fluid resuscitation and evidence of renal dysfunction remains the subject of much debate and controversy. Although there is concern about the use of these drugs, these concerns are unfounded. At this time, the experimental and human data strongly suggest that, in these patients, vasopressor therapy is certainly safe and probably beneficial from a renal (and probably general) point of view. On the basis of currently available evidence in hypotensive vasodilated patients with AKI, restoration of blood pressure within autoregulatory values should occur promptly with norepinephrine and be sustained until such vasodilatation dissipates. The additional role of other vasopressors in these situations remains unclear. The addition of vasopressin may be helpful in individual patients but widespread use is not supported by evidence. α-Dose dopamine has no advantages over norepinephrine and is not as reliably effective in restoring blood pressure and urine output. Its use cannot be supported in patients with vasodilatation and AKI. Other vasopressor drugs, such as epinephrine and phenylephrine, may be similar in efficacy to norepinephrine. However, experience and available data with their use are vastly less than with norepinephrine. Epinephrine, in addition, is associated with hyperglycemia, hyperlactatemia, acidosis, and hypokalemia. Terlipressin appears useful in patients with AKI secondary to hepatorenal syndrome. Whether it is superior to norepinephrine in this setting remains uncertain and more studies are needed before recommendations can be made.

REFERENCES

1. American College of Chest Physicians/ Society of Critical Care Medicine Consensus

Committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101: 1658–1662

2. Schreuder WO, Schneider AJ, Groeneveld ABJ, et al: Effect of dopamine vs norepinephrine on hemodynamics in septic shock. *Chest* 1989; 95:1282–1288

3. Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826–1831

4. Desjars P, Pinaud M, Potel G, et al: A reappraisal of norepinephrine therapy in human septic shock. *Crit Care Med* 1987; 15: 134–137

5. Moran JL, O'Fathartaigh M, Peisach AR, et al: Epinephrine as an inotropic agent in septic shock: A dose profile analysis. *Crit Care Med* 1993; 21:70–77

6. Pawlik W, Sheperd AP, Jacobson ED: Effect of vasoactive agents on intestinal oxygen consumption and blood flow in dogs. *J Clin Invest* 1975; 56:484–490

7. Sheperd AP, Pawlik W, Mailman D, et al: Effects of vasoconstrictors on intestinal vascular resistance and oxygen extraction. *Am J Physiol* 1976; 230:298–303

8. Gombos EA, Hulet WH, Bopp P, et al: Reactivity of renal and systemic circulations to vasoconstrictor agents in normotensive and hypertensive subjects. *J Clin Invest* 1962; 41: 203–207

9. Mills LC, Moyer JH, Handley CA: Effects of various sympathomimetic drugs on renal hemodynamics in normotensive and hypotensive dogs. *Am J Physiol* 1960; 198:1279–1285

10. Richer M, Robert S, Lebel M: Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. *Crit Care Med* 1996; 24:1150–1156

11. Deitch EA, Winterton J, Bey R: The gut as the portal of entry for bacteremia. *Ann Surg* 1987; 205:681–692

12. Schott CA, Gray GA, Stoclet JC: Dependence of endotoxin-induced vascular hyporeactivity on extracellular L-arginine. *Br J Pharmacol* 1993; 108:38–43

13. Kilbourn RO, Gross SS, Jubran A, et al: N-methyl-L-arginine inhibits tumor necrosis factor–induced hypotension: Implications for the involvement of nitric oxide. *Proc Natl Acad Sci USA* 1990; 87:3629–3632

14. Vallet B, Lund N, Curtis SE, et al: Gut and muscle tissue Po_2 in endotoxemic dogs during shock and resuscitation. *J Appl Physiol* 1994; 76:793–800

15. Cronin RE, De Torrente A, Miller PD, et al: Pathogenic mechanisms in early norepinephrine-induced acute renal failure: Functional and histological correlates of protection. *Kidney Int* 1978; 14:115–125

16. Cronin R, Erickson AM, De Torrente A, et al: Norepinephrine-induced acute renal failure: A reversible ischemic model of acute renal failure. *Kidney Int* 1978; 14:187–190

17. Schaer GL, Fink MP, Parrillo JE: Norepinephrine alone versus norepinephrine plus low-dose dopamine: Enhanced renal blood flow with combination pressor therapy. *Crit Care Med* 1985; 13:492–496

18. Anderson WP, Korner PI, Selig SE: Mechanisms involved in the renal responses to intravenous and renal artery infusions of noradrenaline in conscious dogs. *J Physiol* 1981; 321:21–30

19. Korner PI, Dorward PK, Blombery PA, et al: Central nervous β-adrenoreceptors and their role in the cardiovascular action of propranolol in rabbits. *Circulation Res* 1967; 20: 676–685

20. Zhang H, Smail N, Cabral A, et al: Effects of norepinephrine on regional blood flow and oxygen extraction capabilities during endotoxic shock. *Am J Respir Crit Care Med* 1997; 155:1965–1971

21. Bersten AD, Rutten AJ: Renovascular interaction of epinephrine, dopamine, and intraperitoneal sepsis. *Crit Care Med* 1995; 23: 537–544

22. Bersten AD, Rutten AJ, Summersides G, et al: Epinephrine infusion in the sheep: Systemic and renal hemodynamic effects. *Crit Care Med* 1994; 22:994–1001

23. Di Giantomasso D, Morimatsu H, Bellomo R, et al: Effect of low-dose vasopressin infusion on vital organ blood flow in the conscious normal and septic sheep. *Anaesth Intensive Care* 2006; 34:427–433

24. Moreau R, Lebrec D: Diagnosis and treatment of acute renal failure in patients with cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; 21:111–123

25. Bellomo R, Kellum JA, Wisniewski SR, et al: Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. *Am J Respir Crit Care Med* 1999; 159: 1186–1192

26. Martin C, Eon B, Saux P, et al: Renal effects of norepinephrine used to treat septic shock patients. *Crit Care Med* 1990; 18:282–285

27. Desjars P, Pinaud M, Bugnon D, et al: Norepinephrine therapy has no deleterious renal effects in human septic shock. *Crit Care Med* 1990; 18:1048–1049

28. Rudis MI, Basha MA, Zarowitz BJ: Is it time to reposition vasopressors and inotropes in sepsis? *Crit Care Med* 1996; 24:525–537

29. Redl-Wenzel EM, Armbruster C, Edelmann G, et al: The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. *Intensive Care Med* 1993; 19:151–154

30. Bellomo R, Ronco C: The use of inotropic and vasopressor agents in patients at risk of renal dysfunction. *In*: Critical Care Nephrology. Ronco C, Bellomo R (Eds). Dordrecht, The Netherlands, Kluwer Academic Publishers, 1998, pp 1133–1138

31. Martin C, Viviand X, Leone M, et al: Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28:2758–2765

32. Holmes CL, Patel BM, Russel JA, et al: Physiology of vasopressin relevant to management of septic shock. *Chest* 2001; 120: 989–1002

33. Russell JA: Vasopressin in vasodilatory and septic shock. *Curr Opin Crit Care* 2007; 13: 383–391

34. Beale RJ, Hollenberg SM, Vincent JL, et al: Vasopressor and inotropic support in septic shock: An evidence-based review. *Crit Care Med* 2004; 32:S455–S465

35. Schwartz J, Reid IA: Role of vasopressin in blood pressure regulation in conscious water-deprived dogs. *Am J Physiol* 1983; 244: R74–R77

36. Abboud FM, Floras JS, Aylward PE, et al: Role of vasopressin in cardiovascular and blood pressure regulation. *Blood Vessels* 1990; 27: 106–115

37. Landry DW, Levin HR, Gallant EM, et al: Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; 25:1279–1282

38. Tsuneyoshi I, Yamada H, Kakihara Y, et al: Hemodynamic and metabolic effects of low-dose vasopressin infusion in vasodilatory septic shock. *Crit Care Med* 2001; 29:487–493

39. Landry DW, Levin HR, Gallant EM, et al: Vasopressin deficiency contributes to the vasodilatation of septic shock. *Circulation* 1997; 95:1122–1125

40. Holmes CL, Walley KR, Chittock DR, et al: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27: 1416–1421

41. Dunser MW, Mayr AJ, Ulmer H, et al: The effects of vasopressin on systemic hemodynamics in catecholamine-resistant septic shock and postcardiotomy shock: A retrospective analysis. *Anesth Analg* 2001; 93: 7–13

42. Patel BM, Chittock DR, Russell JA, et al: Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002; 96:576–582

43. Sun Q, Dimopoulos G, Nguyen DN, et al: Low-dose vasopressin in the treatment of septic shock in sheep. *Am J Respir Crit Care Med* 2003; 168:481–486

44. Russel JA: Vasopressin in septic shock: Clinical equipoise mandates a time for restraint. *Crit Care Med* 2003; 31:2707–2709

45. Klinzing S, Simon M, Reinhart K, et al: High-dose vasopressin is not superior to norepinephrine in septic shock. *Crit Care Med* 2003; 31:2646–2650

46. Leather HA, Segers P, Berends N, et al: Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. *Crit Care Med* 2002; 30:2548–2552

47. Yatsu T, Kusayama T, Tomura Y, et al: Effects of conivaptan, a combined vasopressin V(1a) and V(2) receptor antagonist, on vasopressin-induced cardiac and haemodynamic changes in anaesthetized dogs. *Pharmacol Res* 2002; 46:375–381

48. Martikainen TJ, Tenhunen JJ, Uusaro A, et al: The effect of vasopressin on systemic and splanchnic hemodynamics and metabolism

in endotoxin shock. *Anesth Analg* 2003; 97: 1756–1763

49. Guzman JA, Rosado AE, Kruse JA: Vasopressin vs norepinephrine in endotoxic shock: Systemic, renal, and splanchnic hemodynamic and oxygen transport effects. *J Appl Physiol* 2003; 95:803–809

50. Voelckel WG, Lindner KH, Wenzel V, et al: Effects of vasopressin and epinephrine on splanchnic blood flow and renal function during and after cardiopulmonary resuscitation in pigs. *Crit Care Med* 2000; 28: 1083–1088

51. Iwao T, Toyonaga A, Oho K, et al: Effect of vasopressin on esophageal varices blood flow in patients with cirrhosis: Comparisons with the effects on portal vein and superior artery blood flow. *J Hepatol* 1996; 25:491–497

52. Westphal M, Freise H, Kehrel B, et al: Arginine vasopressin compromises gut mucosal microcirculation in septic rats. *Crit Care Med* 2004; 32:194–200

53. Van Haren FMP, Rozendal FW, van der Hoven JG: The effect of vasopressin on gastric perfusion in catecholamine-dependent patients in septic shock. *Chest* 2003; 124: 2256–2260

54. Di Giantomasso D, May CN, Bellomo R: Norepinephrine and vital organ blood flow. *Intensive Care Med* 2002; 28:1804–1809

55. DiGiantomasso D, May C, Bellomo R: Norepinephrine and organ blood flow in sepsis. *Intensive Care Med* 2003; 29:1774–1781

56. Edwards RM, Trizna W, Kinter LB: Renal microvascular effects of vasopressin and vasopressin antagonists. *Am J Physiol* 1989; 256:F274–F278

57. Wilson W, Lipman J, Scribante J, et al: Septic shock: Does adrenaline have a role as a first-line inotropic agent? *Anaesth Intensive Care* 1992; 20:470–474

58. Lipman J, Roux A, Kraus P: Vasoconstrictor effects of adrenaline in human septic shock. *Anaesth Intensive Care* 1991; 19:61–65

59. Day NP, Phu NH, Mai NTH, et al: Effects of dopamine and epinephrine infusions on renal hemodynamics in severe malaria and severe sepsis. *Crit Care Med* 2000; 28:1353–1362

60. Lange M, Morelli A, Ertmenr C, et al: Continuous versus bolus infusion of terlipressin in ovine endotoxemia. *Shock* 2007; 28:623–629

61. Leone M, Martin C: Rescue therapy in septic shock—is terlipressin the last frontier? *Crit Care* 2006; 10:131

62. Moreau R, Lebrec D: The use of vasoconstrictors in patients with cirrhosis: Type 1 HRS and beyond. *Hepatology* 2006; 43:385

63. Alessandria C, Ottobrelli A, Debernardi-Vernon W, et al: Noradrenaline vs terlipressin in patients with hepatorenal syndrome: A prospective randomized unblinded pilot study. *J Hepatol* 2007; 47:499–505

64. Therapondos G, Stanley AJ, Hayes PC: Systemic, portal and renal effects of terlipressin in patients with cirrhotic ascites: Pilot study. *J Gastroenterol Hepatol* 2004; 19:73–77

65. Gluud LL, Kjaer MS, Christensen E: Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev* 2006; 4:CD005162