Review

Noradrenaline and the kidney: friends or foes?

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Abstract

Septic shock, systemic inflammation and pharmacological vasodilatation are often complicated by systemic hypotension, despite aggressive fluid resuscitation and an increased cardiac output. If the physician wishes to restore arterial pressure (>80–85 mmHg), with the aim of sustaining organ perfusion pressure, the administration of systemic vasopressor agents, such as noradrenaline, becomes necessary. Because noradrenaline induces vasoconstriction in many vascular beds (visibly in the skin), however, it may decrease renal and visceral blood flow, impairing visceral organ function. This unproven fear has stopped clinicians from using noradrenaline more widely. In vasodilated states, unlike in normal circulatory conditions, however, noradrenaline may actually improve visceral organ blood flow. Animal studies show that the increased organ perfusion pressures achieved with noradrenaline improve the glomerular filtration rate and renal blood flow. There are no controlled human data to define the effects of noradrenaline on the kidney, but many patient series show a positive effect on glomerular filtration rate and urine output. There is no reason to fear the use of noradrenaline. If it is used to support a vasodilated circulation with a normal or increased cardiac output, it is likely to be the kidney's friend not its foe.

Keywords acute kidney failure, kidney, norepinephrine, organ blood flow, septic shock

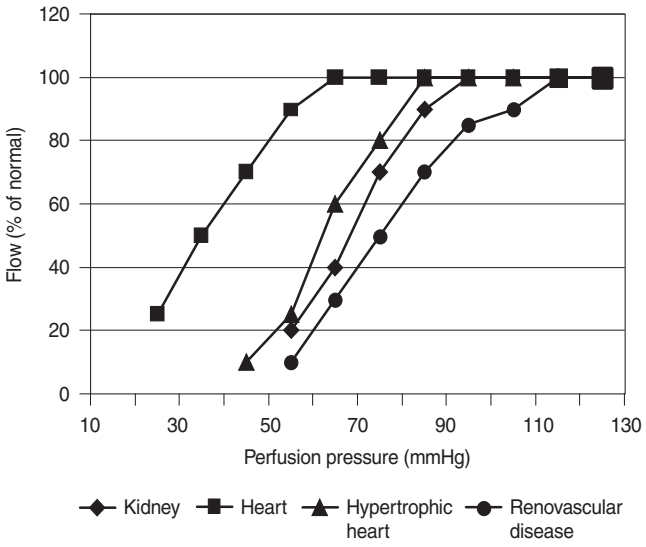
Septic shock, systemic inflammation (resulting from trauma, major surgery, cardiopulmonary bypass etc.), or pharmacological vasodilatation (caused by phosphodiasterase inhibitors, sedative drugs, epidural or spinal block) are usually associated with systemic hypotension, despite normal or increased cardiac output [1]. Under these circumstances, hypotension may persist despite vigorous volume expansion. Potent systemic vasopressor agents, such as noradrenaline or so-called high-dose dopamine can then be used to restore an acceptable mean arterial blood pressure [2–5]. Under these conditions, renal dysfunction is common (oliguria and/or a rising serum creatinine) and the use of noradrenaline is typically fraught with controversy. In this article, we will review the evidence on the renal effects of the use of noradrenaline in critically ill patients and seek to provide clinicians with a clinically relevant update aimed at helping them to make informed decisions in the care of their patients.

Why use vasopressors?

The rationale for vasopressor therapy in hypotensive states is based on the physiological knowledge that, in all regional circulations, including the renal, splanchnic, cerebral and coronary beds, blood flow is autoregulated. This means that, if cardiac output is preserved, as long as blood pressure is maintained at a sufficient value, organ blood flow does not change. When blood pressure falls below a given value (autoregulatory threshold), however, such autoregulation 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 etc.). Furthermore, this fall in blood pressure is likely to occur at a

ARF = acute renal failure; MAP = mean arterial pressure.

Figure 1



The relationship between perfusion pressure and organ flow for the kidney and heart under the pathophysiologic conditions of hypertrophy or renovascular disease. Coronary perfusion pressure = diastolic arterial pressure - left ventricular end diastolic pressure. Renal perfusion pressure = mean arterial pressure – tissue pressure.

higher blood pressure value in these patients, as well as in those with long-standing hypertension. It is also 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 mmHg, while the brain and coronary circulation require a MAP of somewhere between 30 and 50 mmHg (Fig. 1). In addition, the pressure–flow relationship for the kidney appears to follow a steeper slope than that of other regional beds. Thus, for a given fall in blood pressure, the proportional fall in blood flow would be expected to be particularly sharp for the kidney.

These physiological 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.

Noradrenaline

Noradrenaline 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, since noradrenaline induces vasoconstriction via α-adrenergic stimulation, it may also decrease organ blood flow, if regional vascular beds constrict in excess. In such a scenario, intra-organ vascular resistance would increase proportionately more than perfusion pressure and overall blood flow would decrease, particularly for the kidney. In fact, noradrenaline infusions have 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 noradrenaline.

The studies that suggest that noradrenaline may induce splanchnic or renal ischemia, however, are open to several criticisms. Importantly, they do not address the effects of noradrenaline in vasodilated, hypotensive states and may not even accurately reflect the longer-term effect of noradrenaline infusion in normal subjects. On the other hand, if noradrenaline 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 acute renal failure (ARF). In the light of such considerations, concern continues to exist as to the advisability of sustained vasopressor infusions in the hypotensive patient.

It is not clear if 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. Downregulation of vascular smooth muscle α-adrenergic receptor responsiveness [12] and active vasodilatation occur due to massive 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, independently of α-adrenergic tone [14]. Finally, increased cAMP concentrations in the smooth muscle cells of blood vessels, induced by the administration of phosphodiasterase inhibitors, will also decrease vessel tone, as would the loss of sympathetic outflow from epidural blockade.

Under circumstances of marked vasodilatation, it makes physiological sense to think that the restoration of normal or near normal vascular tone and adequate renal perfusion pressure should improve renal blood flow and the glomerular filtration rate. It is controversial, however, whether or not noradrenaline can achieve these goals safely.

Current knowledge about noradrenaline

It is well known that noradrenaline can be used to induce a reversible model of ARF [15,16] when infused into the renal artery. Such ARF is induced by intensive renal vasoconstriction. Once again, such observations make the physician wary of using noradrenaline in the clinical setting of renal dysfunction, in case it may induce or contribute to ARF. A more accurate analysis of the available data, however, is warranted. Noradrenaline-induced intense vasoconstriction has only 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 noradrenaline-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.

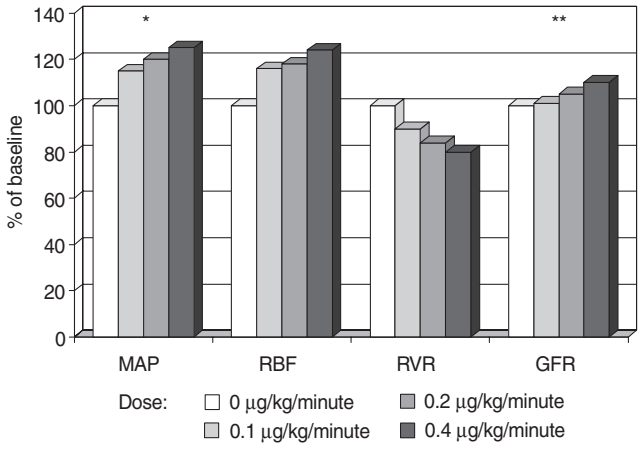
Schaer and co-workers have also reported the renal effects of noradrenaline infusion at different doses, with or without the addition of low-dose dopamine [17]. They measured renal blood flow with the technique of regional thermodilution (an unvalidated approach). They found that, although renal vascular resistance appeared to increase from baseline (there was no placebo arm), total renal blood flow progressively increased with increasing doses of intravenous noradrenaline up to 1.6 μg/kg/minute. In their study, any adverse effects of noradrenaline infusion on renal vascular resistance (please note that total renal blood flow actually increased) were seen in animals with a baseline mean arterial blood pressure of 151 mmHg. No sane clinician would prescribe noradrenaline to a patient with a mean arterial blood pressure of 150 mmHg! Furthermore, noradrenaline infusion increased MAP by approximately 30% to 200 mmHg. The relevance of these data to clinical practice is minimal.

On the other hand, a study by Anderson and co-workers appears to mimic clinical practice more closely [18]. These investigators infused noradrenaline intravenously at 0.2–0.4 μg/kg/minute (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 noradrenaline infusion (Fig. 2). Such noradrenaline-induced renal vasodilatation was unaffected by pretreatment with indomethacin, propranolol, or angiotensin-converting enzyme inhibition. Renal vasodilatation, therefore, was not prostaglandin-mediated and was independent of β-receptor stimulation or of angiotensin-derived changes in vascular tone. Efferent autonomic sympathetic nerve blockade with pentolinium prior to noradrenaline infusion, however, completely abrogated noradrenaline-induced renal vasodilatation. These investigators logically concluded that, in keeping with previous experimental data [19], most of the renal vasodilating effect of intravenous noradrenaline could be attributed to an increase in systemic blood pressure, which decreased renal sympathetic tone through a baroreceptor response, leading to vasodilatation.

The effect of noradrenaline infusion on regional blood flow in the dog has also been recently explored by Zhang and co-workers [20]. These investigators have also demonstrated that, in the endotoxemic dog, noradrenaline did not induce any decrease in renal or hepatic blood flow.

The effects of noradrenaline 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, Bersten and co-workers have recently studied the renal effects of adrenaline, another potent vasopressor agent, with a strong mixed β- and α-adrenergic effect. These investigators administered adrenaline by continuous infusion at clinically relevant doses in normal and septic sheep [21,22]. After a small decrease in renal blood flow at the highest doses tested (0.4–0.8 μg/kg/minute), renal blood flow progressively increased. It remained elevated for up to six hours of noradrenaline infusion. A similar increase in renal blood flow occurred in septic animals.

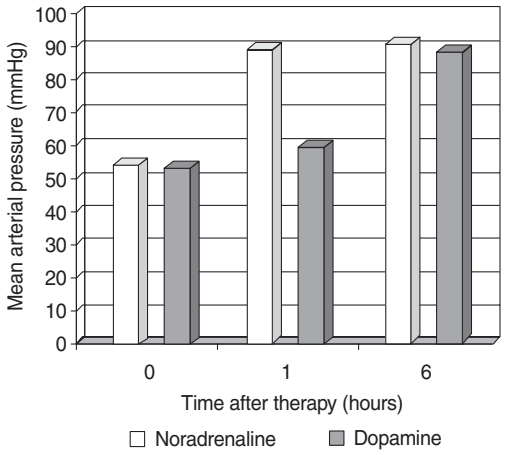
Figure 2



Histogram illustrating the effect of different doses (0–0.4 μg/kg/minute) of noradrenaline on mean arterial pressure (MAP), renal blood flow (RBF), renal vascular resistance (RVR) and glomerular filtration rate (GFR) in the dog. Both MAP and GFR are significantly increased by noradrenaline at clinically relevant doses. *$P < 0.01$; **$P < 0.05$. Published with permission from *The Journal of Physiology* [18].

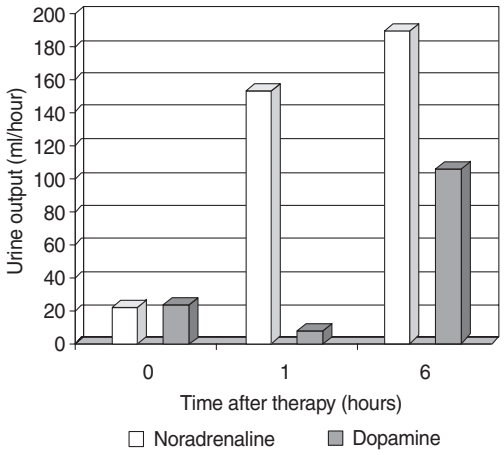
All of the above studies support the notion that mixed β- and α-adrenergic agents (noradrenaline affects both receptors), when given to restore blood pressure during vasodilatation, will generally improve renal blood flow. The physiological question persists, however, concerning the effect of noradrenaline per se on the tone of the renal vasculature. Such analysis demands that effects of noradrenaline on blood pressure should be removed from consideration by statistical methods and that issues of pre-load should also be eliminated by experimental methods. To address this issue, Bellomo *et al*. have recently conducted a complex and highly invasive physiological study in the dog [23]. While a discussion of the methodology is not warranted here, a few points should be emphasized. The vascular occlusion technique for the inferior vena cava was used. Such occlusion induces a fall in pre-load that allows differences in pre-load between different hemodynamic states to be essentially eliminated from the assessment of the effect of the drug itself on the renal vasculature. It should also be noted that both the P/Q

Figure 3



The blood pressure effect of high-dose dopamine (25 μg/kg/minute) compared to noradrenaline (up to 1.5 μg/kg/minute) in patients with hypotensive hyperdynamic septic shock. Noradrenaline is clearly superior in restoring mean arterial pressure to normotensive levels. For all measurements, $P < 0.0001$.

Figure 4



The comparative effects of high-dose dopamine and noradrenaline on urine output in patients with hyperdynamic hypotensive septic shock and oliguria. Noradrenaline is clearly superior in restoring urine output. For all measurements, $P < 0.0001$.

relationship (dynamic resistance) and the point of zero flow were defined. The point of zero flow represents pre-capillary sphincter tone. Another point is that these investigators studied the animal in the septic and normal state with repeated control observations and a crossover design.

Noradrenaline 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, noradrenaline 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 noradrenaline 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 noradrenaline on the determinants of steady state renal blood flow independent of perfusion pressure. Under normal conditions, noradrenaline, infused intravenously at a rate capable of increasing MAP by approximately 15 mmHg, 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. During acute endotoxemic conditions, however, the initial state of the renal vasculature was altered, reflecting the profound effects that endotoxemia has on vascular smooth muscle tone and vascular responsiveness. Under these conditions, the addition of noradrenaline 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, noradrenaline 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 physiological basis for the administration of noradrenaline during septic shock and other vasodilated states.

Noradrenaline or high-dose dopamine

Studies that directly measure renal blood flow and resistance in humans are not available. Many clinical reports, however, support the notion that the continuous infusion of noradrenaline may increase urine output and improve creatinine clearance in hyperdynamic septic shock [24–30]. Of particular interest is a study by Martin and co-workers because it is the only randomized, controlled study available [3]. These investigators randomized 32 patients with hyperdynamic and hypotensive septic shock to receive either high-dose dopamine (up to 50 μg/kg/minute) or noradrenaline (up to 1 μg/kg/minute) in order to achieve a predetermined arterial blood pressure (>80 mmHg). They studied the overall hemodynamic response, as well as lactate level and urinary output after one and six hours of therapy. They found that high-dose dopamine failed to restore normotension in one third of patients, while noradrenaline succeeded in all patients (Fig. 3). In addition, in those patients whose hypotension could not be corrected with dopamine, noradrenaline restored a MAP of >80 mmHg. Urinary output was significantly improved from baseline once blood pressure was increased (Fig. 4). This controlled study strongly suggests that noradrenaline is superior to high-dose dopamine in restoring blood pressure in septic vasodilated patients, and that such correction of blood pressure induces an improve-

ment in urine output. More recently, Martin also reported on the outcome of 97 adult patients with septic shock, of whom 57 were treated with noradrenaline [31]. Patients treated with noradrenaline had a lower mortality than those treated with other pressor drugs, and noradrenaline use was identified as a predictor of survival on multivariate logistic regression analysis. These findings support the argument that noradrenaline is safe and effective in hypotensive vasodilated states and that its renal effects under these circumstances are likely to be beneficial.

Conclusion

The use of noradrenaline in intensive-care-unit patients with hypotension and evidence of renal dysfunction remains the subject of much debate and controversy. Although it would appear that at the time of writing noradrenaline use is seen by many clinicians as somewhat undesirable in these patients, the data suggest otherwise. It may indeed be that restoration of blood pressure with noradrenaline has a nephroprotective effect and that, in vasodilated states, noradrenaline and the kidney are more friends than foes. Much work remains to be done, however, on the renal effects of hemodynamic manipulation with catecholamines before we can make clinical decisions based on level I evidence.

Competing interests

None declared.

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