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The Renal Effect of Low-Dose Dopamine in High-Risk Patients Undergoing Coronary Angiography

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OBJECTIVES The purpose of the study was to examine the potential renal protective effect of low-dose dopamine in high-risk patients undergoing coronary angiography.

BACKGROUND Contrast nephropathy is prevalent in patients with chronic renal failure (CRF) and/or diabetes mellitus (DM). Decreased renal blood flow due to vasoconstriction was suggested as a contributory mechanism. Low-dose dopamine has a dilatory effect on the renal vasculature.

METHODS Sixty-six patients with mild or moderate CRF and/or DM undergoing coronary angiography were prospectively double-blindedly randomized, to either 120 ml/day of 0.9% saline plus dopamine 2 μg/kg/min (Dopamine group) or saline alone (Control group) for 48 h.

RESULTS Thirty-three Dopamine-treated (30 diabetics and 6 with CRF) and 33 Control (28 diabetics and 5 with CRF) patients were compared. Plasma creatinine (Cr) level increased in the Control group from 100.6 ± 5.2 before to 112.3 ± 8.0 μmol/liter within five days after angiography ($p = 0.003$), and in the Dopamine group from 100.3 ± 5.4 before to 117.5 ± 8.8 μmol/liter after angiography ($p = 0.0001$), respectively. There was no significant difference in the *change* of Cr level (ΔCr) between the two groups. However, in a subgroup of patients with peripheral vascular disease (PVD), ΔCr was −2.4 ± 2.3 in the Control group and 30.0 ± 12.0 μmol/liter in the Dopamine group ($p = 0.01$). No significant difference occurred in ΔCr between Control and Dopamine in subgroups of patients with preangiographic CRF or DM.

CONCLUSIONS Contrast material caused a small but significant increase in Cr blood level in high-risk patients. There is no advantage of dopamine over adequate hydration in patients with mild to moderate renal failure or DM undergoing coronary angiography. Dopamine should be avoided in patients with PVD exposed to contrast medium. (J Am Coll Cardiol 1999;34: 1682–8) © 1999 by the American College of Cardiology

Impairment of renal function following exposure to radiographic contrast materials is the third major cause of hospital-acquired renal dysfunction (1). It occurs most often in patients with chronic renal failure (CRF) (2) and/or diabetes mellitus (DM) (3–5) and contributes to morbidity and mortality. Decreased renal blood flow due to vasoconstriction contributes among other mechanisms to contrast-associated nephropathy (6). Various prophylactic measures have been suggested, but to date only appropriate hydration is generally accepted (7). "Renal-dose" (low-dose) dopamine has been proposed to prevent contrast nephropathy via a dilatory effect on the renal vasculature and increased renal plasma flow and glomerular filtration rate (8), direct effect on tubular function (9), and increase in cardiac output. We therefore performed a prospective double-blind randomized study on the effect of dopamine in high-risk patients undergoing coronary angiography.

PATIENTS AND METHODS

Patients with chronic renal failure (CRF) and/or diabetes mellitus (DM) who underwent coronary angiography were prospectively studied. Included were diabetic patients treated with insulin or oral hypoglycemic drugs and patients who had serum creatinine (Cr) concentration exceeding 130 μmol/liter. Excluded were patients with severe renal insufficiency (serum Cr >200 μmol/liter), acute coronary conditions (myocardial infarction or unstable angina associated with ST-T changes less then 48 h before the treatment

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
Cr = creatinine
CRF = chronic renal failure
DM = diabetes mellitus
PVD = peripheral vascular disease
Δ = the difference between preangiographic and postangiographic value

protocol), known intolerance to dopamine, allergy to contrast material or pheochromocytoma.

Study protocol. All patients received intravenous (IV) hydration for 8 to 12 h before and 36 to 48 h after angiography with 0.45% saline/5% dextrose, 100 ml/h or more according to urine output. In addition, the patients were randomly assigned to receive through another IV line either 120 ml/day of 0.9% saline plus dopamine 2 μg/kg/min (Dopamine group), or saline alone (Control group) for 48 h. The randomization scheme and marked vials with the solutions were prepared by the hospital pharmacist, leaving the treating physicians blinded to the treatment. Mannitol was not given to any of the studied patients.

The radiocontrast agent used in the two groups was nonionic low-osmolality (Ultravist 370-lopromide 0.769 g/ml, 370 mg Iodine/ml, courtesy of Schering). Diuretics (if signs of congestion ensued) and/or more IV fluids (if excessive diuresis and dehydration developed) were permitted at the discretion of the treating cardiologist. Diabetic patients received 8 U of short-acting insulin with each 1,000 ml of 0.45% saline/dextrose 5%, and subcutaneous insulin as needed according to glucose blood levels. Urine was collected before angiography, on the first, second, and fifth days after angiography, and upon discharge. Urine and blood samples were taken and examined for Cr, urea, glucose, calcium, phosphate, uric acid, Na^+ and K^+ levels upon termination of every urine collection. Radiocontrast nephropathy was defined as increase in serum Cr concentration of ≥40% of baseline after the injection of the radiocontrast agents.

Preangiographic and the highest postangiographic values of Cr and other biochemical and hematological values measured on the same day were compared in each group. The difference between the preangiographic and postangiographic values (Δ) of each parameter was calculated and compared between groups. Comparison of the Δ between the preangiographic and postangiographic values of each parameter was also performed between subgroups of patients with DM, high preangiographic Cr, or previous radiocontrast nephropathy. Informed consent was given by all patients, and the protocol was approved by the Institutional Review Board.

Statistical analysis. To assess the differences between the treatment and the control groups for continuous variables at study entry, the two-sample *t* test as well as the nonparametric Mann-Whitney test were applied. The chi-square test and the Fisher exact test were applied for assessing the difference between the treatment groups for qualitative variables. A repeated-measures analysis of variance (ANOVA) was performed on all biochemical values to verify group effect, time effect (change in value during the study based on preangiographic and highest postangiographic measurements) and the interaction between both. All p values were two-tailed, and statistical significance was declared if the observed significance level was 5% or less.

RESULTS

Sixty-eight patients entered the study protocol. In one Dopamine group patient the treatment protocol was stopped because of pulmonary edema, and in one Control group patient it was stopped because of cardiogenic shock and mechanical ventilation. This left 33 patients in the Dopamine group and 33 in the Control group. Demographic and clinical data, and basic biochemical and hematological data, were similar in both groups (Table 1). Patients from both groups were treated with similar drugs, including angiotensin-converting enzyme inhibitors, diuretics, beta-blockers, calcium channel blockers, hypoglycemics, nitrates, statins and fibrates.

In the Dopamine group, 23 patients were diabetic, 7 had both CRF and DM, and 3 had CRF (but not DM) due to nephrolithiasis or unknown etiology. In the Control group, 21 patients were diabetic, 7 had both CRF and DM, and 5 had CRF (but not DM) due to hypertension, previous contrast nephropathy, nephrolithiasis or unknown etiology.

The periangiographic complication rate was not different between the Dopamine and the Control groups: palpitations were reported by four Control and one Dopamine patient owing to sinus tachycardia or atrial premature beats (the patient receiving dopamine had sinus tachycardia). In all of them the protocol was stopped for 1 h and then renewed within 1 h with no further disturbances or complications. One patient from the Control group died during hospitalization. This patient underwent coronary artery bypass grafting (CABG) three years before hospitalization, and was catheterized because of unstable angina pectoris and recurrent pulmonary edema. Three days after diagnostic coronary angiography (which revealed severe triple-vessel disease and occluded grafts) he had an acute abdominal pain, the blood pressure fell, and the patient succumbed despite immediate fluid and cardiopulmonary resuscitation. Two patients from the Control group and one patient from the Dopamine group were treated with furosemide.

Six patients (2 Control and 4 Dopamine) developed radiocontrast nephropathy (defined as increase in Cr level by >40% of baseline). These patients had a higher Cr level on admission compared to the remaining patients ($p = 0.003$, Mann-Whitney), and reduced left ventricular function (5 of 6 patients, not statistically significant owing to small num-

Table 1. Demographic and Clinical Data

	Control (n = 33)	Dopamine (n = 33)	p Value
Age (yrs)	59.9 ± 1.7	62.9 ± 1.2	NS
Female	6/33 (18%)	9/33 (27%)	NS
Weight	71.8 ± 2.7	75.5 ± 2.3	NS
Amount of contrast material used (ml)	163.2 ± 13.2	173.8 ± 13.0	NS
Urine volume (per day) during study protocol	1979 ± 174	2106 ± 158	NS
Serum Cr level before angiography (μmol/liter)	100.6 ± 5.2	100.3 ± 5.4	NS
Chronic renal failure	6/33 (18%)	8/33 (24%)	NS
Previous exposure to contrast agents	18/33 (54%)	16/33 (48%)	NS
Previous radiocontrast nephropathy	2/33 (6%)	1/33 (3%)	NS
Diabetes mellitus (DM)	28 (79%)	30 (91%)	NS
Diabetic nephropathy: Proteinuria	9/24 (37.5%)	13/20 (65%)	NS
History of hypertension	14/33 (42%)	22/33 (67%)	NS
Systolic BP on admission	131.4 ± 3.9	141.5 ± 4.9	NS
Diastolic BP on admission	75.7 ± 1.7	79.1 ± 2.7	NS
Hyperlipidemia	16/33 (48%)	16/33 (48%)	NS
Smoking	14/33 (42.4%)	14/33 (42.4%)	NS
Ischemic heart disease	30/33 (90%)	30/33 (90%)	NS
Congestive heart failure	9/33 (27%)	12/33 (36%)	NS
Moderate-poor left ventricular function	17/26 (65%)	13/26 (50%)	NS
Peripheral vascular disease	7/33 (21%)	11/33 (33%)	NS

bers). Amount of contrast material and other clinical and laboratory data in these patients were similar to the rest of the patients.

Laboratory values before and after angiography. There were no significant differences between the two groups with regard to biochemical values including Cr and urea both before and after angiography, or to hematological values (Table 2).

Serum Cr levels before and on days 1, 2 and 5 after angiography were 100.5 ± 6.0, 99.6 ± 6.8, 102.7 ± 6.5 and 117.4 ± 10.6 (24 patients) μmol/liter in the Control group, and 100.2 ± 6.3, 102.5 ± 7.6, 110.3 ± 9.3 and 113.2 ± 10.9 (24 patients) μmol/liter in the Dopamine group.

Serum Cr level increased in the Control group from 100.6 ± 5.2 before, to the highest postangiographic levels of 112.3 ± 8.0 μmol/liter (p = 0.003), and in the Dopamine group from 100.3 ± 5.4 before, to the highest postangiographic levels of 117.5 ± 8.8 μmol/liter (p = 0.0001).

Table 2. Biochemical Values Before and After Catheterization

	Control (n = 33)	Dopamine (n = 33)	p Value
Before Catheterization			
Na (mmol/liter)	138.03 ± 0.49	137.51 ± 0.66	NS
K (mmol/liter)	4.16 ± 0.09	4.08 ± 0.09	NS
Urea (mmol/liter)	7.29 ± 0.54	6.85 ± 0.53	NS
Creatinine (μmol/liter)	100.57 ± 5.19	100.27 ± 5.41	NS
Uric acid (mmol/liter)	380.59 ± 28.66	376.45 ± 33.38	NS
Glucose (mmol/liter)	10.41 ± 1.15	10.00 ± 1.05	NS
Hemoglobin (g%)	13.24 ± 0.29	13.50 ± 0.27	NS
Hematocrit (%)	39.48 ± 0.89	39.94 ± 0.78	NS
After Catheterization			
Na (mmol/liter)	138.75 ± 0.58	138.75 ± 0.59	NS
K (mmol/liter)	4.27 ± 0.10	4.27 ± 0.07	NS
Urea (mmol/liter)	7.92 ± 0.82	7.55 ± 0.61	NS
Creatinine (μmol/liter)	112.27 ± 8.00	117.54 ± 8.80	NS
Uric acid (mmol/liter)	338.88 ± 20.32	401.56 ± 31.11	NS
Glucose (mmol/liter)	11.98 ± 1.09	12.13 ± 0.90	NS
Hemoglobin (g%)	12.9 ± 0.28	13.03 ± 0.28	NS
Hematocrit (%)	38.57 ± 0.89	38.62 ± 0.80	NS

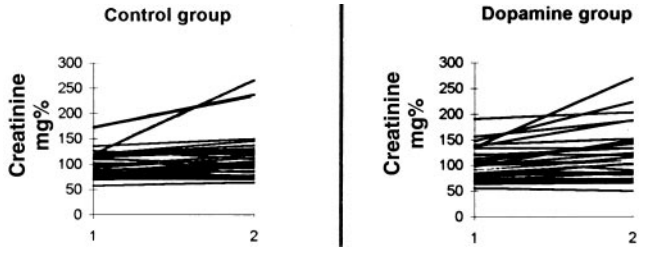

Figure 1. ΔCr (1, before; 2, after angiography) in the Control and Dopamine groups were similar (11.7 ± 4.9 and 19.2 ± 6.0, respectively, p = NS).

There was no difference in ΔCr between the two groups (11.7 ± 4.9 and 19.2 ± 6.0, respectively, p = NS) (Fig. 1). These results were confirmed in the repeated-measures ANOVA (Table 3). There was a significant "within group (time)" effect for Cr, urea, hemoglobin and hematocrit, and K, but no significant "between groups" or "interaction (Group*Time)" effect (Table 3).

In a subgroup of patients with peripheral vascular disease (PVD) (7 Control and 11 Dopamine patients), however, ΔCr was −2.4 ± 2.3 and 30.0 ± 12.0 μmol/liter in the Control and Dopamine groups, respectively ($p < 0.05$) (Fig. 2). There was no difference in other parameters between the patients with and without PVD. There was no significant difference in ΔCr or Δ of other examined parameters in another subgroup of patients (6 Control and 5 Dopamine) with high Cr (>110 μmol/liter) or high urea (>10 mmol/liter) before angiography. Neither was there a difference between Control and Dopamine patients in the subgroups of diabetic patients and patients with previous contrast nephropathy.

Urea levels increased in the Control and Dopamine groups from 7.3 ± 0.5 before to 7.9 ± 0.8 μmol/liter after angiography (p = NS), and from 6.8 ± 0.5 before to 7.5 ± 0.6 μmol/liter after angiography (p = 0.05), respectively. Δ-urea was not statistically different between the two groups. There was no difference in the Δ of other biochemical values between the two groups (Table 4).

Table 3. Two-Way Repeated-Measures ANOVA for the Biochemical Parameters

	Between-Groups Effect	Within-Groups (Time) Effect	Interaction (Group × Time) Effect
Na	p = 0.6166	p = 0.0934	p = 0.7231
K	p = 0.8297	p = 0.0410	p = 0.5069
Urea	p = 0.6332	p = 0.0338	p = 0.9140
Creatinine	p = 0.7900	p = 0.0001	p = 0.4325
Uric acid	p = 0.3880	p = 0.1440	p = 0.6092
Glucose	p = 0.8704	p = 0.0103	p = 0.4688
Hemoglobin	p = 0.6288	p = 0.0054	p = 0.6039
Hematocrit	p = 0.8665	p = 0.0053	p = 0.6081

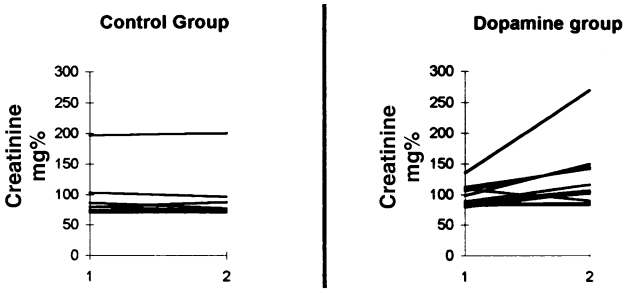

Figure 2. In patients with peripheral vascular disease, ΔCr (1, before; 2, after angiography) was −2.4 ± 2.3 μmol/liter in the Control group and 30.0 ± 12.0 μmol/liter in the Dopamine group, $p < 0.05$.

Of the 66 patients enrolled in the study, 14 patients (7 Dopamine and 7 Control) had both DM and Cr >110 μmol/liter before angiography. Creatinine level in these 14 patients was 134.4 ± 4.9 μmol/liter compared to 91.3 ± 3.3 μmol/liter in the other 52 patients (who had either CRF *or* DM but not both; $p < 0.0001$) before angiography, and it was 155.6 ± 10.1 and 103.9 ± 5.9 μmol/liter in the 14 and 52 patients, respectively (p = 0.0002), after angiography. The ΔCr was 21.3 ± 10.8 and 12.6 ± 3.4 μmol/liter in the 14 and 52 patients, respectively, p = 0.45 (NS). The 14 diabetic–CRF patients did not differ from the 52 patients in other clinical and biochemical parameters or in the amount of contrast medium used during the procedure.

Urea level was 9.9 ± 1.0 and 6.3 ± 0.3 mmol/liter in the 14 and 52 patients, respectively (p = 0.003), before angiography, and it was 10.8 ± 1.1 and 6.9 ± 0.5 mmol/liter in the 14 and 52 patients, respectively (p = 0.001), after angiography. The Δurea was 0.9 ± 0.7 and 0.6 ± 0.3 mmol/liter in the 14 and 52 patients, respectively (p = NS). There were no differences between the seven diabetic–CRF patients from the Dopamine group and the seven diabetic–CRF patients from the Control group in the Cr and urea levels before and after angiography, and in ΔCr and Δurea.

Table 4. The Change (Δ) in Biochemical Values Before and After Catheterization

	Control (n = 33)	Dopamine (n = 33)	p Value
Na (mmol/liter)	0.71 ± 0.59	1.09 ± 0.89	NS
K (mmol/liter)	0.11 ± 0.11	0.21 ± 0.10	NS
Urea (mmol/liter)	0.63 ± 0.51	0.70 ± 0.34	NS
Creatinine (μmol/liter)	11.69 ± 4.94	19.27 ± 6.04	NS
Uric acid (mmol/liter)	−20.12 ± 15.93	−10.00 ± 12.02	NS
Glucose (mmol/liter)	1.57 ± 1.28	2.79 ± 1.08	NS
Hemoglobin (g%)	−0.34 ± 0.20	−0.49 ± 0.21	NS
Hematocrit (%)	−0.97 ± 0.62	−1.39 ± 0.54	NS

JACC Vol. 34, No. 6, 1999
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DISCUSSION

The reported incidence of contrast nephropathy ranges from none to more than 50% (2,10,11), depending on whether the study was retrospective or prospective and on the presence or absence of risk factors or their combination (12). Preexisting renal insufficiency and DM are the most prevalent risk factors (12,13).

Mechanisms of contrast nephropathy. The mechanism of contrast nephrotoxicity is multifactorial. Contrast material stimulates the renin-angiotensin system (14) and blocks renal prostaglandin (15) with subsequent vasoconstriction and reduction in renal blood flow and glomerular filtration rate. Patients with diabetic nephropathy and CRF are at a higher risk owing to an increased vasoconstrictor state, both hormonal and structural (16). The addition of ischemic insult to an already damaged kidney may induce irreversible cell injury (17). Additional mechanisms include increased intrarenal pressure (18), a role for calcium (19), a change in red blood cells morphology (20), and shunting of blood flow from the renal cortex to the renal medulla (21). Other proposed mechanisms include altered glomerular permeability and selectivity, direct cell toxicity, tubule obstruction with proteinaceous casts or uric acid or oxalate crystals (22), immunologic injury (23), and medullary hypoxia causing injury to the thick ascending limb cells (24).

Prevention of contrast nephropathy is of a major interest. Patient selection is the most important imperative. In a nonrandomized study hydration dramatically reduced contrast nephropathy (7), and this may explain the decrease in incidence of contrast nephropathy in recent prospective studies. Prophylactic treatment with mannitol or furosemide was recommended by some investigators (25) and disproved in subsequent studies (26,27). Theophylline, a nonspecific adenosine receptor antagonist, has been suggested recently for prevention of contrast nephropathy (28).

Dopamine and contrast nephropathy in high-risk patients. Dopaminergic receptors of two distinct subtypes (DA1, DA2) are localized in different parts of the kidney. The hemodynamic actions of dopamine are dose-dependent. In low doses (0.5 to 2.5 μg/kg/min) dopamine stimulates dopaminergic receptors in the renal and mesenteric vasculature, resulting in selective vasodilation. Intermediate doses (2 to 5 μg/kg/min) favor beta-adrenergic stimulation, and at the highest doses (>5 μg/kg/min) alpha-adrenergic actions appear. Low dose ("renal dose") of dopamine increases renal plasma flow, glomerular filtration rate (GFR), and sodium excretion in subjects with normal renal function and with congestive heart failure (8,29,30) and may increase urine output in patients with acute oliguric renal failure who do not respond to furosemide (31).

Other mechanisms by which dopamine exerts its renal effects include an increase in cardiac output and a global increase in perfusion through stimulation of beta-adrenergic receptors, increased delivery of diuretics to the distal tubule, decrease in serum aldosterone concentrations, and direct effect on tubular function (9). Seriously ill patients who commonly decrease their renal function with a fall in urine output have been treated with dopamine in intensive care units (9,29). Although to date no controlled study has shown an improved clinical outcome to support this practice, treatment with low-dose dopamine has become routine in many units. Goligorski et al. (32) questioned 50 prominent nephrologists on their preferences and approaches in a patient with ATN (acute tubular necrosis). Of 36 who responded, 33% answered they would use renal-dose dopamine, 48% would use both renal-dose dopamine and loop diuretics, and 33% would add calcium channel blockers. The investigators concluded that although "today's therapeutic management of ATN is an art, rather than a science of medicine," their survey provides consensus therapeutic guidelines. This practice has extended to the postcoronary bypass and aneurysm repair patient in the intensive care unit setting, often extending the stay and increasing the cost of care with little evidence of patient benefit (33).

Many patients who undergo coronary angiography have CRF and/or DM. This large population could benefit from a renal protective effect. Because exposure to contrast material may result in prolonged vasoconstriction and a decline in the renal blood flow, administration of dopamine in a low dose was suggested to induce vasodilation and preserve renal function, and was examined in a few small series of patients undergoing diagnostic peripheral or visceral angiography. A preliminary study by Hall et al. (34) suggested such a protective effect. The study was prospective but not randomized and not blinded, and the patients were treated with dopamine and fluids for less than 24 h. Statistically significant difference was reached only in a subgroup of 11 patients with baseline Cr $\geq$177 μmol/liter who received dopamine. Hans et al. (35) found that dopamine administration during and 12 h after angiography induced a small improvement in Cr clearance compared to controls, but this was not sustained after day 1. In another study, low-dose dopamine did not prevent radiocontrast nephropathy in 15 patients compared to controls (5); dopamine, however, was given for only 2 h after catheterization, and all patients had Cr levels $\geq$1.8 mmol/liter.

In a previous study, intermediate-dose dopamine (5 μg/kg/min) given to diabetic patients for 6 h after coronary angiography suggested a protective effect from contrast nephropathy (36). Biochemical follow-up in that study was short (24 h routinely, and 72 h only when necessary). In the present study we used low-dose dopamine for 36 to 48 h after angiography, a longer period than in previous studies (2 to 24 h). All patients were followed for 48 h after the procedure, and 24 patients in each group were followed for five days. The average amount of contrast material used was 170 cc, higher than the amount (100 to 120 ml) used in previous studies, because many of our patients underwent both angiography and angioplasty at the same session.

Meticulous fluid balance was maintained, and similar urine volumes were measured in the two groups.

We found that contrast material caused a small but significant increase in Cr blood level in both Control and Dopamine groups. This small increase in Cr is similar to that found in other studies when patients were properly hydrated before and after injection of contrast material. The increase in Cr usually started on the second day after angiography and persisted until the fifth day. A comparison of the two groups showed that dopamine did not offer a significant protective renal effect, nor did it have a deleterious effect in the groups and in most subgroups studied. A subgroup of 14 especially high-risk patients who had both CRF and DM had significantly higher Cr and urea levels before angiography compared to the other 52 patients who had either CRF or DM. Creatinine and urea levels increased similarly after angiography in the 14 and 52 patients. Dopamine had neither protective nor deleterious effect in the subgroup of patients with both CRF and DM. Interestingly, uric acid blood level decreased in the Control group and increased in the Dopamine group (statistically insignificant). A similar finding of 6-hydroxydopamine-induced increase in brain tissue uric acid has been reported in the guinea pig (37). The reason for the change in uric acid in our study is not known, but tubular effect of dopamine cannot be excluded.

Effect of dopamine in patients with PVD. In a subgroup of patients with PVD (diagnosed by symptoms of intermittent claudication and noninvasive or invasive vascular investigations), the change in Cr level was significantly greater in dopamine-treated patients compared to the Control group. The reason for the deleterious effect of dopamine in PVD patients is not known. To our knowledge, the use of renal-dose dopamine has not previously been demonstrated to be clearly damaging in patients with PVD.

Reported dopamine complications include cardiac arrhythmias, myocardial ischemia and infarction, blunted hypoxic ventilatory drive, increased pulmonary shunt fraction in critically ill patients, digital necrosis (6,10,38), and possibly intestinal mucosal ischemia leading to translocation of bacterial products (12,39). In our study, the protocol treatment was well tolerated. The complication rate was similar or somewhat higher in the Control group and cannot be attributed to the dopamine. Moreover, although this report deals exclusively with patients undergoing coronary angiography, the general massage is applicable to any diabetic or mild renal failure patient receiving contrast medium.

In summary, contrast material caused a small but significant rise in serum Cr level in patients undergoing coronary angiography. Our findings do not support a renal protective role of dopamine for high-risk patients exposed to contrast material. Patients resistant to diuretic therapy (e.g., with heart failure) may be treated with low-dose dopamine if necessary in conjunction with watchful hydration. Low-dose dopamine infusions for renal prophylaxis should be avoided in patients with PVD until larger series of these patients are examined.

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