Is There Still a Place for Dopamine in the Modern Intensive Care Unit?

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For many years, dopamine was considered an essential drug in the intensive care unit (ICU) for its cardiovascular effects and, even more, for its supposedly protective effects on renal function and splanchnic mucosal perfusion. There is now ample scientific evidence that low dose dopamine is ineffective for prevention and treatment of acute renal failure and for protection of the gut. Until recently, low-dose dopamine was considered to be relatively free of side effects. However, it is now clear that low-dose dopamine, besides not achieving the preset goal of organ protection, may also be deleterious because it can induce renal failure in normo- and hypovolemic patients. Furthermore, dopamine may cause harm by impairing mucosal blood flow and by aggravating reduced gastric motility. Dopamine also suppresses the secretion and function of anterior pituitary hormones, thereby aggravating catabolism and cellular immune dysfunction and inducing central hypothyroidism. In addition, dopamine blunts the ventilatory drive, increasing the risk of respiratory failure in patients who are being weaned from mechanical ventilation. We conclude that there is no longer a place for low-dose dopamine in the ICU and that, in view of its side effects, its extended use as a vasopressor may also be questioned.

(introduced as a therapeutic drug in the late 1960s, dopamine (DA) became the most widely used vasactive drug in the intensive care unit, because it was assumed to improve short-term survival in sepsis and cardiogenic shock (1). This endogenous catecholamine influences different catecholamine receptors in a dose-dependent manner. In adults, infusion rates of 0.5 to 2 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) induce primarily dopaminergic effects. At rates of 2 to 5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), the actions are mainly dopaminergic (80% to 100%), but there may be some \( \beta \)-adrenergic effects (5% to 20%). At rates of 5 to 10 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), \( \beta \)-adrenergic effects predominate, and \( \alpha \)-adrenergic actions gradually become important. Infusion rates of 10 to 20 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) produce primarily \( \alpha \)- and \( \beta \)-adrenergic effects (2). It is important to note that these dose ranges are not cutoff values, at which one set of receptors is activated at the expense of another, but rather ranges within which the effects of one group of receptors predominate over another, with a huge variation between individuals. Furthermore, plasma DA clearance is much smaller in critically ill patients than in healthy people, again with considerable interindividual variation and little correlation between plasma levels and infusion rate (3).

After the pioneering work by Goldberg (1) suggested a protective effect of low-dose DA (LDD) (<5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) on renal function, the drug became widely used in intensive care medicine for optimization of renal and splanchnic perfusion. Recently, these presumed protective effects on renal and splanchnic function have been repeatedly questioned, and an increasing number of side effects have been reported. Doubts are thus increasing about the place of DA in the treatment of critically ill patients.

In this review, we discuss the scientific evidence for and against the use of DA in terms of effect on several organ systems. In addition, we evaluate the scientific basis for the use of DA as a vasopressor.

Renal Effects

For more than two decades LDD has been used worldwide for its presumed renal protective effects. Infusion of LDD into healthy experimental animals and humans causes renal vasodilation associated with a dose-dependent increase in renal blood flow and diuresis (4). Furthermore, the addition of DA may blunt...
norepinephrine-induced renal vasoconstriction in healthy volunteers (5,6). The mechanisms by which DA achieves these effects vary according to dose. At small doses (0.5–3 μg·kg⁻¹·min⁻¹), DA augments renal blood flow predominantly by stimulating dopamine (DA)-1 receptors in the renal vasculature (7) and a possible contributory engagement of DA-2 receptors on presynaptic nerve endings with inhibition of norepinephrine release (7). Larger doses are thought to augment the renal blood flow chiefly by increasing cardiac output through β-adrenergic stimulation.

In addition, DA also triggers natriuresis and diuresis through a direct effect on the tubular cell function. DA binds to DA-1 and DA-2 receptors in the proximal tubule, the thick ascending limb of the loop of Henle, and the cortical collecting ducts inhibiting Na⁺/K⁺-adenosine triphosphatase activity, thereby inducing natriuresis (8). Furthermore, activation of DA-2 receptors in the inner medullary collecting ducts stimulates prostaglandin E₂ (PGE₂) production, which antagonizes the effects of antidiuretic hormone, resulting in a washout of the medullary area and increased clearance of free water (9).

LDD induces regional re-distribution of blood flow within the kidney, preferentially increasing cortical blood flow (7), whereas PGE₂ enhances blood flow in the inner medulla. LDD thus induces a shunting of blood away from the outer medulla. This is potentially detrimental in acute renal failure (ARF), given that the outer medulla, in particular, is highly metabolically active and thus very susceptible to ischemic injury (10,11).

As the result of the pioneering work of Goldberg (1), infusion of LDD was considered an attractive management option in patients with incipient or established ARF. However, at that time there were no clinical studies demonstrating the beneficial effect of LDD on renal function in critical illness and, indeed, although LDD may selectively increase renal blood flow in healthy volunteers (4), one cannot extrapolate this effect to critically ill patients.

Clinical trials have now investigated the use of LDD for the prevention of ARF in patients at risk, as well as its therapeutic use in patients with established ARF. Some of these studies have shown that LDD increases urine output (2,12–17), whereas others found no effect (5,18–20). The renal effect of DA also seems to decrease progressively with increasing severity of renal dysfunction and is lost in patients with a glomerular filtration rate less than 50 mL/min per 1.73 m² (21). One study even suggested a detrimental effect of LDD on the tubular function, because LDD increases urinary excretion of retinol binding protein in patients undergoing coronary bypass surgery (18). As is often the case in the critical care setting, these inconsistencies are due to the heterogeneity of the studied patient population, the dose of DA used, or the timing and duration of DA administration.

Other problems are related to the study design, such as absence of concurrent control groups, absence of randomization, and relatively small sample sizes, which prevented adequate statistical analysis and conclusions. DA-induced diuresis may also be falsely reassuring because an increased urine output is not automatically associated with an improved renal function (16,17). Because renal hypoperfusion is a leading cause of ARF (10,11), one should be aware of the risk of inducing renal failure by increasing urine output in normovolemic and hypovolemic patients (20,22). Although several of these studies concluded that LDD influences renal function directly without significant effects on systemic hemodynamics, many did not report measurements of cardiac output. An opinion more recently gaining acceptance postulates that LDD increases urine output by enhancing cardiac output and thus not primarily by a direct renal effect (14,15,22).

In addition to the poor evidence for any beneficial effect of DA on renal function in the critically ill patient, evidence for any benefit on survival was also lacking until recently. A large study by the Australian and New Zealand Intensive Care Society group (23) clearly showed that LDD does not prevent or reverse ARF, nor does it improve outcome. It was the first large, prospective, randomized, double-blinded, placebo-controlled trial investigating the potential of LDD (2 μg·kg⁻¹·min⁻¹) in critically ill patients with systemic inflammatory response syndrome and early renal dysfunction. In the 324 patients included, no differences in mortality, requirement for renal replacement therapy, renal recovery, or peak serum creatinine were found (23) (Fig. 1).

The Australian and New Zealand Intensive Care Society study thus confirmed the results of two large retrospective analyses. In a retrospective analysis of the North American Septic Shock Trial (NORASEPT)-II, LDD did not reduce the incidence of ARF, the need for hemodialysis, or the 28-day mortality in septic shock patients with oliguria (24). A similar analysis of the placebo arm of the Auriculin Anaritide ARF Study (25) also failed to show a beneficial effect of LDD on survival or the need for hemodialysis in patients with ARF. In addition, two meta-analyses of the effect of LDD on ARF were recently published. In the first meta-analysis, Kellum and Decker (26) analyzed data from 58 trials of 2149 patients and found that LDD did not prevent mortality, ARF, or the need for hemodialysis. In the second, Marik (27) reviewed 15 randomized, controlled studies that compared LDD with placebo for the prevention or treatment of ARF and, again, no benefits of LDD were found in terms of absolute change in serum creatinine and the incidence of ARF.
Some authors suggest that the addition of LDD in patients who require norepinephrine may limit the vasopressor-induced adverse effects on renal function. Experimental studies have shown that infusion of LDD improves renal hemodynamics in healthy animals (28) and volunteers (5,6). However, LDD had no effects on renal flow in experimental animal models of septic shock treated with norepinephrine (29). Likewise, in patients with septic shock treated with catecholamines, LDD had no effect on renal function (16,22). Although the addition of LDD can increase urine output in patients with septic shock treated with norepinephrine (15,22), an effect that is probably directly related to its increase of cardiac output, this does not improve renal function (15). In sepsis, the renal vascular autoregulation and vasodilation are probably already maximal and not amendable by pharmacological vasodilators. There is thus no justification for the routine use of LDD to improve renal function in patients treated with large doses of catecholamines (16).

We can conclude that LDD may increase urine output in critically ill patients, but it neither prevents nor improves ARF. When DA does increase diuresis, it may actually increase the risk of ARF in normovolemic and hypovolemic patients.

Effects on Splanchnic Perfusion

The gut may be particularly susceptible to ischemia in shock, and disruption of the gut mucosal barrier is thought to play a key role in the development of multiple organ failure (30). Theoretically LDD may increase splanchnic blood flow by stimulation of the splanchnic dopaminergic receptors. The evidence, however, is poor.

In experimental animal models, DA increases splanchnic and hepatic blood flow (31,32). However, this is not necessarily accompanied by an improvement of mucosal perfusion (33). In dogs, LDD reduced intestinal oxygen uptake and mucosal blood flow (32), and in a porcine model of hemorrhagic shock, LDD hastened the onset of gut ischemia (34). A decrease in the ability of the gut to extract oxygen during infusion of DA could be explained by redistribution of blood flow within the gut, resulting in a reduced blood flow selectively in the mucosa (32,33). In other animal studies, however, LDD did improve mucosal blood flow, as well as oxygenation (31,35,36). These different effects can be explained, at least in part, by the different models and drug doses used (37).

Human data are even more controversial. LDD has been reported to increase splanchnic blood flow in septic shock and cardiac surgery patients (38,39), whereas other investigators found no effect (40). The observed increase in splanchnic blood flow in septic patients seems to vary between individuals, depending on the initial fractional splanchnic blood flow (38). Furthermore, LDD was recently shown to decrease the splanchnic oxygen consumption in septic patients despite an increase in systemic and splanchnic blood flow, an effect not seen in cardiac surgery patients (37). The same group of investigators previously showed a variable effect of the use of DA as a vasopressor on splanchnic oxygen consumption: 3 of 5 patients decreased and two increased splanchnic oxygen consumption (39). This controversy can be explained by several methodological differences between these two studies, such as the severity of illness on the start of DA and the timing and dose of DA infusion. Although LDD increases oxygen transport in septic patients, it decreases the gastric mucosal flow (41) and does not affect intramucosal pH (pHi), a surrogate marker of gut mucosal perfusion (17,40–42). Larger doses of DA are associated with an even further decrease of pHi (43).

Thus, as for the renal effect of LDD, there is no evidence that LDD has beneficial effects on the splanchnic function or reduces the progression to multiple organ failure in sepsis. Recent data even suggest a potentially detrimental effect of LDD on splanchnic oxygen uptake.

Effects on Gastrointestinal Motility

DA-2 are present in the human enteric nervous system, and DA-antagonistic drugs, such as metoclopramide and domperidone, improve the antroduodenal coordination, which is required for optimal gastric emptying. One can thus suspect that infusion of DA...
will interfere with the gastrointestinal motility. Indeed, in healthy volunteers short-term DA administration has been shown to interrupt the fed gastrointestinal motility pattern (44). In critically ill patients, the use of DA (2.5–5 µg·kg⁻¹·min⁻¹) was found to be the most significant factor associated with poor gastric emptying (45), and it was clearly shown that LDD adversely affects gastroduodenal motility in mechanically ventilated critically ill patients both during fasting and nasogastric feeding (46). Hence, the use of DA cannot be reconciled with the current recommendation to preferentially use enteral rather than parenteral nutrition in critically ill patients. Indeed, because DA may aggravate digestive intolerance to enteral feeding, its use is not advisable.

Respiratory Effects

There are two potentially detrimental effects of LDD on respiratory function that are often overlooked. First, DA has been shown to impair the ventilatory drive in response to hypoxemia and probably hypercapnia by depressing the carotid body (47). Second, DA reduces arterial oxygen saturation by impairing regional ventilation/perfusion matching in the lung (48). Both mechanisms are synergistic and can usually be counterbalanced by a larger oxygen supplement. In mechanically ventilated patients, depression of the ventilatory drive by DA does not impose a clinically relevant problem. However, such problems can arise when the patient is taken off mechanical ventilatory support, because LDD blunts the conscious discomfort evoked by arterial hypoxemia and hypercapnia (47). Thus, when a patient is being weaned from ventilatory support while still receiving DA, he or she may not be able to give the physician important symptomatic feedback about impaired gas exchange (47,49). Paradoxically, patients receiving LDD may be easier to wean, but with the potential danger of precipitating respiratory failure (49). In summary, also from a respiratory point of view, the use of LDD cannot be advised.

Endocrine and Immunological Effects

The anterior pituitary gland plays a crucial role in metabolic and immunologic homeostasis; the corticotropic, lactotropic, gonadotropic, and thyrotropic axes are key determinants of normal growth, metabolism, and host defense. Critical illness is associated with various alterations in these neuroendocrine axes, depending on the phase (acute versus chronic) of illness (50). In the initial stress response, the release of all anterior pituitary hormones is stimulated, whereas in more prolonged critical illness, a uniform suppression of the hypothalamic-pituitary axes ensues while cortisol secretion remains increased through a peripheral drive. Although the functional implications and clinical relevance of these changes are unclear, it is conceivable that the acute changes are part of the body’s protective mechanism against disease. However, in prolonged critical illness, hypothalamic hypopituitarism has been found to evoke inappropriate and harmful metabolic changes (51). DA has been shown to further suppress the secretion and function of a number of key anterior pituitary hormones (Fig. 2) and may thus aggravate impairment of anabolism and cellular immune function.

Prolactin is an immunoregulatory hormone with receptors on T- and B-lymphocytes, and reduced levels of prolactin have been associated with compromised cellular immune function and increased susceptibility to infection in animals (56). DA is a key regulator of prolactin release from the pituitary gland, and exogenously administered DA effectively reduces serum prolactin levels and thus potentially influences the immune status, rendering patients more susceptible to infection (57). Devins et al. (58) showed that a dose of >5 µg·kg⁻¹·min⁻¹ DA resulted in a 90% reduction of serum prolactin, which was associated with a transient reduction in T-cell response and lymphocyte count. Furthermore, the use of DA at “low dose” has also been reported to suppress prolactin secretion in critically ill children and adults (59,60). Besides immunodepressive effects mediated by hyperprolactinemia, DA has been shown to increase the expression of human immunodeficiency virus in cells of the immune system (61).

Other neuroendocrine hormonal axes are also affected by DA administration during critical illness. Growth hormone (GH) is a typical stress hormone that has high levels in response to several types of insults, whereas in prolonged critical illness, GH secretion is blunted and insulin-like growth factor-I (IGF-I) levels are low (50). This conceivably contributes to impaired anabolism, because it has been shown that the co-infusion of GH secretagogues and thyrotropin releasing hormone (TRH) restores pulsatile GH secretion and normalizes serum IGF-I levels, which results in anabolism in peripheral lean tissues, such as bone (51). Prolonged DA infusion further suppresses pulsatile GH secretion and is associated with even lower levels of IGF-I (52). Dehydroepiandrosterone sulfate, an anabolic and immunostimulating steroid secreted by the adrenal cortex, is also suppressed by LDD administration during critical illness (62) (Fig. 3).

Normal thyroid function is essential for protein metabolism, GH secretion, and responsiveness and for normal glucose and lipid metabolism. In critical illness, the thyroid axis is disturbed, with low serum TSH, thyroxine, and triiodothyronine (T₃) and increased reverse T₃. Reduced pulsatile TSH secretion seems to play a key role in this process, because the
low thyroid hormone levels correlate positively with reduced pulsatile TSH production and the number of TSH bursts (63). This constellation used to be labeled “euthyroid sick syndrome,” referring to the assumption that it is does not reflect true hypothyroidism. This concept has been challenged by the observation that reactivating the thyroid axis in critically ill patients reverses hypercatabolism (51). Indeed, restoration of physiological levels of thyroid hormones by continuously infusing TSH-releasing hormone reduces protein breakdown. DA profoundly aggravates the low-T₃ syndrome through direct inhibition of TSH release, resulting in a further decrease of thyroxine and T₃ (Fig. 3), and the duration of the DA infusion is related to the severity of the impaired thyroid function (53,60). In the neonate, the effect of iatrogenic hypothyroidism may be even greater, because thyroid hormone is of the utmost importance for the development of the central nervous system during the first weeks after birth and impaired thyroid function in the neonatal period is associated with irreversible neurological damage (52,55).

When given in the acute phase of illness, DA induces the pituitary impairment seen in prolonged critical illness. When used in the chronic phase of critical
illness, infusion of DA further aggravates the suppression of circulating concentrations of pituitary hormones. Although the full effect of the endocrine abnormalities seen in intensive care patients remains unclear, the additional suppressive effects of DA, especially when given for more than a few days, are unlikely to be beneficial and may be harmful (55).

**DA as a Vasopressor**

Which vasopressor to use when hypotension persists after volume resuscitation in distributive shock remains an unanswered question. Both norepinephrine and DA in the appropriate dose are excellent α-adrenergic agents (vasopressor) with an associated lesser degree of β-adrenergic activity (inotrope). Because of the fear of excessive vasoconstriction, norepinephrine is still considered by many to be deleterious, causing end-organ hypoperfusion and severe ischemia of vital organs; this explains its nickname (“Le-thalpheid”). Therefore, DA is still often preferred as the first-choice vasopressor when hypotension persists despite adequate fluid resuscitation (64). However, for patients in whom DA fails to restore an adequate hemodynamic status, norepinephrine has been found to be beneficial. In recent years, an increasing number of favorable reports on the use of norepinephrine in effectively volume-resuscitated septic shock patients have shown that the fear of deleterious effects of norepinephrine is unwarranted. Martin et al. (65) reported a faster decline of circulating lactate levels in patients with septic shock treated with norepinephrine as compared with DA. In a septic setting, DA seems to act largely by increasing cardiac output, whereas norepinephrine more specifically increases vascular resistance without compromising flow (43).

The use of norepinephrine, as compared with DA, prevents delay in the restoration of mean arterial blood pressure and reduces the time to resuscitation. When excessively large doses of norepinephrine are avoided and volume resuscitation is adequately performed by using optimized monitoring, the adverse effects of norepinephrine can be effectively minimized or even avoided. Animal data suggest that there may even be a protective effect of norepinephrine on renal blood flow in septic shock (66). Human studies have also shown an improvement of urine output in patients treated with norepinephrine (65). Furthermore, no deleterious effects of norepinephrine on the splanchnic circulation have been demonstrated in animal models of endotoxin shock (67), as well as in patients with septic shock (68). In patients with septic shock, norepinephrine may even increase pH, whereas DA tends to decrease the pH further (43). In line with these data, it was recently shown that DA (4 μg · kg⁻¹ · min⁻¹) reduces hepatosplanchnic oxygen uptake in septic patients despite an increase in systemic and regional perfusion, an effect not seen with dobutamine (37). Hence, there is actually no evidence that reversing hypotension with norepinephrine compromises mesenteric or renal flow after adequate volume resuscitation, and the fear that norepinephrine might contribute to the progression of multiple organ failure has been vitiated (69). One study even observed a survival advantage of norepinephrine treatment as compared with other vasopressors in septic shock patients (70).

There are strong arguments for the addition of an inotrope to the vasopressor therapy in patients with septic shock whenever suppressed myocardial function is suspected, to optimize regional perfusion and oxygen delivery (71). However, the theoretical advantage of DA to also exert inotropic effects through β-agonism does not annihilate its side effects. Instead, adding a more specific β-agonist, such as dobutamine, not only abrogates these side effects but also, through separate titration, allows a more targeted intervention tailored by the patient’s condition. Therefore, although there are few valid studies comparing the use of DA versus norepinephrine, norepinephrine may be emerging as the vasopressor of choice for severe hypotension in adequately volume-resuscitated septic shock patients.

**Conclusion**

Although sound scientific evidence for its presumed benefits is clearly lacking, DA is still often used as a first-choice vasoactive drug, with dopaminergic and α- and β-adrenergic effects. These effects are believed to be dose dependent and vary considerably between patients. DA is used to support cardiac output and blood pressure in patients with cardiac failure and distributive shock. Because of the work of Goldberg (1), which suggested that LDD induces protective effects on renal and splanchnic function, and because of the general belief that LDD is relatively free of side effects, the drug also became widely used in intensive care to protect kidney and gastrointestinal function in critically ill patients. However, these assumptions were proven incorrect. There is indeed no evidence that low “renal” dose DA has any beneficial effect on renal function or on the outcome of patients with ARF. Furthermore, there is no evidence that LDD has beneficial effects on hepatosplanchnic circulation, and recent data suggest that DA may even have detrimental effects on splanchnic oxygen uptake.

In addition to the lack of efficiency, side effects of LDD have increasingly been reported and documented. It has been clearly shown that DA suppresses the secretion and function of anterior pituitary hormones, aggravating the impairment of anabolism and.
cellular immune function. DA also aggravates the digestive tolerance of enteral feeding and suppresses the ventilatory drive.

We conclude that there is now ample scientific evidence demonstrating that LDD is ineffective and has several serious side effects. The widespread use of LDD for renal protection can thus no longer be justified. In view of its side effects, there are clearly much better alternatives to use as first-choice vasopressors or inotropes in patients with septic shock.

References


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