'Low-dose' dopamine worsens renal perfusion in patients with acute renal failure

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'Low-dose' dopamine is frequently used in intensive care units (ICU) for its presumed renoprotective effects, but prospective and retrospective studies have so far not proven prevention or amelioration of renal injury. Data on renal perfusion following dopamine infusion are limited. In order to circumvent the problem of patient heterogeneity in the ICU setting, we used a crossover design in a prospective, double-blind randomized controlled study to investigate the effect of 'low-dose' dopamine on renal resistance indices, as determined by Doppler ultrasound. Forty patients, 10 without and 30 with acute renal failure (ARF, defined as doubling of baseline creatinine or an increase above 2 mg/dl), were included. Dopamine (2 μg/kg min) or placebo was given intravenously in alternating sequence for four subsequent periods of 60 min, starting randomly with either dopamine or placebo. Resistive (RI) and pulsatility index (PI) were closely correlated, positively related to serum creatinine values at baseline and highly reproducible during the two paired infusion periods. Dopamine reduced renal vascular resistance in patients without ARF (median RI/PI from 0.70 to 0.65/1.20 to 1.07, $P<0.01$) but increased resistance indices in patients with ARF (median RI/PI from 0.77 to 0.81/1.64 to 1.79, $P<0.01$) in the absence of effects on systemic hemodynamics. Subgroup analysis of patients with ARF revealed that dopamine induced renal vasoconstriction above 55 years ($n=22$) and in patients not receiving norepinephrine ($n=20$). In conclusion 'low-dose' dopamine can worsen renal perfusion in patients with ARF, which adds to the rationale for abandoning the routine use of 'low-dose' dopamine in critically ill patients.

Kidney International (2006) **69,** 1669–1674. doi:10.1038/sj.ki.5000310; published online 29 March 2006

KEYWORDS: acute renal failure; dopamine; Doppler ultrasound; catecholamines; renal vascular resistance

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Received 1 April 2005; revised 7 October 2005; accepted 18 November 2005; published online 29 March 2006

Dopamine is an endogenous catecholamine that influences different catecholamine receptors in a dose-dependent manner. Infusion rates of 2–5 μg/kg min induce primarily dopaminergic effects, whereas at rates above 5 μg/kg min β-adrenergic effects predominate and α-adrenergic actions gradually become more important. For more than three decades, the so-called 'low-dose' dopamine (<5 μg/kg min) has been widely used in intensive care patients for presumed renal protective effects. The rationale for this application is based on findings in healthy humans and experimental animals, where 'low-dose' dopamine was found to cause renal vasodilatation associated with an increase in renal blood flow and diuresis.[1–5] Additional evidence suggested that the infusion of dopamine may blunt endogenous norepinephrine-induced vasoconstriction.[6,7] These effects are thought to be mediated by stimulation of (i) dopamine-1 receptors in the renal vasculature,[8,9] (ii) dopamine-2 receptors inhibiting norepinephrine release from presynaptic nerve endings,[8,10,11] and (iii) dopamine-1 and -2 receptors in tubular cells inhibiting Na^+/K^+ ATPase activity and thereby inducing natriuresis.[8,12] Larger doses of dopamine are thought to augment renal blood flow chiefly by increasing cardiac output.[13–15]

Several clinical trials have meanwhile investigated the use of 'low-dose' dopamine for the prevention of acute renal failure (ARF) in patients at risk, as well as its therapeutic use in patients with established ARF. Some of these studies have shown that dopamine increases urine output,[3,5,16–19] whereas others found no effect.[20–22] A prospective, randomized controlled trial by the Australian and New Zealand Intensive Care Society group found that low-dose dopamine does not prevent or reverse ARF, nor does it improve outcome.[20] The largest retrospective analysis also failed to show a beneficial effect of 'low-dose' dopamine on survival or the need of hemodialysis in patients with ARF.[23–25] In view of these data, reviewers concluded that the use of 'low-dose' dopamine cannot be recommended.[1] On the other hand, given the heterogeneity of ICU patient populations, lack of evidence does not necessarily imply evidence of absence of an effect in all patient subgroups. In order to circumvent problems of patient heterogeneity and to obtain further evidence for the effect of 'low-dose' dopamine on renal blood flow under

different clinical circumstances, we measured renal perfusion indices in a placebo-controlled crossover design in patients on a medical ICU with and without ARF.

RESULTS

Patient characteristics

Given the setting of a general medical ICU, the spectrum of diseases was broad and, as expected, it differed between patients with and without ARF. The primary diagnosis of patients without ARF included cardiothoracic surgery with protracted recovery ($n=2$), gastrointestinal bleeding ($n=2$), postresuscitation syndrome ($n=1$), acute coronary syndrome ($n=1$), near drowning ($n=1$), heart failure ($n=1$), complicated urinary tract infection ($n=1$), and pneumothorax ($n=1$). Two of these patients were ventilated. In contrast, 73% of the patients with ARF were ventilated. Their primary diagnosis were sepsis ($n=5$), pancreatitis ($n=3$), cholangitis ($n=1$), pneumonia ($n=3$), heart failure ($n=3$), liver failure ($n=2$), cardiothoracic surgery ($n=2$), endocarditis ($n=1$), intracerebral infarction ($n=3$), rhabdomyolysis ($n=1$), opiate intoxication ($n=1$), gastrointestinal bleeding ($n=2$), postresuscitation syndrome ($n=1$), necrotizing fasziits ($n=1$), and partial occlusion of iliac arteries ($n=1$). Baseline characteristics of all patients are shown in Table 1. As expected, patients with ARF had significantly higher serum creatinine and urea concentrations as compared to patients without ARF. Eleven patients with ARF were oligo-anuric (daily urine volume <500 ml). Mean RI and PI were higher in patients with ARF, reflecting increased renal vascular resistance. Moreover, there was a positive, nonlinear relationship between renal resistance indices and the degree of renal failure, as determined by the serum creatinine value (Figure 1). Blood pressure was not different between patients with and without ARF. In patients receiving norepinephrine, the heart rate was higher, but other baseline parameters were not different (Figure 1 and Table 1).

Correlation and reproducibility of resistance measurements

Measurements of RI and PI were closely correlated with each other during each treatment period (Figure 2), and comparison of renal resistance between groups using either RI and PI always gave identical results. Moreover, it turned out that the measurements of both indices at the end of both

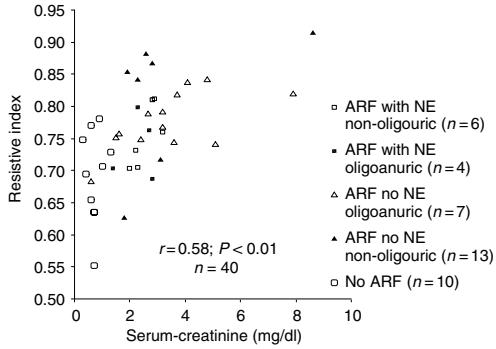

Figure 1 | Relationship between the baseline RI and serum creatinine in all patients. NE, norepinephrine.

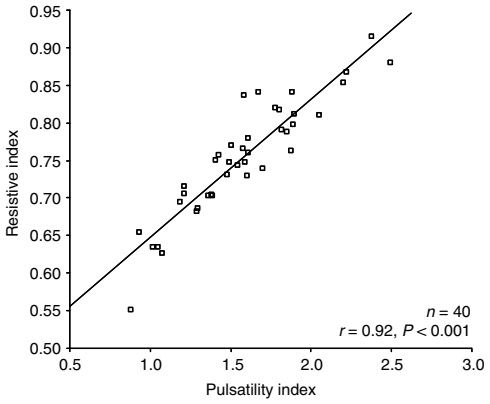

Figure 2 | Correlation between the baseline RI and PI in all patients.

Table 1 | Baseline characteristics of study patients

		ARF	
	No ARF (n=10)	Without norepinephrine (n=20)	With norepinephrine (n=10)
Age (years)	54±15.0	61±14.3	62±14.1
Sex	5 m, 5 w	11 m, 9 w	6 m, 4 w
Systolic BP (mmHg)	127±26	130±23	120±23
Diastolic BP (mmHg)	63±16	63±17	69±17
Mean arterial pressure (mmHg)	88±17	86±18	87±16
Heart rate (beats/min)	83±16.1	81±14.3	100±22.1**
Mechanical ventilation	1	12	10
Duration of ICU stay before study (days)	7.5±7.1	7.2±4.6	5.7±5.7
Serum urea (mg/dl)	39.9±9.6	128.3±50.5*	109.8±56.7*
Serum creatinine (mg/dl)	0.7±0.3	3.4±2.0*	2.5±0.5*
RI	0.69±0.08	0.81±0.07*	0.75±0.05*
PI	1.20±0.27	1.92±0.51*	1.67±0.40*

ARF, acute renal failure; BP, blood pressure; ICU, intensive care unit.
Values are means±s.d.
*Significant difference between the two patient groups with and without ARF (acute renal failure) ($P<0.001$; Mann–Whitney)
**indicates significant difference in patients treated with norepinephrine as compared to the two other groups (P=0.03).

placebo and dopamine periods were highly reproducible (Figure 3) and not different from each other. For subsequent analysis, the arithmetic mean was therefore calculated for the placebo and the dopamine period, respectively, and used for comparisons between groups.

Effects of dopamine on renal perfusion indices

'Low-dose' dopamine resulted in measurable effects on renal perfusion indices both in patients with and without ARF, but the effect occurred in the opposite direction (Figure 4). In patients without ARF, dopamine decreased median RI from 0.70 to 0.65 ($P<0.01$) and PI from 1.20 to 1.07 ($P<0.01$). In marked contrast, in patients with ARF, RI increased significantly under dopamine infusion (median RI from 0.77 to 0.81; $P<0.01$; median PI from 1.64 to 1.79; $P<0.01$).

Considering the patients with ARF receiving and not receiving norepinephrine separately, dopamine increased resistance indices significantly in the absence of norepinephrine (median RI from 0.79 to 0.82 and median PI from 1.69 to 1.84; $P<0.01$), whereas there was no effect in patients treated with norepinephrine (median RI 0.75 vs 0.75, median PI 1.54 vs 1.58) (Figure 5).

Renal vascular resistance is known to increase with age,[26,27] and we also observed a weak correlation between RI/PI and age in patients with and without ARF (not shown). In order to investigate if age had an influence on the effect of dopamine on renal resistance, data were analyzed separately for patients <55 years and $\geqslant 55$ years. As shown in Figure 6, the decrease in renal resistance in patients without ARF was absent in older patients and the increase in RI in patients with ARF only occurred in patients $\geqslant 55$ years.

Effects of dopamine on systemic hemodynamics and urine production

The observed effects of 'low-dose dopamine' on renal perfusion occurred in the absence of systemic hemodynamic

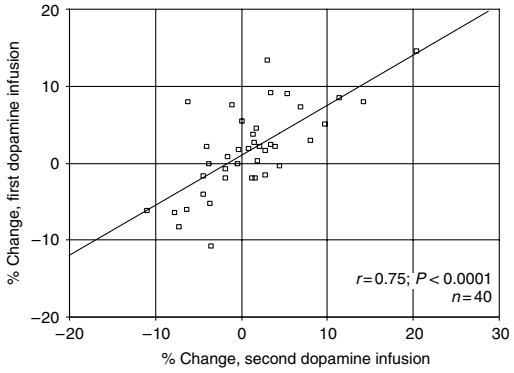

Figure 3 | Percentage change of RI compared to baseline value after first and second dopamine infusion. A close linear relationship between both values ($r=0.74$, $P<0.0001$) indicates high reproducibility of the effect of dopamine.

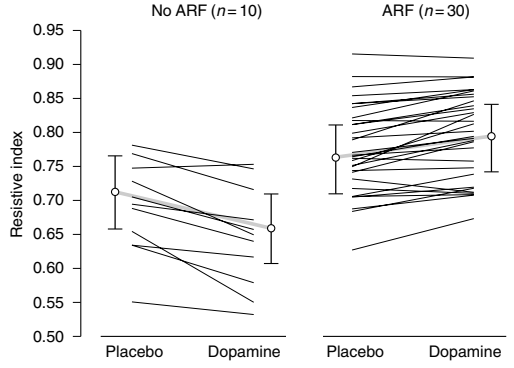

Figure 4 | Intraindividual comparison and mean ± s.d. of RI values during placebo and dopamine infusion in patients with and without ARF. In patients without ARF dopamine reduced the RI significantly ($P<0.01$, Wilcoxon test), whereas there was a significant increase in patients with ARF ($P<0.01$).

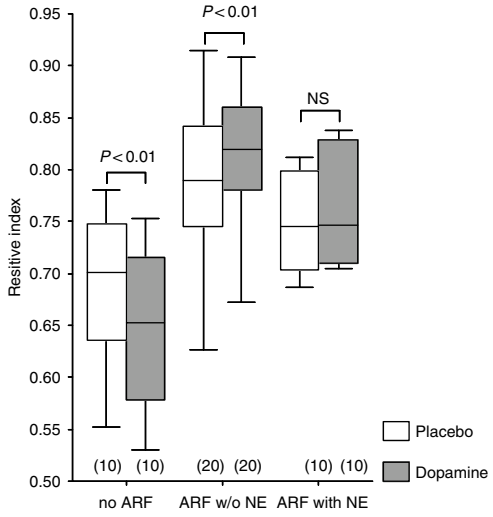

Figure 5 | Effect of dopamine on RI values in patients with and without norepinephrine (NE) infusion.

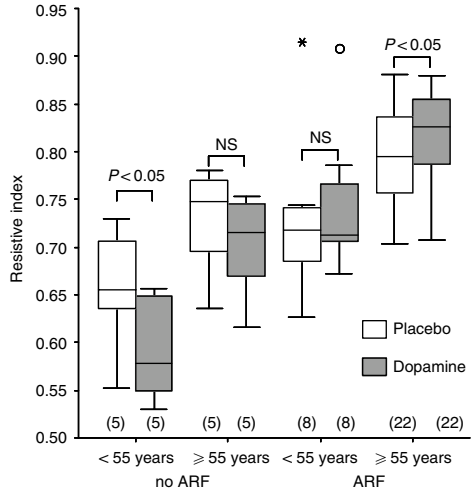

Figure 6 | Effect of dopamine on RI values in patients below or above 55 years. * and ° indicate outliers.

Table 2 | Hemodynamic parameters during placebo and dopamine infusion

	No ARF (n=10)		ARF without norepinephrine (n=20)		ARF with norepinephrine (n=10)	
	Placebo	Dopamine	Placebo	Dopamine	Placebo	Dopamine
Heart rate (beats/min)	82±16	83±11	84±14	87±17	104±26	102±29
Systolic BP (mmHg)	122±23	123±22	129±17	134±23	110±23	123±23
Diastolic BP (mmHg)	60±14	60±7	61±13	62±13	63±8	64±10
Mean arterial pressure (mmHg)	81±16	81±10	85±15	84±13	78±10	84±13

Values are means±s.d.
ARF, acute renal failure; BP, blood pressure.

Table 3 | Urine and electrolyte excretion during placebo and dopamine infusion

	No ARF (n=7)		ARF			
			Without norepinephrine (n=11)		With norepinephrine (n=4)	
Urine values	Placebo	Dopamine	Placebo	Dopamine	Placebo	Dopamine
Urine output (ml/h)	106±94	156±145	125±76	154±142	140±148	112±105
Sodium (mmol/h)	10.9±3.4	15.2±10.2	10.1±5.8	11.5±9.7	15.1±10.5	11.9±4.9
Potassium (mmol/h)	5.3±2.6	5.0±2.2	3.8±2.4	4.4±3.5	4.5±1.7	3.6±1.8
Creatinine (g/h)	0.09±0.04	0.08±0.05	0.03±0.02	0.05±0.05	0.07±0.05	0.06±0.04
Urea (g/h)	1.5±0.4	1.9±0.8	1.2±0.14	1.6±2.5	1.2±1.1	0.9±0.5

Values are means±s.d. In none of the three groups of patients were any of the parameters significantly different between the placebo and the dopamine period. In three patients without ARF (acute renal failure) and in four patients with ARF, urine collection during the study periods was inaccurate, because patients had no bladder catheters and their values were therefore not included.

effects (Table 2); heart rate and systolic, diastolic, and mean blood pressure were not significantly different between dopamine and placebo infusion periods (Wilcoxon test).

Effects of dopamine on urine output and electrolyte excretion are given in Table 3. There were no differences between urine flow and the amount of sodium, potassium, creatinine, or urea excreted per hour between the placebo or dopamine administration, neither in patients with ARF nor in those without ARF.

DISCUSSION

Although previous discussions on the therapeutic value of 'low-dose' dopamine focused on the lack of effect of dopamine and potential adverse effects outside the kidneys, this study is to our knowledge the first to demonstrate that dopamine may actually deteriorate renal perfusion in patients with ARF.

Hypoperfusion is considered to play a significant role in the pathogenesis of ARF and can arise from either a decrease in renal perfusion pressure or an increase in renal vascular resistance. Importantly, renal vascular resistance increases, even when systemic vascular resistance is low, as in sepsis.[28] In line with this concept, we found a significant elevation of RI in the renal cortex in patients with ARF as compared to intensive care patients not fulfilling ARF criteria. This increase was reversible and disappeared in parallel with a decline of serum creatinine during the recovery phase of ARF (data not shown).

The rationale for the use of dopamine for preservation of renal function is based on findings in healthy humans and experimental animals, where it increases renal blood flow.[1–5] In a previous study, also using Doppler flow measurements, Stevens *et al.*[29] showed that 'low-dose' dopamine reduces renal vascular resistance in intensive care patients without ARF. Confirming these data, we also observed a decline of RI and PI in this patient group. However, in marked contrast, RI and PI increased in patients with ARF (Figure 4), thus indicating a further deterioration of renal perfusion in the presence of acute renal injury. The application of norepinephrine was not part of our study protocol, but 10 patients received norepinephrine as part of their therapy. When analyzing patients treated with and without norepinephrine separately, the deterioration of renal perfusion appeared to be confined to those patients not on norepinephrine, but given the small sample size this conclusion needs to be drawn with care. In contrast to observations in healthy volunteers[7] however, we could not detect an improvement in renal perfusion when 'low-dose' dopamine was added to norepinephrine (Figure 5).

We did not study the functional significance of the reduction in renal perfusion in ARF patients, but if renal hypoperfusion and subsequent ischemic injury play a dominant role in the perpetuation of renal failure, this effect of dopamine might well increase tubular damage and retard recovery. Our findings are consistent in this respect with a previous study inferring detrimental effects of 'low-dose' dopamine on renal tubular integrity from increased urinary excretion of retinol binding protein.[30]

Animal studies also found that the effect of 'low-dose' dopamine on renal perfusion may vary depending on circumstances and that a vasodilatation occurs under baseline conditions, but not in sepsis,[31] or in animals with ischemic, postischemic, or gylcerol-induced ARF.[32,33] Although our findings in patients go beyond these observations in showing

that dopamine may even worsen renal perfusion, the pathophysiological basis for the difference of dopamine effects remains unclear. As established acute tubular necrosis is characterized by an imbalance between renal vasoconstrictors and vasodilators, it is possible that the effect of dopamine varies depending on the array of vasoactive substances co-influencing renal resistance.[34] Alternatively, despite identical infusion rates of dopamine, its local concentration in the kidney could be higher in patients with ARF owing to endogenous production of dopamine[35] and/or reduced renal clearance.[36] As the vascular effects of dopamine are dose-dependent, with vasoconstrictive actions becoming more important with increasing concentrations, an increase in dopamine concentrations could theoretically account for a change in its net effect. Noteworthy, however, systemic hemodynamics were unaffected in all patient groups in this study (Table 2), suggesting that if an accumulation of dopamine does play a role, it would mainly be local.

Interestingly, we also found an association of patient age with the effects of dopamine on renal perfusion. The vasodilatation in the absence of ARF was more marked in the younger patient group, and dopamine-induced vasoconstriction tended to be more pronounced in elderly patients (Figure 6). Other studies also found an age-dependent increase in renal vascular resistance[26,27] and revealed that dopamine-induced renal vasodilatation was blunted with increasing baseline resistance and age.[4] As the average age of intensive care patients is increasing, this observation underscores the clinical relevance of the observed adverse effect of dopamine on renal perfusion.

Different effects of dopamine on vascular resistance are not only of interest in single vascular beds, but also in comparison between different organs. In particular, potential vasoconstrictive effects of the so-called 'low-dose' dopamine in the splanchnic circulation are of concern[1] and they may promote bacterial translocation. In addition, there is also evidence that 'low-dose' dopamine through mechanisms that are poorly understood can also suppress the ventilatory drive.[37]

A limitation of this study is its focus on renal hemodynamic effects of 'low-dose' dopamine. Since recently, there is renewed interest in potential non-hemodynamic tissue protective effects of dopamine, following the observation that the use of 'low-dose' dopamine in organ donors is associated with improved outcomes of renal transplants.[38] However, this finding was not made in all studies,[39] prospective data supporting a beneficial effect of dopamine in this setting are not yet available, and the impact of potential immunomodulatory functions in the intensive care population is unpredictable. Given the failure to demonstrate a benefit of 'low-dose' dopamine in preventing or ameliorating incipient or established renal damage in intensive care patients, we believe that our data, by showing the potential of dopamine to reduce renal perfusion, add strongly to the rationale to discontinue its use in critically ill patients.

MATERIALS AND METHODS

Patients

Forty patients treated on a medical ICU were included: 10 patients (five male and five female patients) without ARF and 30 patients (17 male and 13 female patients) with ARF. Ten patients with ARF required treatment with norepinephrine (median 1.2 ± 1.0 mg/h) independent of study medication. ARF was defined as an increase in serum creatinine above 2.0 mg/dl or twice the baseline value in the absence of preexisting chronic renal failure. Patients with ARF were only included when the onset of ARF occurred less than10 days ago.

Study protocol

Renal perfusion indices were measured by Doppler ultrasonography using a randomized, double-blind, placebo-controlled crossover design. Dopamine at a dose of 2 μg/kg min in NaCl 0.9% or placebo (isovolemic 0.9% NaCl) was given by continuous intravenous infusion in alternating sequence for four subsequent periods of 60 min, starting randomly with either dopamine or placebo (Figure 7).

All measurements were performed by one investigator who was blinded with respect to the sequence of dopamine and placebo in each patient, using a Hitachi EBU 525 ultrasound machine with a 3.75 MHz convex-array transducer. Each patient's right or left kidney was selected for study depending on ease of access. After visualizing the kidney in gray scale and color Doppler mode and verification of the absence of signs of chronic renal damage, an interlobar or arcuate artery was selected and measured with pulse wave Doppler. At least three readings per measurement were taken from the same artery. The same artery was restudied after each 60 min period. Doppler spectra were analyzed for PI ((peak systolic frequency shift−minimum diastolic frequency shift)/mean frequency shift) and RI ((peak systolic frequency shift−minimum diastolic frequency shift)/peak systolic frequency shift). Measurements of heart rate, arterial pressure, and urine output were recorded hourly and a urine sample for analysis of electrolytes, creatinine, and urea excretion was taken after each hour. When patients were treated with intermittent dialysis, the measurements were scheduled with at least a 15-h interval between the end of the dialysis and the start of Doppler measurements. Patients on continuous hemofiltration were investigated while the hemofiltration was ongoing.

The local ethics committee approved the study protocol and written informed consent was obtained from the patient or next of kin.

Statistical analysis

All results in the same patient were considered as paired observations, with each patient serving as his or her own control. The significance of differences was analyzed by the non-parametric Wilcoxon test for two related samples, and to test for significant

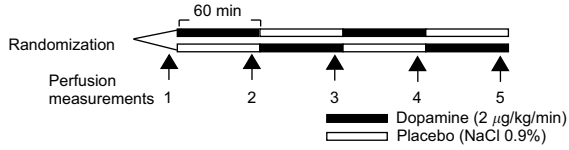

Figure 7 | Schematic presentation of the study design. All patients received 'low-dose' dopamine or placebo for two periods of 1 h in alternating sequence and were randomly assigned to two groups receiving either dopamine or placebo first.

differences between different groups, the non-parametric Mann–Whitney test was used. A *P*-value of less than 0.05 was considered as statistically significant. To examine the relation between the RI, PI, and other patient variables, the correlation after Spearman between the baseline values of RI or PI was determined, thus excluding the influence of dopamine. SPSS was used for data analysis and calculation.

ACKNOWLEDGMENTS

We are grateful to Dr I Küchler for help with the statistical analysis.

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