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"Renal-dose" dopamine for the treatment of acute renal failure: Scientific rationale, experimental studies and clinical trials

"Renal-dose" dopamine (1 to 3 μg/kg/min) is employed worldwide by its proponents in the treatment of acute renal failure (ARF) and oliguria for its putative selective renal vasodilator, natriuretic, diuretic and renoprotective properties that are mediated through stimulation of renal dopaminergic receptors and occur in the absence of systemic pressor activity. This practice continues despite editorials urging its discontinuation on the basis of lack of efficacy, expense and potential toxicity [1–3]. Here, we attempt to shed some light on this festering clinical controversy by: (a) reviewing the influence of dopamine on renal function in healthy subjects, (b) discussing the rationale for "renal-dose" dopamine therapy in patients with ARF, and (c) summarizing and critically analyzing experimental and clinical studies evaluating the efficacy of "renal-dose" dopamine in ARF. To this end, a computerized *MEDLINE* literature search and manual review of *Index Medicus* were employed to identify English language articles on the use of "renal-dose" dopamine in patients with ARF published between 1966 and 1994. Special attention was paid to the results of prospective, randomized, controlled trials in humans. Trials were examined for the influence of "renal-dose" dopamine on renal blood flow (RBF), glomerular filtration rate (GFR), sodium excretion, requirement for dialysis, renal recovery, and patient outcome.

Influence of dopamine on normal renal function

Infusion of "renal-dose" dopamine into healthy experimental animals or humans induces a dose-dependent increase in renal blood flow (RBF), natriuresis and diuresis (Table 1) [4–9; extensively reviewed in 10]. Dopamine also improves RBF in patients with chronic renal impairment, renovascular disease and mild to moderate sodium depletion, albeit to a lesser extent than in healthy individuals [11, 12]. Some investigators report augmentation of GFR, however, this response is usually less dramatic and varies among species [10]. The mechanisms by which dopamine modulates RBF differ depending on the rate of infusion. At low doses (threshold ~0.5 and maximal ~3.0 μg/kg/min), dopamine augments RBF principally by inducing intrarenal vasodilatation. This response is mediated predominantly through the DA-1 subclass of dopamine receptors located on the renal vasculature [13]. Engagement of DA-2 receptors on presynaptic sympathetic nerve terminals with inhibition of norepinephrine release and possibly post-synaptic DA-2 receptors may also contribute [10]. Intermediate doses of dopamine (threshold ~3.0 and maximal ~10 μg/kg/min) can also augment renal perfusion by increasing cardiac index through stimulation of cardiac β1 adrenoreceptors. At higher doses (threshold ~5.0 and maximal ~20 μg/kg/min), the potentially beneficial effects mediated through stimulation of DA receptors and β1 adrenoreceptors may be offset by systemic vasoconstriction triggered by activation of peripheral α1 adrenoreceptors. In evaluating the efficacy of dopamine in the treatment of ARF (*vide infra*), it should be noted that these dose-response relationships were generated in studies of normal subjects, and may not be applicable to patients with true or "effective" volume depletion in whom myocardial function and systemic vascular resistance are already markedly perturbed, or among individuals with atherosclerotic, hypertensive, diabetic or otherwise abnormal vascular structure. Furthermore, there is generally poor correlation between plasma dopamine levels and the rate of dopamine infusion; thus, one or all of these actions may be operative at any given infusion rate.

The natriuretic effect of dopamine is rapid in onset and typically wanes within 12 hours [14–17]. Natriuresis is characteristically reduced or absent in sodium-depleted patients [18]. Interestingly, some DA-1 receptor antagonists inhibit urine sodium excretion under basal conditions without affecting RBF, GFR or systemic hemodynamics [13, 19], suggesting that endogenous dopamine may be an important modulator of tubular sodium reabsorption [extensively reviewed in 10]. Proximal tubule cells synthesize dopamine from L-dopa via a reaction catalyzed by L-amino acid decarboxylase [20, 21]. Maneuvers that induce natriuresis (such as increased dietary sodium intake, saline infusion, head-out water immersion) increase dopamine biosynthesis and urinary dopamine levels [22–24]. Furthermore, L-amino acid decarboxylase inhibitors [25, 26] and dopamine antagonists [19] attenuate sodium excretion under the latter circumstances. Dopamine induces natriuresis by attenuating tubular reabsorption of sodium, in large part, by inhibiting basolateral Na,K-ATPase activity in proximal tubule, medullary thick ascending limb of the loop of Henle and cortical collecting duct epithelial cells through engagement of DA-1 and probably DA-2 receptors [27–37]. Dopamine also promotes renal excretion of free water, probably by inhibiting central antidiuretic hormone (ADH) release and antagonizing the actions of ADH (*vide infra*) on collecting duct cells [38].

Rationale for "renal-dose" dopamine therapy in acute renal failure

Renal hypoperfusion is the leading cause of acute renal failure (ARF) in humans [reviewed in 39, 40]. True or "effective" volume depletion is sensed by carotid baroreceptors which, in turn, trigger ADH release and activation of the sympathetic nervous and renin-angiotensin systems. Norepinephrine, angiotensin II and ADH act in concert to provoke systemic vasoconstriction and retention of salt and water in an attempt to restore blood pressure and perfusion of "essential" organs (such as brain, heart) at the

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Table 1. Some effects of dopamine on renal physiology

Structure	Effect
Whole kidney	Increased renal blood flow Increased GFR[a] Natriuresis Diuresis
Glomerular hemodynamics	Afferent arteriole vasodilation Variable effect on efferent arteriole No effect on ultrafiltration coefficient
Juxtaglomerular apparatus	Altered tubuloglomerular feedback Inhibits renin release
Proximal tubule	Inhibition of Na-K-ATPase Inhibition of Na-H exchange Inhibition of Na-PO_4 cotransport Antagonism of angiotensin II
Thick ascending limb of Henle	Inhibition of Na-K-ATPase
Collecting duct	Inhibition of Na-K-ATPase Antagonism of ADH action

[a] Variable response

expense of relatively "non-essential" organs (such as skin, muscle, gastrointestinal tract). Renal blood flow and GFR are relatively preserved during mild systemic circulatory failure through several compensatory mechanisms: the selective vasoconstrictive action of angiotensin II on efferent arterioles, intrarenal generation of vasodilator prostaglandins, and afferent arteriolar vasodilation triggered by a local myenteric reflex within the vessel wall. In moderate forms of systemic circulatory failure, these compensatory mechanisms are overwhelmed and prerenal azotemia ensues. The integrity of renal parenchymal tissue is preserved in this syndrome and ARF is rapidly reversible upon restoration of effective circulatory volume. More severe or prolonged hypoperfusion can provoke ischemic renal parenchymal injury, particularly to endothelium and to epithelial cells with high transport rates and oxygen requirements in the medullary portions of the proximal tubule and thick ascending limb of the loop of Henle [ischemic acute tubular necrosis (ATN)]. Mild to moderate ischemic injury perturbs epithelial cell cytoskeletal function, polarity, solute transport, cell volume regulation, and barrier function. Severely ischemic tubule epithelial cells detach from their basement membrane, in part due to disruption of integrin-mediated cell-matrix interactions, and slough into the tubule lumen where they form urinary casts. GFR falls as a consequence of impaired glomerular perfusion and ultrafiltration pressure, obstruction of renal tubules by casts and backleak of glomerular filtrate through injured tubular epithelium. In contrast to prerenal azotemia, ARF characteristically persists for days to weeks after restoration of systemic hemodynamics in patients with ischemic ATN. The latter "maintenance phase" of ATN appears due, at least in part, to persistent hypoperfusion of the outer medulla triggered by local imbalance of vasodilators and vasoconstrictors released by endothelium, congestion of medullary blood vessels, oxidant injury triggered by release of reactive oxygen species from leukocytes and resident glomerular cells, and possibly activation of tubuloglomerular feedback [reviewed in 39, 40]. In addition to its well-defined role in ischemic ARF, intrarenal vasoconstriction and tubule epithelial cell injury are important events in the pathogenesis of ARF induced by sepsis and nephrotoxins (such as cyclosporine, radiocontrast, myoglobin, hemoglobin). Recovery from ATN requires clearance of fatally injured cells and debri, and regeneration and repair of epithelium.

It should be apparent from the foregoing discussion that "renal-dose" dopamine exerts several actions on the renal vasculature and tubule epithelium that are potentially beneficial in the management of patients with ARF. In prerenal ARF, "renal-dose" dopamine may temporarily improve renal perfusion and oxygenation and promote natriuresis, while the primary defect in systemic hemodynamics is rectified. In subjects at high risk of ischemic ATN, prophylactic "renal-dose" dopamine may potentially prevent or limit ischemic cell injury by improving RBF and oxygenation and reducing oxygen demands through inhibition of sodium transport. In patients with established ischemic ATN, "renal-dose" dopamine may limit further injury through similar mechanisms and accelerate resolution of ARF by augmenting medullary blood flow and by increasing urine flow rate, thereby promoting "washing out" of intraluminal casts and the relief of intratubular obstruction. Finally, the natriuretic and diuretic actions of "renal-dose" dopamine may prove useful in supportive care of patients with established non-oliguric ARF and prevent the development of hypervolemia and pulmonary edema.

Efficacy of "renal-dose" dopamine in experimental ARF

Table 2 summarizes studies evaluating the influence of "renal-dose" dopamine on renal function in laboratory animals with experimental ARF [41–47]. Several classic models have been examined, including ischemic ARF induced by occlusion of either the renal arteries or aorta and nephrotoxic ARF induced by uranyl nitrate or glycerol [45]. Most studies were adequately controlled and compared infusions of "renal-dose" dopamine and diluent, started prior to induction of disease. RBF and GFR were usually determined by clearance of para-aminohippurate (PAH) and inulin, respectively, and most investigators also assessed urine sodium excretion and/or urine volume.

In general, animals receiving "renal-dose" dopamine suffered less compromise of GFR than diluent-treated controls upon induction of ischemic ARF [43, 44, 47, 48]. Renal perfusion, GFR and sodium excretion were better preserved with dopamine therapy or even increased when compared with pre-ARF levels. These differences were usually statistically significant, although the degree of protection varied markedly among studies. Dopamine was beneficial even when started four hours after bilateral clamping of renal arteries in rats, an important observation if these results are to be extrapolated to the management of human ARF. The use of dopamine and atrial natriuretic peptide in rats afforded greater protection when used together than dopamine alone [48], suggesting potential additivity or synergy with combination therapy (*vide infra*). In contrast, dopamine and mannitol were not additive in preventing ARF induced by aortic occlusion [47].

Dopamine appeared less efficacious in nephrotoxic ARF, albeit based on more limited data than for ischemic ARF. A renoprotective action of prophylactic dopamine was observed in uranyl nitrate-induced ARF in dogs only when dopamine was administered with furosemide [41]. Furthermore, dopamine did not alter the course of uranyl nitrate-induced ARF when administered to rabbits with established disease [42]. Interestingly, the oral administration of glutamyl L-dopa, a substrate for endogenous dopamine synthesis, prior to and after the induction of ARF with glycerol was associated with a small, but nevertheless statistically

Table 2. Studies on the influence of 'renal dose' dopamine on the course of experimental acute renal failure

Study	Species	Model	Dopamine regimen	Parameter
Lindner et al	Dog	Uranyl nitrate	3 μg/kg/min and furosemide 15 min pre and 6 hr post	RBF GFR $U_{Na}V$
Hammond et al	Rabbit	Uranyl nitrate	5 μg/kg/min 24 hrs post, for 172 hrs	RBF GFR S_{Cr}
Goldfarb et al	Rat	R. nephrectomy plus occlusion of renal artery for 70 mins	6 μg/kg/min 15 mins pre, for 85 mins.	RBF GFR S_{Cr} UO
Iana et al	Rat	as above	6 μg/kg/min 15 mins pre, for 85 mins	RBF GFR S_{Cr} $U_{Na}V$
Casson et al	Rat	Glycerol	Glutamyl L-Dopa 56 mg/kg iv bolus 30 mins pre and 6 hrs post	RBF GFR S_{Cr} UO
Conger et al	Rat	Bilateral renal artery clamp for 55 mins	0.4-1.6 μg/kg/min for 4 hrs started post-clamp	RBF GFR $U_{Na}V$
Pass et al	Dog	Cross clamp aorta for 60 mins	1.2 μg/kg/min infused 20 min pre and during clamp	RBF GFR UO

Abbreviations are: ANP, atrial natriuretic peptide; S_{Cr}, serum creatinine; C_{Cr}, creatinine clearance; GFR, glomerular filtration rate; NR, not reported; RBF, renal blood flow; UO, urine output; U[Na], urine sodium concentration; $U_{Na}V$, urine sodium excretion.

[a] 'Yes' denotes $P < 0.05$ when comparing parameters post-ARF

Units are: RBF and C_{Cr} are expressed as ml/min, serum creatinine as mg/100 ml, and UO as ml/min unless otherwise stated, $U_{Na}V$, μmol/min.

Data are expressed as means and were estimated from figures where not reported in original text. Standard errors of means are included where reported or derivable from figures.

significant improvement in GFR, as determined by serum creatinine. These findings raise the intriguing possibility that it may be feasible to augment renal function in ARF via manipulation of renal dopamine synthesis, perhaps even by nutritional intervention [45].

It is important to appreciate that renal function was measured during or shortly after dopamine infusion in most studies of ischemic or nephrotoxic ARF. There are insufficient data to draw meaningful conclusions regarding the influence of "renal-dose" dopamine on long-term renal function or animal survival [42, 44]. Nevertheless, the short-term benefits of "renal-dose" dopamine on RBF, GFR and sodium excretion observed under these controlled experimental conditions suggest that "renal-dose" dopamine may be useful in the treatment of human ARF.

Value of "renal-dose" dopamine for preventing ARF in high risk patients

Table 3 summarizes studies investigating the efficacy of "renal-dose" dopamine in the prevention of ARF in high risk clinical situations [49–58]. These include major cardiac, vascular or biliary surgery, renal and liver transplantation, and exposure to radiocontrast. Most studies were controlled, prospective assessments of relatively small numbers of patients, and compared the efficacy of dopamine and saline infusions. Unfortunately, as illustrated in the Table, the non-exchangeability of patients and clinical settings (that is, variation in surgery type, different dopamine infusion regimens, variation in the timing and techniques used to assess renal function) preclude meaningful assessment by meta-analysis.

Two major studies evaluated the efficacy of "renal-dose" dopamine in preventing ARF after major cardiovascular surgery. In a prospective, randomized controlled trial of 52 patients undergoing elective coronary artery bypass surgery, the infusion of dopamine beginning at induction of anesthesia and continued for 24 hours was not associated with increased urine output during the first 24 hours or lower serum creatinine during the first postoperative week, despite improving cardiac index and reducing systemic vascular resistance [50]. In a similar study of 37 patients undergoing elective abdominal aortic surgery, 24 hours infusion of dopamine started post-operatively did not alter creatinine clearance and serum creatinine measured after one and five days, respectively [49]. A controlled, randomized trial also failed to demonstrate a beneficial effect of prophylactic "renal-dose" dopamine on GFR or urine output after elective surgery for obstructive jaundice [53]. It should be stressed, however, that there was little clinically-significant ARF in the control groups in these three studies making it extremely difficult to detect a benefit of "renal-dose" dopamine in these settings.

Patients undergoing liver transplantation have a high incidence of post-operative ARF precipitated by the stresses of major

Renal function				Statistically significant difference?[a]	Comments
Vehicle		Dopamine			
Pre-ARF	Post-ARF	Pre-ARF	Post-ARF		
197 ± 15	140 ± 10	186 ± 5	263 ± 9	Yes	Parameters assessed at 6 hrs. The infusion of dopamine or furosemide alone did not prevent the fall in RBF or GFR.
54 ± 5	10 ± 3	68 ± 6	29 ± 6	Yes	
15 ± 3	120 ± 36	29 ± 18	1015 ± 251	Yes	
NR	NR	NR	NR	—	Parameters assessed at day 8. No difference between groups. All rabbits became anuric and died.
NR	NR	NR	NR	—	
1.5 ± 0.3	14 ± 0.5	1.5 ± 0.3	14 ± 0.3	No	
NR	NR	NR	NR	—	Parameters assessed 2 hrs post-clamping. Long term outcome assessed in study below. GFR and UO expressed μmol/min/100 g body weight.
329 ± 58	30 ± 9	329 ± 58	93 ± 15	Yes	
NR	NR	NR	NR	—	
3.6 ± 1.0	25 ± 4.0	3.6 ± 1.0	20 ± 3.0	No	
NR	NR	NR	NR	NR	Parameters assessed at 24 hrs post-uranyl nitrate. GFR expressed as μmol/liter/g kidney weight
700 ± 60	100 ± 15	700 ± 60	350 ± 175	Yes	
1.6 ± 0.2	4.0 ± 0.4	1.6 ± 0.2	2.8 ± 0.4	Yes	
0.16 ± 0.05	0.42 ± 0.12	0.16 ± 0.05	0.16 ± 0.05	Yes	
NR	NR	NR	NR	—	Parameters measured 48 hrs post-glycerol. Glutamyl L-dopa is a substrate for renal dopamine synthesis. S_{Cr} expressed as μmol/liter and UO as ml/24 hr.
NR	NR	NR	NR	—	
30 ± 2.5	67 ± 3.5	30 ± 2.5	52 ± 3.5	Yes	
—	27 ± 2	—	20 ± 2	Yes	
6.9 ± 0.4	5.3 ± 0.8	6.9 ± 0.4	8.6 ± 0.6	Yes	Parameters assessed at end of 4 hr infusion. Greater protection of renal function was seen with the combination of ANP and dopamine.
0.72 ± 0.04	0.35 ± 0.04	0.72 ± 0.04	0.5 ± 0.03	Yes	
0.24 ± 0.05	0.58 ± 0.02	0.24 ± 0.05	1.54 ± 0.09	Yes	
234 ± 58	130 ± 32	231 ± 21	116 ± 10	No	Parameters assessed at 150 mins post-clamp. No added benefit with addition of mannitol.
53.6 ± 9.5	30.5 ± 6.2	58.4 ± 12.6	42.9 ± 10.8	No	
2.69 ± 0.79	1.29 ± 0.25	4.85 ± 1.0	3.27 ± 0.67	No	

hepatobiliary surgery superimposed on the chronic renal hypoperfusion that complicates liver failure. Two studies assessed the efficacy of "renal-dose" dopamine in liver transplant recipients. In the larger prospective, randomized, blinded, controlled study of 48 patients, perioperative infusion of dopamine was not associated with a lower BUN or serum creatinine in the immediate postoperative period or improved GFR measured one month after transplantation [51]. The influence of dopamine on urine output was not reported. Again, the interpretation of these results is difficult as ARF was observed in only 4% of control subjects as compared with 40 to 60% in most other series [59, 60]. In a smaller, retrospective study of 34 patients, prophylactic dopamine was associated with a lower incidence of oliguria (10% vs. 67%) and ARF (10% vs. 27%) after liver transplantation [52].

Several controlled studies evaluated the influence of perioperative "renal-dose" dopamine on the incidence of ARF following renal transplantation [56–58, 61]. Two prospective studies reported no difference between dopamine-treated and control allograft recipients when assessed for the incidence of ARF, dialysis requirements, creatinine clearance or serum creatinine during the first post-operative week, or renal function assessed three months after transplantation [56, 58]. Two retrospective studies drew similar conclusions [57, 61]. The influence of dopamine on renal sodium and water excretion in these allograft recipients was not reported. Together, these studies argue strongly against the use of prophylactic "renal-dose" dopamine after renal transplantation.

Two small studies investigated the influence of "renal-dose" dopamine on GFR and/or RBF, but not urine output, in patients with pre-existing renal insufficiency exposed to radiocontrast. A randomized control study of 30 patients failed to show any beneficial effect of dopamine on RBF [55], whereas a controlled non-randomized study of similar size demonstrated a small, but nevertheless statistically significant benefit of dopamine on serum creatinine [54]. The latter result would not justify the routine use of dopamine in this setting, given that contrast nephropathy is relatively uncommon and usually a transient biochemical phenomenon in volume-replete patients, even in the presence of pre-existing impairment of renal function [62].

In summary, the results of these studies do not support the use of prophylactic dopamine for the prevention of ARF in high risk patients. However, it should be noted that most, if not all, of these studies could have missed a significant renoprotective action of dopamine either because of the low incidence of post-operative renal dysfunction in the control group, perhaps related to study participation ("study effect") or because of insufficient statistical power. For instance, if one were to assume that high-risk patients were subject to a 20% risk of acute renal failure, even the detection of a 10% reduction in risk in an intervention group (clearly a clinically important effect) would require approximately 400 patients, assuming a two-tailed a error equal to 0.05 and 80% power (that is, the likelihood of demonstrating a true difference between groups). More subtle effects, perhaps still of clinical utility, would be even more difficult to detect.

Influence of "renal-dose" dopamine on established ARF in humans

In clinical practice, "renal-dose" dopamine is usually initiated for treatment of established ARF in critically ill patients in intensive care units. Tables 4 and 5 summarize studies evaluating

Table 3. Studies on the value of 'renal-dose' dopamine for preventing acute renal failure in high risk patients

Study (*N*)	Study design	Clinical setting	Dopamine regimen	Parameter
Baldwin et al (*N* = 37)	Controlled Prospective Randomized Blinded	Elective abdominal aortic surgery	3 μg/kg/min post-surgery for 24 hrs post	BUN S_{Cr} C_{Cr} UO
Myles et al (*N* = 52)	Controlled Prospective Randomized Blinded	Elective CABG	3 μg/kg/min pre-surgery, and 24 hrs post	BUN S_{Cr} C_{Cr} UO
Swygert et al (*N* = 48)	Controlled Prospective Randomized Blinded	Liver transplant	3 μg/kg/min pre-surgery, and 24 hrs post	BUN S_{Cr} GFR UO
Polson et al (*N* = 34)	Controlled Retrospective Not randomized Not blinded	Liver transplant	2 μg/kg/min pre-surgery, and 48 hrs post	BUN S_{Cr} C_{Cr} UO
Parks et al (*N* = 23)	Controlled Prospective Randomized Not blinded	Elective surgery for obstructive jaundice	3 μg/kg/min pre-surgery, and 48 hrs post	BUN S_{Cr} C_{Cr} UO
Hall et al (*N* = 24)	Controlled Prospective Not randomized Not blinded	IV contrast with basal Creat >2.0	3 μg/kg/min 12 hrs pre- and 24 hrs post-contrast	BUN S_{Cr} C_{Cr} UO
Weisberg et al (*N* = 30)	Controlled Prospective Randomized Blinded	IV contrast	2 μg/kg/min 15 mins pre- and 2 hrs post	BUN RBF S_{Cr} C_{Cr}
Grundmann et al (*N* = 50)	Controlled Prospective Randomized Not blinded	Renal transplant	2 μg/kg/min post-op for 4 days	BUN S_{Cr} C_{Cr} UO
Sandberg et al (*N* = 167)	Controlled Retrospective Not randomized Not blinded	Renal transplant	3 μg/kg/min post-op for 24-48 hrs.	BUN S_{Cr} C_{Cr} UO
Kadieva et al (*N* = 60)	Controlled Prospective Not randomized Not blinded	Renal transplant	3 μg/kg/min started during and for 48 hrs	BUN S_{Cr} C_{Cr} UO

Abbreviations are: ARF, acute renal failure; CABG, coronary artery bypass grafting; S_{Cr}, serum creatinine; C_{Cr}, creatinine clearance; GFR, glomerular filtration rate; NR, not reported; RBF, renal blood flow; UO, urine output; U[Na], urine sodium concentration; $U_{Na}V$, urine sodium excretion; UO, ml/hr.

Units are: RBF and C_{Cr} are expressed as ml/min and serum creatinine expressed as mg/100 ml unless otherwise stated.

Data are expressed as means and were estimated from figures where not reported in original text. Standard errors of means are included where reported or derivable from figures.

[a] 'Yes' denotes $P < 0.05$ when comparing parameters post-op

the influence of dopamine on renal function in this setting when used alone (Table 4) or as an adjunct to diuretic therapy (Table 5) [63–73]. Unfortunately, most studies were small and consisted of either uncontrolled case series or serial uncontrolled measurements of serum creatinine, GFR, urine volume and/or urine sodium excretion before and after dopamine infusion. The diagnosis of acute renal impairment frequently hinged on the presence of oliguria, a notoriously weak measure of renal function. Again, the dopamine infusion regimens and timing of assessment of renal function varied markedly among studies.

Many investigators report that "renal-dose" dopamine improved diuresis, natriuresis and occasionally RBF and GFR when administered to oliguric volume-replete patients after major surgery (Table 4). Similar findings have been reported in smaller series evaluating the influence of dopamine on renal function in patients receiving cyclosporine A or anti-cancer immunotherapy with interleukin-2 (Table 4) [69, 71]. Interpretation of these results should be extremely cautious, however, as it is impossible to definitively distinguish a "response" from spontaneous resolution (that is, the natural history) of ARF in the absence of an

Renal Function				Statistically significant difference?[a]	Comments
Control		Dopamine			
Pre-op	Post-op	Pre-op	Post-op		
6.8	5.8	6.8	5.8	No	Parameters assessed at day 5.
1.3	1.2	1.2	1.2	No	No ARF in control group.
72	83	89	85	No	Trend towards increased UO in dopamine
NR	NR	NR	NR	—	group. BUN in mmol/liter
NR	NR	NR	NR	—	CrCl and UO assessed at 24 hrs.
1.02 ± 0.05	1.03 ± 0.05	1.05 ± 0.05	1.13 ± 0.14	No	Creat assessed at day 7 post-op.
127 ± 12	107 ± 15	104 ± 16	91 ± 16	No	No ARF in control group.
NR	342 ± 120	NR	305 ± 160	No	BUN in mmol/liter
14 ± 1.7	33.5 ± 4.5	19.4 ± 3.7	31.6 ± 5.3	No	BUN/Creat assessed at day 7 and GFR
1.0 ± 0.1	1.4 ± 0.1	1.3 ± 0.2	1.4 ± 0.2	No	(Isothalamate) at 1 month post-op
82	58 ± 10	84	59 ± 6	No	(after 30 days cyclosporine). Incidence
NR	NR	NR	NR	—	of post-op ARF in both groups was 4%.
NR	NR	NR	NR	—	CrCl/UO assessed at day 1–2.
0.9 ± 0.1	NR	0.9 ± 0.1	NR	—	Data is from subgroup of 7 paired pts.
NR	23 ± 8	NR	63 ± 17	Yes	Incidence of ARF was 10% in dopamine
NR	30 ± 9	NR	60 ± 9	Yes	group vs 27% in control.
5.1 ± 0.6	4.8 ± 0.6	4.9 ± 0.6	6.0 ± 1.0	No	Parameters assessed at day 5.
72 ± 6	70 ± 7	72 ± 6	68 ± 8	No	No ARF in control group. All patients received
70 ± 17	75 ± 10	90 ± 10	78 ± 12	No	a bolus of saline and furosemide pre-op.
46 ± 10	60 ± 20	62 ± 10	55 ± 15	No	BUN in mmol/liter.
NR	NR	NR	NR	—	Creat assessed at day 3. Subgroup
2.6 ± 0.1	3.9 ± 0.6	3.0 ± 0.5	2.5 ± 0.5	Yes	analysis of 22 patients. Control group
NR	NR	NR	NR	—	received mannitol. There was no benefit
NR	NR	NR	NR	—	of dop.infusion in groups with S_{Cr} <2.0.
NR	NR	NR	NR	—	RBF assessed at 65 mins. Both groups showed
247 ± 55	424 ± 93	171 ± 23	483 ± 136	No	increased RBF at 65 mins vs. pre-contrast.
2.7 ± 0.2	NR	2.4 ± 0.2	NR	—	30–40% incidence of ARF in both groups.
29 ± 3	NR	32 ± 4	NR	—	
NR	NR	NR	NR	—	C_{Cr} assessed at day 4. No difference
NR	NR	NR	NR	—	in requirement of hemodialysis in the
NR	9.0 ± 3.2	NR	7.0 ± 2.2	No	1st post-op week between groups (76%).
NR	6	NR	56	Yes	
NR	NR	NR	NR	—	S_{Cr} assessed at 3 weeks.
NR	3.0 ± 0.2	NR	2.6 ± 0.3	No	No difference in the mean time of onset
NR	NR	NR	NR	—	of renal function post-transplantation.
NR	NR	NR	NR	—	
NR	NR	NR	NR	—	C_{Cr} assessed at day 7.
NR	NR	NR	NR	—	Incidence of ARF in dopamine group 33%
NR	55.2 ± 1.6	NR	57.5 ± 1.7	No	vs. 23% in controls
NR	NR	NR	NR	—	

appropriate randomized control group. Indeed, even among published randomized studies with appropriate controls, the likelihood of demonstrating a modest, clinically important difference in any of the usual parameters of interest (such as natriuresis, RBF, GFR) with less than several hundred subjects is extremely low (*vide supra*).

Even when dopamine appeared to trigger a significant improvement in RBF, GFR or sodium excretion, these benefits were usually not sustained after therapy was discontinued (Tables 4 and 5). There is either no or extremely limited published information on the influence of dopamine on the course of ARF, dialysis requirements, long-term renal outcome or patient survival. Indeed, in those reporting on survival, many patients who responded to dopamine subsequently required dialysis or died [63, 67, 74].

Similar caveats should be entertained when interpreting trials evaluating the efficacy of "renal-dose" dopamine as an adjunct to furosemide or mannitol for the prevention or treatment of ARF (Table 5). The addition of dopamine to furosemide conferred striking renoprotection in a controlled study of 23 patients with ARF secondary to falciparum malaria [70]. This study clearly warrants confirmation, particularly since dialysis facilities are rarely available in endemic areas. Dopamine also improved creatinine clearance or urine output when used with mannitol in a controlled, partially randomized study of 27 patients undergoing elective infrarenal aortic surgery [68]. The clinical significance of these findings is uncertain, however, as few patients treated with mannitol alone developed ARF.

Two other clinical scenarios warrant mention in a discussion of combination therapy. Norepinephrine is a useful inotrope and vasopressor in hypotensive patients and "renal-dose" dopamine is

Table 4. Studies on the influence of 'renal dose' dopamine on oliguria and/or established acute renal failure in humans

Study (*N*)	Study design	Clinical setting	Dopamine regimen
Davis et al (*N* = 15)	Uncontrolled Prospective Case series	Oliguria post-cardiac surgery	100 μg/min for 4 hrs
Flancbaum et al (*N* = 19)	Uncontrolled Prospective Case series	Oliguria post-surgery	2.5 μg/kg/min for 4 hrs
Henderson et al (*N* = 11)	Uncontrolled Prospective Case series	Oliguria post-surgery	1 μg/kg/min for 12 hrs
Parker et al (*N* = 52)	Uncontrolled Prospective Case series	Oliguria in ICU	2 μg/kg/min for 12 hrs
Marik et al (*N* = 9)	Uncontrolled Prospective Case series	Oliguria in ICU	2 μg/kg/min for 6 hrs
Conte et al (*N* = 8)	Uncontrolled Prospective Case series	CsA-induced ARF	2 μg/kg/min started 3 hrs post-CsA for 1 hr
Palmieri et al (*N* = 9)	Uncontrolled Retrospective Case series	IL-2 induced ARF	2 μg/kg/min for 24 hrs

Abbreviations are: ARF, acute renal failure; Cr, creatinine; C_{Cr} creatinine clearance; CsA, cyclosporine A; GFR, glomerular filtration rate; IL-2, interleukin 2; Obs, observations; RBF, renal blood flow; PRA, plasma renin activity; UO, urine output; U[Na], urine sodium concentration; $U_{Na}V$, urine sodium excretion. Units are: creatinine: mg/100 ml; C_{Cr} and GFR, ml/min; RBF, ml/min; UO, ml/hr; U[Na], mmol/liter; $U_{Na}V$, mmol/hr.

Data are expressed as means and were estimated from figures where not quoted in original text. Standard errors of means are included where reported or derivable from figures.

[a] 'Yes' denotes $P < 0.05$ when comparing values pre- and post-dopamine

Table 5. Studies on the influence of 'renal-dose' dopamine in combination with diuretic agents on established ARF in humans

Study (*N*)	Study design	Clinical setting	Dopamine regimen	Additional agent	Parameter
Graziani et al (*N* = 24)	Uncontrolled Prospective Case series	Oliguria post-surgery	1-3 μg/kg/min	Furosemide	S_{CR} C_{CR} $U_{NA}V$
Lindner et al (*N* = 8)	Uncontrolled Prospective Case series	Oliguria post-surgery	1-3 μg/kg/min for 1-2 days	Furosemide 100-200 mg q6-8 hr	S_{CR} C_{CR} UO
DeLosAng. et al (*N* = 40)	Controlled Retrospective Not randomized Not blinded	Renal transplant	3 μg/kg/min started pre-op, for 1-2 days	Furosemide 200 mg q6 hr for 1-2 days	BUN S_{CR} CrCl UO
Paul et al (*N* = 27)	Controlled Prospective Not randomized Not blinded	Elective infrarenal aortic clamping	3 μg/kg/min started pre-op, for 40 mins post-clamp	Mannitol 200 mg/kg/hr	S_{CR} C_{CR} UO
Lumlertgul et al (*N* = 8)	Controlled Prospective Randomized Not blinded	Malaria induced ARF	1 μg/kg/min for 4 days	Furosemide 200 mg q6 hr for 4 days	S_{CR} C_{CR}

Abbreviations are ARF, acute renal failure; BUN, Blood urea nitrogen; S_{CR}, serum creatinine; C_{CR}, creatinine clearance; GFR, glomerular filtration rate; RBF, renal blood flow; UO, urine output; U[Na], urine sodium concentration; $U_{NA}V$, urine sodium excretion.

Units are: BUN and serum creatinine, mg/100 ml; creatinine clearance, ml/min; UO, ml/hr; and $U_{NA}V$, mmol/hr.

Data are expressed as means and were estimated from figures where not reported in original text. Standard errors of means are included where reported or derivable from figures. In addition to studies summarized above, dopamine was used in conjunction with a single dose of either furosemide or mannitol in some studies outlined in Tables 2-4.

[a] 'Yes' denotes $P < 0.05$ when comparing parameters pre- vs. post-dopamine (studies 1 and 2) or dopamine vs. control

Response to dopamine			Significant difference?[a]	Comments
Parameter	Pre	Post		
Cr	1.1 ± 0.1	NR	—	Parameters assessed at end of infusion. Both UO and GFR returned to pre-infusion levels after stopping dopamine. No pts required dialysis.
C_{Cr}	70 ± 10	115 ± 13	Yes	
U[Na]	15 ± 5	29 ± 10	Yes	
UO	22 ± 2	54 ± 9	Yes	
Cr	1.1 ± 0.5	NR	No	Parameters assessed after infusion. No patients developed ARF. No change in mean creat UO expressed as ml/kg/hr.
C_{Cr}	NR	NR	—	
U[Na]	55 ± 13	77 ± 13	No	
UO	0.4 ± 0.05	1.0 ± 0.1	Yes	
Cr	3.8 ± 0.6	4.2 ± 0.6	No	$U_{Na}V$ assessed at end of infusion. 3 patients required dialysis but maintained a good UO. 4 patients died.
C_{Cr}	NR	NR	—	
U[Na]	45 ± 6.6	74 ± 6.3	Yes	
Cr	NR	NR	—	Parameters assessed at end of infusion. For each pt parameters measured on and off dopamine. No information given on long term outcome.
C_{Cr}	<30	by 3.8 ± 1.0	Yes	
UO	<1 ml/kg/min	by 42%	Yes	
Cr	1.1 ± 0.1	NR	—	Parameters assessed at end of influsion. Natriuresis in only 5 of 9 pts and inversely proportional to PRA. 2 pts required dialysis. Mortality not reported.
C_{Cr}	NR	NR	—	
$U_{Na}V$	1.6 ± 0.6	5.8 ± 2.2	Yes	
RBF	410 ± 30	600 ± 70	Yes	Parameters assessed at end of infusion. RBF and GFR returned to baseline on stopping dopamine. GFR measured by inulin clearance.
GFR	90 ± 5	115 ± 5	Yes	
UO	13 ± 1	18 ± 1	Yes	
Cr	2.3 ± 0.2	1.8 ± 0.2	Yes	Parameters assessed at end of infusion. Dopamine infusion shortened the mean recovery from 10 days to 5 days in the subgroup with a baseline Cr >1.1.
C_{Cr}	NR	NR	—	
UO	530 ± 130	1275 ± 225	Yes	

Renal function				Statistically significant difference?[a]	Comments
Control		Dopamine + agent			
Pre	Post	Pre	Post		
—	—	1.5	7.2	—	S_{CR} is peak during ARF. 5 pts with longer delay in starting dop. did not diurese and were dialyzed. In total, 10 pts were dialyzed and 5 pts died.
—	—	54 ± 3.7	9 ± 1.2	—	
—	—	0.5 ± 0.1	8.4 ± 1.0	Yes	
—	—	4.4 ± 0.4	4.5 ± 0.6	No	Dop. started 1-3 days post oliguria. Parameters assessed after 1-2 days of infusion. 2 pts required dialysis but maintained UO. 4 patients died.
—	—	NR	NR	—	
—	—	9 ± 2	90 ± 7	Yes	
NR	64 ± 6	NR	56 ± 6	No	Parameters assessed at 24 hrs post-transplant. No difference in C_{CR} or incidence of oliguria post-op between groups.
NR	9.6 ± 1.4	NR	10.2 ± 1.4	No	
NR	NR	NR	NR	—	
NR	144	NR	227	No	
NR	NR	NR	NR		Parameters assessed at 1 day post-op. C_{CR} decreased in both groups by approx 50% during clamp period.
96 ± 10	92 ± 7	91 ± 8	92 ± 7	No	
150 ± 30	115 ± 30	130 ± 30	100 ± 30	No	
3.5 ± 0.8	9.9 ± 0.2	3.7 ± 0.4	2.9 ± 0.4	Yes	Parameters assessed at day 6. Mean recovery time was 9 days in dopamine group vs. 17 days in control.
13 ± 0.8	NR	12.8 ± 0.6	NR	Yes	

commonly used with norepinephrine in an effort to preserve renal perfusion under these circumstances. Experimental studies indicate that dopamine augments RBF in healthy animals receiving norepinephrine; however, it has yet to be demonstrated convincingly that therapeutic doses of norepinephrine compromise renal function in human shock and that "renal-dose" dopamine prevents this complication [75]. These considerations also apply to the use of "renal-dose" dopamine as an adjunct to dobutamine

therapy in patients with cardiac failure. The combination is attractive on theoretical grounds in that dobutamine should improve cardiac index and induce arterial vasodilatation through stimulation of myocardial $\beta 1$ and peripheral $\beta 2$ adrenoreceptors, respectively, whereas dopamine should maximize RBF and sodium excretion through engagement of DA-1 and DA-2 receptors in the kidney. Whereas it has been shown convincingly that "renal-dose" dopamine can enhance urine output in oliguric patients with left ventricular failure on dobutamine [76], it remains to be determined if dopamine prevents ARF or improves survival in this setting.

Potentially deleterious effects of dopamine

Proponents frequently advocate "renal-dose" dopamine on the grounds that it may improve renal function in some patients and is unlikely to harm. The latter may be a gross misconception. Few studies have rigorously evaluated the potential toxicity of "renal-dose" dopamine in critically ill patients. Indeed, several physiologic and clinical observations suggest that "renal-dose" dopamine may be harmful in some patients. Dopamine administration requires venous cannulation and local extravasation of dopamine adjacent to an artery may provoke distal ischemia and gangrene [77]. Dopamine can depress respiratory drive and may increase cardiac output and myocardial oxygen consumption, even at "renal-doses" (*vide supra*), and trigger tachyarrhythmias and myocardial ischemia [1, 10]. Dopamine may potentially induce or exacerbate hypovolemia and prerenal ARF through its natriuretic effects and trigger hypokalemia and hypophosphatemia, other dangerous complications in critically ill patients. It is worrysome that low dose dopamine hastened the onset of gut ischemia in a porcine model of hemorrhagic shock [78]. The latter complication appeared due to shunting of blood away from the bowel mucosa rather than an absolute reduction in mesenteric blood flow [78]. Finally, "renal-dose" dopamine therapy is relatively expensive and, in the absence of more convincing data on efficacy, may be viewed as a waste of resources in an age of increasing fiscal responsibility.

Summary and recommendations

In summary, there is compelling evidence that "renal-dose" dopamine augments RBF, GFR and/or natriuresis in healthy humans and experimental animals, and limits ATP utilization and oxygen requirements in nephron segments at high risk for ischemic injury; actions that could potentially limit renal injury and accelerate recovery in ARF. In keeping with these findings, "renal-dose" dopamine augments RBF, GFR and natriuresis in several experimental models of ischemic and nephrotoxic ARF. Most studies in humans, however, have failed to demonstrate convincingly that "renal-dose" dopamine either prevents ARF in high risk patients, or improves renal function or outcome in patients with established ARF. It remains to be determined whether this apparent ineffectiveness reflects a true lack of efficacy in human ARF or failure to detect an important improvement in renal function due to limitations in study design or statistical power. "Renal-dose" dopamine can precipitate serious cardiovascular and metabolic complications in critically ill patients. We suggest that "renal-dose" dopamine should not be used for its selective renal vasodilatory and natriuretic actions in patients with ARF and/or oliguria until its efficacy is established conclusively in randomized, controlled trials. In this respect, we contend that "renal-dose" dopamine should be subject to the same criteria for acceptance as any new agent seeking approval for clinical use. We urge that such studies are undertaken, given the attractive theoretical rationale for using "renal-dose" dopamine, its apparent efficacy in laboratory animals, and the current lack of effective therapies for the prevention or treatment of ARF. Funding for such studies would probably have to come from federal sources or "not-for-profit" agencies since the "off-patent" status of dopamine makes it is unlikely that support could be generated from the pharmaceutical industry unless a dopamine analogue was being evaluated. "Renal-dose" dopamine may ultimately prove most valuable when combined with agents targeted at other pivotal pathophysiologic events in renal ischemia-reperfusion injury, such cast formation and intratubular obstruction (such as RGD peptides), ischemic tubule cell injury (such as $MgATPCl_2$) or tubule cell regeneration (such as growth factors) [reviewed in 40]. These recommendations should not preclude the use of dopamine for its systemic effects in heart failure or septic shock when dopamine, like other inotropes, may afford a valuable increase in cardiac output and tissue perfusion. Indeed, pressor doses of dopamine, when used in conjunction with other supportive measures, augment cardiac output and oxygen delivery to tissues in septic shock, parameters associated with improved survival [reviewed in 79].

MARK D. DENTON, GLENN M. CHERTOW, and HUGH R. BRADY
Boston, Massachusetts, USA
and Dublin, Ireland

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Reprint requests to Hugh R. Brady M.D., Ph.D., Department of Medicine and Therapeutics, University College Dublin, Mater Miseracordiae Hospital, 41 Eccles Street, Dublin 7, Ireland. Email: hrbrady@mater.ie

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