critical care reviews

Bad Medicine*

Low-Dose Dopamine in the ICU

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Low-dose dopamine administration (*ie*, doses < 5 μg/kg/min) has been advocated for 30 years as therapy in oliguric patients on the basis of its action on dopaminergic renal receptors. Recently, a large, multicenter, randomized, controlled trial has demonstrated that low-dose dopamine administered to critically ill patients who are at risk of renal failure does not confer clinically significant protection from renal dysfunction. In this review, we present the best evidence and summarize the effects of low-dose dopamine infusion in critically ill patients. We review the history and physiology of low-dose dopamine administration and discuss the reasons why dopamine is not clinically effective in the critically ill. In addition to the lack of renal efficacy, we present evidence that low-dose dopamine administration worsens splanchnic oxygenation, impairs GI function, impairs the endocrine and immunologic systems, and blunts ventilatory drive. We conclude that there is no justification for the use of low-dose dopamine administration in the critically ill. ***(CHEST 2003; 123:1266–1275)***

Key words: acute; critical illness; dopamine; kidney failure; multiple organ failure; renal circulation; sepsis syndrome; splanchnic circulation

Abbreviations: DHEAS = dehydroepiandrosterone sulfate; RCT = randomized controlled trial

Low-dose dopamine is defined as the dose that produces preferential dopaminergic and β-adrenergic effects over its α-adrenergic effects (< 5 μg/kg/min),[1] and therefore causes renal and splanchnic vasodilation in animals and healthy humans. Since its clinical application in patients with congestive heart failure 40 years ago,[2] there has been a confusing profusion of experimental evidence arguing both for and against the use of low-dose dopamine administration in the treatment of patients who are in oliguric states that are associated with critical illness. Advocates cite increased renal and splanchnic blood flow, and natriuresis as arguments for its use.[3] Detractors point to the lack of benefit, and even to evidence of harm, of low-dose dopamine administration in disease states.[4–7] How do we reconcile this paradox? What is the current evidence for the use of low-dose dopamine administration in critically ill oliguric or at-risk patients? We argue that there is now compelling evidence that low-dose dopamine administration is not effective in critically ill patients and may induce harm. In this review, we will present the type I evidence, a meta-analysis, and will review the history of the use of low-dose dopamine. We then present reasons why low-dose dopamine is not clinically effective and may induce harm in critically ill patients. We conclude that low-dose dopamine has no place in the critical care armamentarium and that this therapy should be relegated to the place of high-tidal volume ventilation and liberal transfusion practices.

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The Best Evidence: Low-Dose Dopamine Administration in Oliguric Patients With Sepsis Syndrome Is Not Therapeutic

Despite the widespread use of low-dose dopamine administration in oliguric patients,[8–10] there have

only been two randomized controlled trials (RCTs) examining the efficacy of dopamine in the treatment of acute renal failure in critically ill patients,[11,12] and only one was a large, multicenter RCT.[12]

In the first study,[11] the effects of furosemide and furosemide with dopamine on renal function were studied in 23 patients with acute renal failure due to falciparum malaria whose serum creatinine levels ranged from 230 to 947 μmol/L (2.6 to 10.7 mg/dL). Furosemide given IV at the dosage of 200 mg every 6 h for a period of 4 days did not alter the clinical course of renal failure. The IV administration of furosemide (200 mg every 6 h) with dopamine (1 μg/kg/min) for 4 days increased creatinine clearance and arrested the progress of renal failure when the serum creatinine level was < 400 μmol/L (4.5 mg/dL) but failed to alter the course of renal failure when the serum creatinine level exceeded 600 μmol/L (6.8 mg/dL). The results of this trial were encouraging but need to be repeated in a larger population with nonmalarial sepsis.

Olson and coworkers[13] conducted an RCT of low-dose dopamine administration vs placebo administration in 16 nonoliguric, mechanically ventilated patients with sepsis syndrome, which was designed to assess the effects of low-dose dopamine on surrogate markers of renal and gastric perfusion. In this well-conducted study, a 2-h infusion of dopamine (3 μg/kg/min) increased urine volume but did not significantly alter creatinine clearance, gastric pH, cardiac output, or the gastric-to-arterial P_{CO_2} gradient. The study power was > 95% to detect a difference in these prospectively identified variables at the $p < 0.05$ level. The authors concluded that in critically ill patients, the use of low-dose dopamine results in diuresis but does not improve other markers of renal or gut perfusion.

A rigorously conducted multicenter RCT of low-dose dopamine in patients with early renal dysfunction was published in December 2000[12] (Fig 1). This trial randomized 328 patients who met the criteria for systemic inflammatory response syndrome and acute renal dysfunction to infusions of dopamine at 2 μg/kg/min or placebo. Renal dysfunction was defined as follows: urine output averaging < 0.5 mL/kg/h for > 4 h; serum creatinine concentration, > 150 μmol/L (1.7 mg/dL) in the absence of premorbid renal dysfunction; a rise in serum creatinine concentration of > 80 μmol/L (0.9 mg/dL) in < 24 h in the absence of a creatine kinase level of > 5,000 IU/L; or myoglobin in the urine. The criteria for stopping infusion included death, progression to renal replacement therapy, improvement in systemic inflammatory response syndrome and renal function, or discharge from the ICU. After randomization, dopamine was infused for a mean duration of

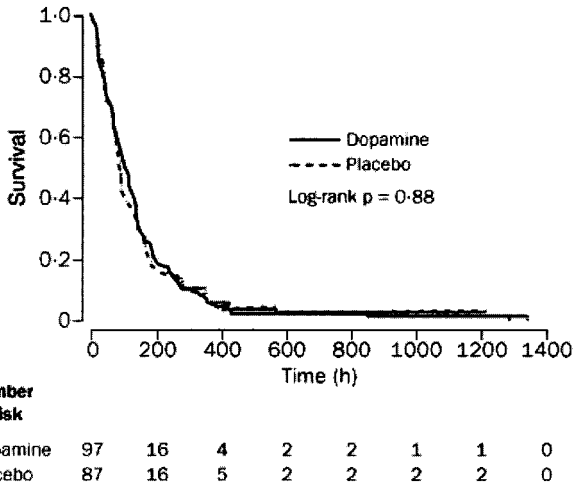

FIGURE 1. RCT of low-dose dopamine in patients with early renal dysfunction. Kaplan-Meier curve of time to recovery of normal renal function for patients in whom the trial drug was stopped because of early renal dysfunction is shown. Reprinted with permission from Bellomo et al.[12]

4.7 days and placebo was infused for a mean of 5.2 days. The primary end point was the peak serum creatinine level reached during the trial, and the secondary end points were duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, duration of cardiac arrhythmias, duration of survival to hospital discharge, and time to renal recovery. The trial was powered to detect a 20% decrease in serum creatinine level, but after two interim analyses the size of the trial was increased to > 300 patients to increase the statistical power. This trial found no difference between the dopamine and placebo groups in peak serum creatinine concentration during treatment (dopamine group, 245 ± 144 μmol/L [2.8 ± 1.6 mg/dL]; control group, 249 ± 147 μmol/L [2.8 ± 1.7 mg/dL]; $p = 0.93$), in the increase from baseline to the highest value during treatment (dopamine group, 62 ± 107 μmol/L [0.7 ± 1.2 mg/dL]; control group, 66 ± 108 μmol/L [0.75 ± 1.2 mg/dL]; $p = 0.82$), or in the numbers of patients whose serum creatinine concentrations exceeded 300 μmol/L or 3.4 mg/dL (dopamine group, 56 patients; control group, 56 patients; $p = 0.92$), or the number of patients who required renal replacement therapy (dopamine group, 35 patients; control group, 40 patients; $p = 0.55$). Durations of ICU stay (dopamine group, 13 ± 14 days; control group, 14 ± 15 days; $p = 0.67$) and durations of hospital stay (dopamine group, 29 ± 27 days; control group, 33 ± 39 days; $p = 0.29$) were also similar. There were 69 deaths in the dopamine group and 66 deaths in the placebo group. The authors concluded, "Administration of low-dose dopamine by continuous IV infusion to critically ill patients at risk of renal failure does not

confer clinically significant protection from renal dysfunction." The three following questions remain: How does this RCT compare to previous, underpowered studies? How did this therapy become so widely used? Why does low-dose dopamine not work in critically ill patients?

We now review the only meta-analysis of the use of low-dose dopamine in patients with acute renal failure and of a systematic review of low-dose dopamine in the neonatal and pediatric ICUs.

The Meta-Analyses: Low-Dose Dopamine Does Not Prevent or Treat Renal Dysfunction

Adult Literature

Kellum and Decker[6] conducted a comprehensive meta-analysis of dopamine in patients with acute renal failure to evaluate the impact of dopamine on the prevention, development, and course of acute renal failure, mortality, and hemodialysis requirements in critically ill patients. These authors evaluated 58 studies (2,149 patients) published over > 33 years. Only 24 studies (1,019 patients) reported outcomes, and only 17 studies (854 patients) were RCTs. Dopamine did not prevent mortality, the onset of acute renal failure, or the need for dialysis (Fig 2). There was sufficient statistical power to exclude any large effect of dopamine on the risk of acute renal failure or the need for dialysis. The authors concluded that, "there is no evidence to support the use of low-dose dopamine to prevent or treat acute renal failure, and, therefore, dopamine should be eliminated from routine clinical use for this indication."

In this meta-analysis,[6] the studies all suffered from a lack of sufficient numbers of patients to exclude a type II (false-negative) error, and none of the studies satisfied the requirements of a level I study (*ie*, large, randomized trials with clear-cut results; and low risk of false-positive [α] error or false-negative [β] error). For example, there were 11 studies examining the use of dopamine in patients with acute oliguria or acute renal failure, but only 4 were level II studies (small randomized trials with uncertain results or moderate-to-high risk of false-positive error and/or false-negative error), and the remainder were case reports. Of the three studies involving septic patients, two were level II studies and one was a case report.

Subsequent to the literature search in this meta-analysis, Marik and Iglesias[14] reported the largest observational study of the use of low-dose dopamine in a subgroup of patients in the NORASEPT II study who had acute renal failure associated with septic shock. Of 395 patients who had oliguria at the start of the study, 44% received low-dose dopamine, 32% received high-dose dopamine, and 24% received no dopamine. Although dopamine was administered at the discretion of the treating physician, the only significant difference among the three groups was in the use of vasopressor agents, which was by study design. Norepinephrine was the most commonly used pressor other than dopamine. The main findings were as follows: no significant differences in the incidence of acute renal failure, the need for dialysis, or 28-day survival among the three groups of patients (Table 1). These authors concluded, "dopamine has

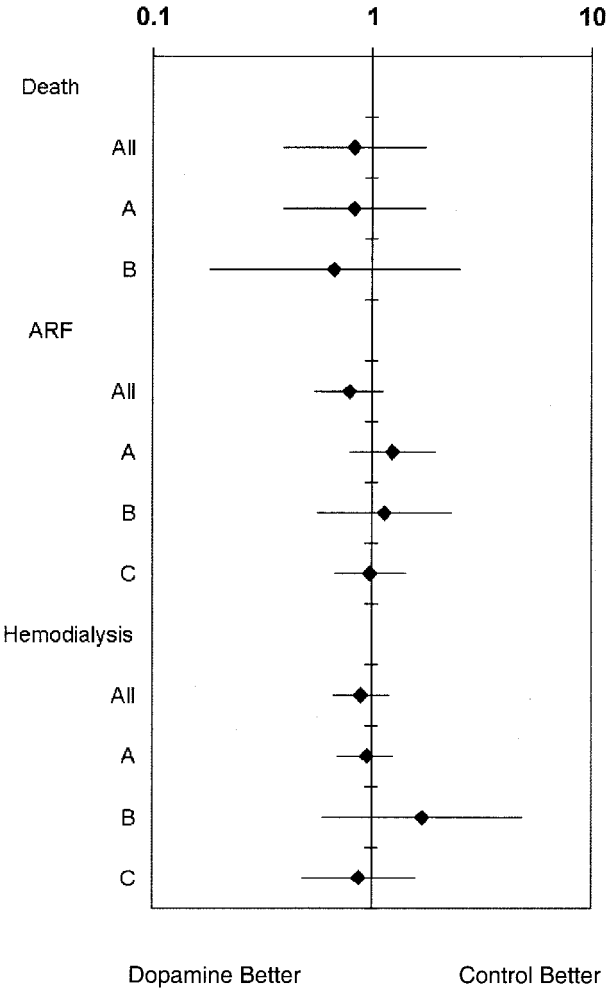

Figure 2. A meta-analysis of the use of dopamine in acute renal failure. Forrest plot showing relative risks (diamonds) and 95% confidence intervals (lines) for all studies and for subgroups A, B, and C. Subgroup A: 14 studies enrolling 661 patients but excluding studies using radiocontrast dye. Subgroup B: four studies enrolling 271 patients and limited to patients with heart disease. Subgroup C: excluded statistical outliers in terms of either control group event fate or the effect size for each outcome, as determined by analysis of variance. ARF = acute renal failure. Reprinted with permission from Kellum and Decker.[6]

Table 1—*Acute Renal Failure, Need for Dialysis, and 28-Day Survival by Dosage of Dopamine in 395 Oliguric Patients With Septic Shock

Variables	Low-Dose Dopamine (n = 174)	High-Dose Dopamine (n = 127)	No Dopamine (n = 94)
Acute renal failure	51 (29)	39 (31)	27 (29)
Dialysis	23 (13)	18 (14)	12 (13)
28-day survival	112 (64)	74 (58)	62 (66)

*Values given as No. (%). There were no significant differences between groups ($p > 0.05$). Reprinted with permission from Marik and Iglesias.[14]

no role in preventing acute renal failure in these patients, and the routine use of low-dose dopamine to prevent or attenuate acute renal failure cannot be recommended."

Pediatric Literature

Prins and coworkers[10] surveyed all 19 neonatal and pediatric ICUs in the Netherlands in 1999 and found that all but one used low-dose dopamine more or less regularly. In two ICUs, low-dose dopamine was used regularly. The authors then undertook a systematic review of low-dose dopamine use in the pediatric literature and identified 11 studies meeting their inclusion criteria. Only one study was an RCT and the exact method of treatment allocation was unclear. In this one RCT,[15] the effects of low-dose dopamine on urine volume were negative. All other studies that were identified in their extensive literature search were nonrandomized and inconclusive. As the studies differed so greatly in patient selection, design, end point classification, treatment regimens, and overall validity, a meaningful meta-analysis was not feasible. The authors conclude that, "Clinical evidence to support low-dose dopamine use in critically ill infants and children is basically lacking."

History of Low-Dose Dopamine

Dopamine was described in 1910 by Barger and Dale.[16] The unique vasodilatory properties of dopamine were first suggested by Gurd[17] in 1937 (infusion of dopamine in guinea pigs and rabbits caused a decrease in BP) and were in contrast to the known pressor effects of norepinephrine and epinephrine.

The 1960s heralded a great deal of interest in the physiologic effects of dopamine, particularly in heart failure patients. One of the first reports of the unique renal effects of dopamine was a description of a marked increase in sodium excretion using dopamine in four patients with end-stage congestive heart failure.[2] Dopamine appeared to augment cardiac output (and to precipitate angina) in each of these patients at doses that varied between 100 and 1,000 μg/min, but it was noted that marked increases in sodium excretion occurred at lower doses with minimal cardiovascular changes. These investigators went on to demonstrate that dopamine increased effective renal plasma flow, glomerular filtration, and sodium excretion in normal human subjects.[18] The dose that was used in each patient was the largest that could be infused without increasing mean arterial pressure and ranged from 2.6 to 7.1 μg/kg/min in this group of subjects. Cardiac output increased in all patients, but the renal fraction of cardiac output did not change significantly. The authors concluded that the renal effects of dopamine are different from those reported for other sympathomimetic amines.

The same investigators[19] went on to determine the mechanism of the renal effects of dopamine. They carried out a set of experiments infusing renal and femoral dopamine and norepinephrine into anesthetized dogs. Dopamine infused IV at an average rate of 7.5 μg/kg/min increased renal blood flow and decreased renal vascular resistance by 30%. Denervated animals responded to dopamine in the same manner. Norepinephrine decreased renal blood flow and increased renal vascular resistance. Intra-arterial dopamine infused at 1.2 μg/kg/min caused an increase in renal blood flow too quickly to be due to the systemic effects. Higher doses caused renal vasoconstriction at doses that were highly variable even under these controlled experimental conditions, highlighting the individual variability in the vasoconstrictor response. The vasodilation of dopamine was not antagonized by β-adrenergic blocking agents, therefore they postulated that dopamine must have been acting on an undescribed receptor in the kidney. Similar findings regarding the effect of dopamine in the mesenteric vascular bed had just been reported by another group of investigators.[20] Dopamine infused in the femoral vascular bed produced only vasoconstriction,[19] an effect that could be totally blocked by α-adrenergic blocking agents. They concluded that dopamine "may offer the possibility of redistributing cardiac output in favor of visceral organs," and that "It would also be interesting to learn the effect of dopamine in conditions in which pathologically high renal and mesenteric vascular resistances exist, such as experimentally induced shock." These discoveries ushered in an era of investigation of the use of dopamine in varied pathologic states such as acute renal failure, septic shock, congestive heart failure, cardiac surgery, vascular surgery, liver transplantation, obstetrics and gynecology, pediatrics, and contrast-related nephropathy.[3]

Physiology of Low-Dose Dopamine

In 1984, D'Orio and colleagues[1] compiled a series of dose-response curves based on hemodynamic and renal effects in patients treated with varying doses of dopamine (Fig 3). On the basis of these observations, the "suppressor dose" of dopamine, which was defined as the dose at which the combination of dopaminergic and β-adrenergic stimulation predominates over α-adrenergic stimulation, corresponds to an infusion rate of < 5 μg/kg/min. The term *low-dose* or *renal-dose* dopamine therefore is used when the desired effect of dopamine infusion is to stimulate the dopamine receptor (and possibly the β-receptor) without any change in BP.

In animals and healthy humans, low-dose dopamine augments renal blood flow, sodium excretion, and glomerular filtration, and limits adenosine triphosphate utilization and oxygen requirements in nephron segments that are at risk of ischemic injury.[21] These physiologic effects, which are mediated primarily by the D1, D2, and D4 receptors (Table 2), have made low-dose dopamine an attractive candidate for the prevention and treatment of acute renal failure.

In 1996, Denton and coworkers[7] summarized the animal evidence for low-dose dopamine in experimental acute renal failure and concluded that, "the short-term benefits of 'renal-dose' dopamine on renal blood flow, glomerular filtration and sodium excretion observed under these controlled experimental conditions suggest that 'renal-dose' dopamine may be useful in the treatment of human acute renal failure." They then summarized the studies investigating the efficacy of renal-dose dopamine for preventing acute renal failure in high-risk patients.

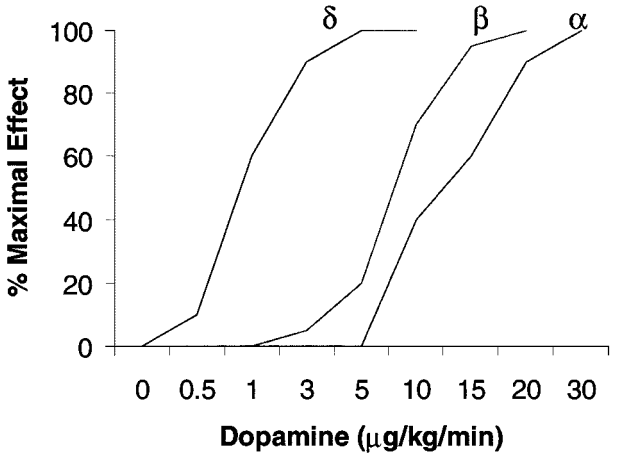

Figure 3. Dopamine dose-related effects in humans. δ = dopaminergic receptors; β = β receptors; α = α receptors. Reprinted with permission from D'Orio et al.[1]

They concluded that the results of these studies did not support its use, but they cited a lack of statistical power to detect a difference. They went on to evaluate the human studies of renal-dose dopamine in patients with acute renal failure either with or without diuretic therapy. Again, most studies were small and consisted of either uncontrolled case series or serial uncontrolled measurements of serum creatinine, glomerular filtration, urine volume, and urine sodium excretion. They pointed out that even when dopamine appeared to trigger a significant improvement in renal blood flow, glomerular filtration, or sodium excretion, these benefits usually were not sustained. They also cited a lack of information on the influence of dopamine on the course of acute renal failure, dialysis requirements, long-term survival, or patient survival. They concluded that although there is compelling evidence that low-dose dopamine augments renal blood flow, glomerular filtration, and natriuresis in healthy humans and experimental animals, such findings in human cases of acute renal failure were lacking. Clearly, an RCT with sufficient numbers of patients using meaningful clinical outcomes was required. Such a trial[12] was completed in 1999, and the findings were completely negative. How do we explain this? We now present the reasons why the renal effects of low-dose dopamine do not produce clinical benefit in critically ill humans and the evidence for harm in other organ systems.

The Top Nine Reasons That Low-Dose Dopamine Is Not Effective in the Critically Ill

The Renal Dose of Dopamine Is Not Predictable in the Critically Ill

Selective stimulation of the renal dopamine receptors is thought to occur at doses of < 5 μg/kg/min,[1] which is the definition of a *renal dose* of dopamine. However, it was demonstrated in critically ill infants and children that great interindividual variation exists in dopamine clearance and that plasma dopamine levels cannot be predicted accurately from the infusion rate.[22] Juste and coworkers[23] also have demonstrated that there is a very poor correlation between plasma dopamine level and infusion rate in 48 hemodynamically stable critically ill adults. This correlation actually worsened when only those patients receiving a renal dose of 2 to 5 μg/kg/min were considered. The authors concluded that, "the concept of a selective renovascular low-dose dopamine infusion is invalid in critically ill patients."

Table 2—*Effects of Dopamine on Human Physiology

Structure	Effect	Receptor
Whole kidney	Increased blood flow; increased glomerular filtration; natriuresis; diuresis	D1 and α_1 adrenoreceptors
Glomerular hemodynamics	Afferent arteriolar vasodilation; variant effect on efferent arteriole; inhibition of renin release	D1
Juxtaglomerular apparatus		
Proximal tubule	Inhibition of Na^+/K^+-ATPase; inhibition of Na^+-H^+ exchange; inhibition of Na^+-PO_4 cotransport; antagonism of angiotensin II	D1 and D2
Thick ascending loop of Henle	Inhibition of Na^+/K^+-ATPase	D1 and D2
Collecting duct	Inhibition of Na^+/K^+-ATPase; antagonism of ADH action; PGE_2 production	D4
		D4
		D2
Sympathetic presynaptic nerve endings	Renal vasodilation via inhibition of noradrenaline release	D2
Systemic vasculature	Increased BP; decreased BP	α-adrenoreceptor
Heart	Reduced heart rate; increased heart rate; increased contractility	D2
		β_1-adrenoreceptor
		β_1-adrenoreceptor
Hypothalamus	Facilitation of vasopressin release	D2

*ADH = antidiuretic hormone; PGE_2 = prostaglandin E_2; ATPase = adenosine triphosphatase. Adapted with permission from Power et al.[5]

Increased Plasma Renin Activity Counteracts the Effects of Dopamine in the Critically Ill

Marik[24] proposed that the renal response to low-dose dopamine might depend on the balance between the vasodilating natriuretic effect of dopamine and the vasoconstricting antinatriuretic effects of the renin-angiotensin-aldosterone system. Nine oliguric critically ill patients who were receiving vasopressor therapy were administered low-dose dopamine (2 μg/kg/min). Five patients had an increase in urine output of 58 mL/h (*ie*, *responders*), and four patients did not have an increase in urine volume (*ie*, *nonresponders*). The mean plasma renin activity was 5.7 ng/mL/h in the responders compared with 26.8 ng/mL/h in the nonresponders ($p < 0.05$). A significant inverse correlation existed between the plasma renin activity and the increase in urinary output. Marik concluded that the response to "renal-dopamine" in critically ill patients was negated in patients with high plasma renin activity.

Hysteresis Exists in the Effect of Dopamine on Renal Blood Flow in Severe Sepsis

Most studies have evaluated the renal effects of short-term (*ie*, 1 to 4 h) dopamine infusion. Prolonged low-dose dopamine infusions induce a transitory improvement in renal function, although tolerance occurs after 2 to 48 h. In a dog model of heart failure,[25] it was demonstrated that the initial renal vasodilation was lost after 2 h of dopamine infusion. Similar findings have been reported in hypertensive adults[26] and critically ill humans.[27] Lherm and coworkers[27] found that the renal effects of low-dose dopamine in patients with sepsis syndrome decreased after 48 h of infusion. They proposed that "these findings suggest a desensitization of renal dopaminergic receptors." Ichai and coworkers[28] similarly found that the renal effects (*ie*, diuresis, increased creatinine clearance, and fractional excretion of sodium) of low-dose dopamine reached a maximum during 8 h and disappeared after 48 h in critically ill patients. Again, the down-regulation of dopaminergic receptors was suggested.

In an elegant study, Day and coworkers[29] measured the effect of low-dose dopamine (*ie*, 2.5 to 5 μg/kg/min) on renal blood flow as measured by a thermodilution catheter placed in the renal vein in 19 patients with severe falciparum malaria or severe sepsis. Although renal blood flow and renal blood flow as a fraction of cardiac output increased at dopamine infusion rates of 2.5 and 5.0 μg/kg/min, at 10 μg/kg/min both decreased to a level that was not significantly different from baseline and failed to increase again when the dose was reduced to renal doses again. The authors postulated that this hysteresis in the dose-response curve was due to tolerance to dopamine over time, or that the α-adrenergic agonist dose of dopamine somehow made the kidney refractory in terms of hemodynamic response to further doses of "solely dopaminergic" dopamine. They concluded that whatever the underlying patho-

physiologic reasons for the hysteresis, "there is no evidence for any sustained beneficial effect of dopamine in terms of either renal hemodynamics or renal oxygen transport in severely ill patients."

Medullary Dysoxia Is a "Demand-Side" Problem, Not a Renal Blood-Flow Problem

The renal medulla has a limited blood supply[30] and high-energy demands due to tubular transport activity. Medullary oxygen extraction approaches 90%,[31] and therefore the renal medulla is said to be "always on the brink of dysoxia" due to high demand and low delivery of oxygen.[6] This may explain why vasodilator agents, such as radiocontrast dye, cause renal injury. The high ionic load places an oxygen demand on the medulla that outstrips the supply. It has been hypothesized[32] that dopamine actually can increase medullary oxygen demand by inhibiting proximal solute reabsorption and by delivering a higher solute load to the distal tubular cells, increasing the risk of ischemia. In support of this hypothesis, dopamine has been shown[33] to increase renal medullary blood flow but not to improve renal medullary dysoxia in hypovolemic animals. In humans, dopamine has been shown[34] to worsen renal tubular injury due to radiocontrast agents. Thus, agents (such as low-dose dopamine) that increase renal blood flow may not be "renoprotective" if they worsen medullary oxygen demand and tip the precarious balance in favor of dysoxia.

Diuresis May Be Harmful in the Oliguric Critically Ill

Overwhelmingly, the predominant effect of low-dose dopamine in critically ill patients appears to be diuresis.[13,28,35–37] However, diuresis by itself has no apparent benefit on important clinical outcomes.[12,28] Since fluid resuscitation is the cornerstone of therapy in patients with sepsis, it is not surprising that diuresis in oliguric septic patients does not result in any clinical benefit and indeed could cause harm. Interestingly, in a study of critically ill oliguric patients,[24] 200 patients were screened and only 9 were entered into the study. Many oliguric patients were excluded because of an improvement in their urine output after fluid challenges. That is, inappropriate diuresis with low-dose dopamine may give a false clinical impression of adequate intravascular volume and conceivably could worsen acute renal failure.

Low-Dose Dopamine Harms the Splanchnic Circulation in the Critically Ill

A number of studies in both animals and humans have demonstrated that dopamine increases splanchnic blood flow and yet, paradoxically, that dopamine worsens splanchnic mucosal ischemia. GI mucosal ischemia leads to the translocation of endotoxin and microorganisms into the portal circulation,[38] and hepatic ischemia leads to increased production and decreased clearance of proinflammatory cytokines.[39] This sequence of events leads to the clinical manifestations of sepsis and to the inevitable development of multiple organ failure.[38,39] Thus, it has been proposed that, "the gut is the motor of multiple organ failure,"[40] and therapy for sepsis has focused on adequate resuscitation of the splanchnic circulation.[41] In this section, we review the evidence that dopamine harms the splanchnic circulation.

If dopamine is a splanchnic vasodilator, how can this be detrimental to the splanchnic circulation? Eble[20] first described the vasodilatory properties of dopamine on the splanchnic circulation in 1964, a finding that was confirmed by many other investigators.[42–44] Giraud and MacCannell[45] went on to demonstrate that dopamine administration resulted in a net increase in splanchnic blood flow but that redistribution away from the gut mucosa also occurred, resulting in decreased splanchnic oxygen extraction. In addition, endotoxemia may worsen the mismatch between splanchnic oxygen delivery and oxygen demand, and the increased oxygen demand in the splanchnic region may be the main risk factor for splanchnic tissue hypoxia in patients with septic shock.[44]

Low-dose dopamine actually hastens the onset of gut ischemia, as demonstrated by Segal and colleagues,[46] who compared whole-body and gut oxygen uptake and delivery using progressive phlebotomy in anesthetized pigs. In animals treated with dopamine at a rate of 2 μg/kg/min, the onset of gut ischemia occurred before whole body ischemia, and this was associated with a decreased ability of the gut to extract oxygen. The authors proposed that, "low-dose dopamine, used frequently to treat oliguria in shocked patients, is causing a far more important detrimental effect on oxygen transport and utilization in gut that could lead to development of occult gut ischemia and multiple system organ failure."

The detrimental effect of high-dose dopamine on the splanchnic circulation was demonstrated in humans with hyperdynamic sepsis by Marik and Mohedin[47] utilizing gastric tonometry as a surrogate of splanchnic mucosal perfusion. Twenty patients were randomized to infusions of norepinephrine (mean infusion rate, 0.18 μg/kg/min) or dopamine (mean infusion rate, 26 μg/kg/min), and hemodynamic measurements and gastric mucosal pH were recorded. Both norepinephrine and dopamine increased oxygen delivery and oxygen uptake, but gastric pH increased significantly in patients who had

been treated with norepinephrine and decreased significantly in patients who had been treated with dopamine. They postulated that, "dopamine may increase gut mucosal oxygen needs and at the same time redistribute blood flow within the gut, resulting in reduced mucosal blood flow."

The detrimental effect of low-dose dopamine (*ie*, 5 μg/kg/min) on gastric mucosal perfusion in septic humans was confirmed by Nevière and colleagues[48] in 1996. Dopamine infusion was associated with a significant decrease of gastric mucosal blood flow ($-28 \pm 8\%$ from baseline; $p < 0.05$), despite a significant increase in whole-body oxygen delivery. In contrast, they found that dobutamine (5 μg/kg/min) increased gastric mucosal blood flow ($32 \pm 14\%$ from baseline; $p < 0.05$), suggesting that despite an increase in systemic oxygen transport, dobutamine and dopamine may have different effects on gastric mucosal perfusion in septic patients.

Finally, low-dose dopamine (4 μg/kg/min) has been shown to adversely effect gastroduodenal motility in mechanically ventilated, critically ill patients both during fasting and nasogastric feeding.[49] We conclude that low-dose dopamine has a detrimental effect on the splanchnic system in septic and critically ill humans and that this negative effect is not necessarily shared by other vasoactive agents such as norepinephrine and dobutamine.

Low-Dose Dopamine Harms the Endocrine System in the Critically Ill

Critical illness is a maladaptive endocrinologic and metabolic state characterized by muscle wasting and organ system failure. Low therapeutic doses of dopamine infusion (2 to 5 μg/kg/min) result in plasma levels that are 40-fold to 100-fold higher than those generated by endogenous secretion[50] and have been shown to induce partial hypopituitarism in critically ill newborns,[51] infants and children,[52] and adults.[53–56]

Van den Berghe and coworkers[54] studied the effect of low-dose dopamine on the endocrine system in 12 critically ill polytrauma patients. The authors measured strikingly low serum thyroid-stimulating hormone concentrations in critically ill patients who had received brief or prolonged dopamine infusions, and a sharp rise occurred immediately after dopamine withdrawal. Similarly, prolonged dopamine infusion (3 days) was associated with lower thyroxine and triiodothyronine levels, which rose to virtually normal values within 24 h after dopamine withdrawal. The results suggest that low-dose dopamine infusion appears to induce or aggravate the sick euthyroid syndrome in critical illness by suppressing thyroid-stimulating hormone secretion and decreasing thyroxine and triiodothyronine concentrations.

The same investigators analyzed the effect of low-dose dopamine infusion on growth hormone secretion in a group of critically ill adults.[56] They found that pulsatile growth hormone secretion is low in patients with critical illnesses and that dopamine infusion further attenuates growth hormone secretion by amplitude modulation. They postulate that this iatrogenic growth hormone suppression might further aggravate the catabolic state that is observed in critically ill patients.

Low-dose dopamine was shown to suppress serum dehydroepiandrosterone sulfate (DHEAS) concentrations and circulating prolactin levels in 20 critically ill adult polytrauma patients.[53] The withdrawal of dopamine therapy was associated with a median 25% increase in serum DHEAS concentrations within 24 h of dopamine withdrawal, and prolactin levels also rebounded after 24 h of dopamine withdrawal. Cortisol levels were not affected, suggesting a differential regulation of DHEAS and cortisol metabolism in patients with critical illnesses. The authors postulated that the dopamine-induced suppression of DHEAS might be mediated by hypoprolactinemia or hypothyroidism. Others[57] have confirmed that dopamine infusion was associated with a 10-fold reduction in serum prolactin levels. Serum DHEAS and prolactin levels may affect the immune system (see below), which further lends support to the hypothesis that low-dose dopamine administration induces hypopituitarism in the critically ill.

Finally, the effect of low-dose dopamine on luteinizing hormone secretion was studied in 15 critically ill men.[53] Low luteinizing hormone secretion and low serum testosterone concentrations were demonstrated in these men. Low-dose dopamine infusion (*ie*, 5 μg/kg/min) further lowered luteinizing hormone secretion. The withdrawal of dopamine therapy was associated with a significant increase in luteinizing hormone levels at 3 h and by a failure of testosterone levels to rebound. The authors concluded that this is further evidence that low-dose dopamine contributes to the impaired endocrine dysfunction of patients with critical illnesses.

Dopamine Harms the Immunologic System in the Critically Ill

The immune dysfunction of critical illness is characterized by anergy, by a failure of the delayed hypersensitivity response, by primarily neutrophil chemotaxis, and by T-lymphocyte dysfunction.[58] The presence of dopamine receptors has been demonstrated on thymocytes,[59] and dopamine interacts with lymphocytes.[60] Dopamine agonists suppress T-lymphocyte function,[61] and dopamine produces T-cell defects[62] in animal models *in vivo*. *In vitro*,

dopamine inhibits the transformation of lymphocytes by mitogens.[63] Devins and coworkers[57] demonstrated a reduction in T-cell responsiveness in six critically ill patients receiving dopamine infusion compared to 20 critically ill patients not receiving dopamine. It has been suggested that dopamine-induced suppression of serum DHEAS may aggravate T-helper type 1 T-lymphocyte dysfunction.[53] Prolactin is also an important immune-regulating hormone, and dopamine-induced hypoprolactinemia could be another mechanism of T-cell hyporesponsiveness.[53,57] Thus, dopamine affects lymphocytes directly through surface receptors and indirectly through an altered endocrine hormonal milieu.

Low-Dose Dopamine Blunts Ventilatory Drive

Low-dose dopamine infusion (*ie*, 3 μg/kg/min) has been shown to blunt ventilatory drive in healthy humans by reducing the sensitivity of the fast chemoreflex loop to carbon dioxide.[64] Low-dose dopamine is also a potent depressant of hypoxic ventilatory response.[64,65] The effect of low-dose dopamine on ventilatory drive in critically ill patients is not known, but we hypothesize that a blunting of chemoreceptor responsiveness could delay liberation from mechanical ventilation in patients with marginal ventilatory drive.

Conclusion

In conclusion, although low-dose dopamine augments renal blood flow and increases urine volume and sodium excretion in animals and healthy humans, this therapy does not alter the course of acute renal failure in critically ill humans. Both renal pathophysiology and the extrarenal effects of low-dose dopamine can explain this paradox. First, the renal-dose of dopamine is not predictable in critically ill humans. Second, dopaminergic receptor down-regulation and hysteresis to the effect of low-dose dopamine occurs. Third, renin-angiotensin system activation in patients with critical illnesses negates the effects of dopaminergic stimulation. Fourth, renal medullary dysoxia appears to be a demand-side problem, not a supply problem, and dopamine may increase medullary oxygen demand. Fifth, the predominant effect of dopamine in critically ill humans appears to be diuresis, which is contraindicated in patients who are in most oliguric states that are associated with critical illness. Finally, there is compelling evidence that dopamine is harmful to the GI, endocrine, immunologic, and respiratory systems in patients with critical illnesses. We conclude that there is no longer a justification for using low-dose dopamine in treating critically ill patients.

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