"Renal Dose" Dopamine in Surgical Patients
Dogma or Science?

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Objective
"Renal dose" dopamine is widely used in the perioperative period to provide renal protection. A comprehensive review of the literature was performed to determine whether dopamine does in fact confer protection on the kidneys of surgical patients.

Summary Background Data
Studies in healthy animals and human volunteers reveal that dopamine causes diuresis and natriuresis, as well as some degree of renal vasodilatation.

Results
Studies of the perioperative use of dopamine fail to demonstrate any benefit of dopamine in preventing renal failure. Studies in congestive heart failure, critical illness, and sepsis also fail to show any benefit of dopamine other than diuresis. Further, dopamine administration is not completely without risk, because of dopamine's catecholamine and neuroendocrine functions.

Conclusions
Routine use of prophylactic "renal dose" dopamine in surgical patients is not recommended.

Low-dose dopamine is widely used in an attempt to protect the kidneys of surgical patients from the myriad of ischemic, nephrotoxic, inflammatory insults that threaten renal function in the perioperative period. This practice is well entrenched, and at some centers low-dose dopamine is administered prophylactically to all surgical patients at risk for renal insufficiency. Nevertheless, the literature on low-dose dopamine suggests that its effects on the kidney are complex and its value for preventing perioperative renal complications is unproven. Our purpose is to review succinctly the literature to establish what role, if any, dopamine should play in the perioperative period.

EARLY HUMAN STUDIES
The renal effects of dopamine were first reported in the early 1960s when Goldberg et al. demonstrated that low-dose dopamine (100 μg/min) caused natriuresis in four patients with congestive heart failure. Soon thereafter, McDonald et al. showed that dopamine (2.6 to 7.1 μg/kg/min) significantly increased glomerular filtration rate (GFR), effective renal plasma flow, and sodium excretion in nine normal volume-loaded volunteers. Although not emphasized, in five of the subjects in whom cardiac output measurements were obtained, the cardiac index (CI) increased an average of 1.4 L/min. When slightly lower doses (1.3 to 3.6 μg/kg/min) were administered to an additional six patients with congestive heart failure, increases in cardiac output, GFR, or renal plasma flow were small and statistically insignificant; only sodium excretion was significantly increased. Despite the observed increase in cardiac output and the fact that renal function improved only in normal volunteers, stability of arterial pressure led to the suggestion that dopamine produces selective renal vasodilatation. This review evaluates the available data regarding whether dopamine is indeed a selective vasodilator in surgical patients and focuses on two critical issues: whether dopamine enhances renal function and whether it provides any protection from developing renal failure.

ANIMAL STUDIES
Numerous human and animal studies demonstrate increased renal blood flow and decreased renal vascular resistance after dopamine administration. However, these studies either demonstrate a concurrent increase in cardiac output or do not report cardiac output data. Studies that look at the effects of dopamine on renal vessels and renal blood flow, independent of cardiac effects, have produced mixed results. In a rat, split-kidney, hydronephrotic model that allowed direct observation of renal vessels, an
increase in the diameter of renal arcuate, interlobar, and afferent and efferent arterioles was seen with direct application of low concentrations of dopamine (1 to 30 μM). At higher concentrations (>100 μM), dopamine decreased renal vessel diameter. This vasoconstrictive effect was blocked by phentolamine, suggesting a direct alpha-adrenergic effect of dopamine at higher concentrations. Another study noted decreases in renal vascular resistance (19%) and increases in renal blood flow (17%) during infusion of fenoldopam (a specific dopamine DA-1 receptor agonist). Despite this increase in renal blood flow, there was no increase in GFR or single nephron GFR. More importantly, urinary flow rate, sodium excretion, and potassium excretion increased with DA-1 stimulation, independent of any effect on GFR, reflecting a diuretic effect of the dopamine agonist. Dopamine is known to have direct effects on renal function independent of its hemodynamic effects. In renal tubular cells, dopamine inhibits Na/K ATPase, causing decreased sodium reabsorption and impaired tubuloglomerular feedback. The diuresis and natriuresis seen after dopamine administration are more likely caused by this direct effect of dopamine rather than to hemodynamic alteration.

**STUDIES IN SURGICAL PATIENTS**

A number of studies examining the use of low-dose dopamine in the perioperative period have been published in the last 10 years. Most involve relatively small numbers of patients and lack the statistical power to detect any benefit in preventing renal failure, fortunately a relatively rare complication. A prospective, randomized, double-blind study of 48 liver transplant patients examined the effect of low-dose dopamine (3 μg/kg/min for 48 hours) on the incidence of renal insufficiency; the treatment group failed to show any benefit in postoperative urine output, GFR, or the need for dialysis. Similarly, dopamine had no effect on liver function, portal venous flow, or hepatic artery flow; the only measured parameter that dopamine significantly increased was heart rate. In another prospective, randomized, double-blind, placebo-controlled study of 37 aortic surgery patients receiving 3 μg/kg/min of dopamine for 24 hours, an insignificant increase in urine output was detected (9 cc/hr), but there was no effect on creatinine clearance or the incidence of renal failure. Of note, three of the four patients who had perioperative myocardial infarction were in the treatment arm. A third prospective, randomized, nonblinded study of low-dose dopamine in 23 patients undergoing surgical relief of obstructive jaundice showed no significant improvement in creatinine clearance, urine output, or the incidence of renal failure.

In patients with cardiac surgery, the data supporting low-dose dopamine as a selective renal protective agent are similarly inconclusive. In one study performed in postoperative coronary bypass patients, significant increases in urinary output, creatinine clearance, and sodium excretion were seen with dopamine infusions of 200 μg/min. The cardiac index also was significantly increased, although heart rate was unaffected. However, in another study of coronary artery bypass patients, the same dose of dopamine increased CI but did not change urine output, creatinine clearance, free water clearance, or the incidence of renal insufficiency. When dopamine and dobutamine were titrated to the same CI in postoperative cardiac surgical patients, both agents increased renal plasma flow and glomerular filtration; however, diuresis, natriuresis, and kaliuresis were greater with dopamine. Although some animal and human studies have suggested that dopamine may additionally increase renal blood flow by a direct effect on renal arterioles, the functional significance of this mechanism is unclear because indices of renal function (GFR, creatinine clearance) were not measured in those studies. Direct renal vasodilatory action could actually be detrimental to glomerular filtration if both efferent and afferent arterioles are affected, via a reduction in glomerular capillary hydrostatic pressure. Taken together, these studies suggest that although dopamine may have a diuretic effect, it appears to increase renal function (creatinine clearance, GFR) only when cardiac output is increased.

**STUDIES IN CONGESTIVE HEART FAILURE AND CRITICAL ILLNESS**

Because low-dose dopamine is both an inotrope and a diuretic, one might expect salutary effects in patients with congestive heart failure; however, available data do not support this contention. When administered to elderly patients with congestive heart failure, low-dose dopamine did not increase GFR, effective renal plasma flow, or urine output. Similarly, in patients with cardiomyopathic heart failure, dopamine (4 μg/kg/min) increased CI, but the number of premature ventricular contractions also increased. In this study, no improvement in creatinine clearance, renal blood flow, or urine output was observed. In a diverse population of critically ill patients, dopamine (200 μg/min) increased heart rate and urine volume but not creatinine clearance. Dobutamine (175 μg/kg/min), on the other hand, significantly increased heart rate, mean arterial pressure, CI, and creatinine clearance but had no effect on urine output. Low-dose dopamine appears to have weak diuretic effects in critically ill patients and serves as a poor substitute for more effective inotropic regimens when renal function is compromised.

The concomitant use of low-dose dopamine and norepinephrine is clinically popular because of the belief that dopamine can ameliorate norepinephrine-induced mesenteric and renal vasoconstriction. However, in critical illness, no studies have shown any beneficial effect of dopamine other than diuresis. Nonseptic animal studies and studies in human volunteers suggest that low-dose dopamine does reverse norepinephrine-induced renal vasoconstriction and increase renal blood flow. The effects of norepinephrine and dopamine in sepsis and critical illness may be different.
than in the normal state, however. In septic shock patients, by improving mean arterial pressure, norepinephrine may actually increase rather than decrease renal blood flow.\textsuperscript{21,22} Furthermore, the renal hemodynamic effects of low-dose dopamine in septic shock are completely unknown. In a dog endotoxin shock model treated with norepinephrine, low-dose dopamine failed to increase renal blood flow or improve renal function.\textsuperscript{23} Similarly, in a recent prospective trial of norepinephrine or epinephrine infusion to support blood pressure in patients with septic shock, the addition of low-dose dopamine (2 \mu g/kg/min) failed to improve either creatinine clearance or urine output.\textsuperscript{24} The observed effects of dopamine in reversing vasopressor-induced renal vasoconstriction in healthy animals and volunteers may not be transferable to critically ill patients and should not be the only basis for the use of low-dose dopamine in those situations.

**STUDIES IN ESTABLISHED ACUTE RENAL FAILURE**

Recent trials have evaluated the benefit of low-dose dopamine therapy in established acute renal failure.\textsuperscript{25–27} No data exist that demonstrate that dopamine prevents the development or limits the progression of acute renal failure in critically ill patients. A recent retrospective analysis evaluating acute renal failure found that the subgroup of patients in acute renal failure receiving low-dose dopamine (86 patients, \(<3 \mu g/kg/min\) had no significant benefit in mortality or progression to dialysis compared to 79 patients who did not receive dopamine.\textsuperscript{27}

**DETRIMENTAL EFFECTS**

Because it is a naturally occurring neurotransmitter, exogenous dopamine administration may influence many neurohormonal pathways. For example, even after brief administration of dopamine (<24 hours), levels of prolactin, thyroid-stimulating hormone, T\textsubscript{3}, T\textsubscript{4}, and growth hormone are significantly decreased.\textsuperscript{28–30} T-cell proliferation is also significantly inhibited by dopamine infusion.\textsuperscript{29} The significance of these effects on hormones and immune function is unknown.

In an endotoxin pig model, dopamine had no beneficial effect on splanchic or renal blood flow compared to norepinephrine or placebo.\textsuperscript{31} Furthermore, dopamine may have deleterious effects on splanchic blood flow. Splanchic ischemia during hemorrhage, when assessed by mesenteric oxygen extraction, appeared to worsen when pigs received 2 \mu g/kg/min of dopamine.\textsuperscript{32} In a study of septic humans, high-dose dopamine administration appeared to decrease splanchic perfusion (measured by gastric tonometry) despite increasing CI and total oxygen delivery.\textsuperscript{33}

Dopamine also has substantial effects on cardiopulmonary hemodynamics. In several studies, low-dose dopamine increased pulmonary artery wedge pressure while decreasing pulmonary vascular resistance.\textsuperscript{6,15,18} Calculated intrapulmonary shunt also increases with dopamine, but this may reflect only an increase in cardiac output.\textsuperscript{34,35} Contrary to popular opinion, even low-dose dopamine (<5 \mu g/kg/min) may have considerable \beta\textsubscript{-}agonist activity and increase CI; although this results initially from an increase in stroke volume, an accelerated heart rate often follows.\textsuperscript{6,14,18,19} These \beta\textsubscript{-}adrenergic actions increase myocardial oxygen consumption and could potentially induce myocardial ischemia. Further, in low concentrations (1 \mu M), dopamine has been implicated in provoking coronary artery vasospasm \textit{in vitro}.\textsuperscript{36}

Dopamine also produces direct effects on cardiac conduction pathways. Specifically, dopamine increases automaticity in Purkinje fibers and exerts a biphasic effect on action potential duration, shortening the action potential during short-term administration (<30 minutes) but lengthening it during prolonged administration.\textsuperscript{37} Dopamine also causes sinus tachycardia and ventricular extrasystoles, even at doses considered to be renal-protective.\textsuperscript{18} More importantly, low-dose dopamine may contribute to the formation of dysrhythmias. In a prospective study examining risk factors for dysrhythmias in Holter-monitored postoperative cardiac surgical patients (including age, sex, type of operation, aortic cross-clamp time, cardiopulmonary bypass time, and preoperative ejection fraction), only low-dose dopamine administration (1 to 5 \mu g/kg/min) was identified as an independent predictor of postoperative ventricular dysrhythmias.\textsuperscript{38}

In essence, “renal dose” dopamine is two drugs in one: a mild sympathomimetic providing weak inotropic and chronotropic support, and a potent diuretic with direct natriuretic effects on the nephron. Although laboratory data suggest that dopamine may increase renal blood flow directly through dilation of the renal vasculature, the clinical significance of this remains uncertain. Clinical studies seem to indicate that dopamine improves renal function only when cardiac performance is concurrently enhanced, and it may be an appropriate alternative in clinical situations that require low-dose inotropic support and diuresis. However, because oliguria in the perioperative period is most commonly a consequence of hypovolemia, these patients may be poorly served by receiving a diuretic such as dopamine. They would be better served by aggressive fluid management and inotropic support aimed at optimizing cardiac output and increasing renal perfusion. Because of the diuretic properties of dopamine, urine output after dopamine administration may reflect only diuresis and not really improved renal perfusion. Finally, dopamine is a neurotransmitter as well as a catecholamine, and administration can produce marked changes in neuroendocrine function, the consequences of which are mostly unknown.

Because of these factors, we believe that there is little role for low-dose dopamine in the perioperative period and in most critical illness, and that the term “renal dose” dopamine should be retired. Unless randomized, controlled clin-
clinical trials can document significant benefit from the routine use of dopamine in perioperative or critical care settings, we will actively discourage its use.

References


