Lack of Renoprotective Effects of Dopamine and Furosemide during Cardiac Surgery

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Abstract. Because development of acute renal failure is one of the most potent predictors of outcome in cardiac surgery patients, the prevention of renal dysfunction is of utmost importance in perioperative care. In a double-blind randomized controlled trial, the effectiveness of dopamine or furosemide in prevention of renal impairment after cardiac surgery was evaluated. A total of 126 patients with preoperatively normal renal function undergoing elective cardiac surgery received a continuous infusion of either "renal-dose" dopamine (2 μg/kg per min) (group D), furosemide (0.5 μg/kg per min) (group F), or isotonic sodium chloride as placebo (group P), starting at the beginning of surgery and continuing for 48 h or until discharge from the intensive care unit, whichever came first. Renal function parameters and the maximal increase of serum creatinine above baseline value within 48 h ($\Delta Crea_{max}$) were determined. The increase in plasma creatinine was twice as high in group F as in groups D and P ($P < 0.01$). Acute renal injury (defined as $\Delta Crea_{max} > 0.5$ mg/dl) occurred more frequently in group F (six of 41 patients) than in group D (one of 42) and group P (zero of 40) ($P < 0.01$). (The difference between group D and group P was not significant.) Creatinine clearance was lower in group F ($P < 0.05$). Two patients in group F required renal replacement therapy. The mean volume of infused fluids, blood urea nitrogen, serum sodium, serum potassium, and osmolar- and free-water clearance was similar in all groups. It was shown that continuous infusion of dopamine for renal protection was ineffective and was not superior to placebo in preventing postoperative dysfunction after cardiac surgery. In contrast, continuous infusion of furosemide was associated with the highest rate of renal impairment. Thus, renal-dose dopamine is ineffective and furosemide is even detrimental in the protection of renal dysfunction after cardiac surgery.

Acute renal failure (ARF) develops in 5 to 30% of patients undergoing cardiac surgery, and it has been convincingly shown that renal dysfunction is associated with a more complicated clinical course and with an excessive mortality of up to 80% (1–4). In a recent analysis, Chertow *et al.* showed that development of ARF is one of the most potent predictors of outcome in cardiac surgery patients and that the adjusted odds ratio for death in patients with postoperative ARF was 7.8 (5). ARF was more potent in predicting outcome than were other postoperative complications such as infection, bleeding, myocardial infarction, or coma. Thus, identification of risk factors, tight monitoring of renal function, early institution of preventive measures, and adequate treatment of established ARF are some of the major tasks in perioperative care of patients undergoing cardiac surgery (6).

The pathophysiology of ARF in cardiac surgery patients includes a broad pattern of mechanisms, such as hemodynamic factors, especially intraoperative hypoperfusion of the kidney, effects of nephrotoxic drugs, the sequels of the systemic inflammatory reaction induced by cardiopulmonary bypass, and the interactions of blood components and artificial membranes (1,7,8). During cardiopulmonary bypass, the release of vasoconstrictor compounds, including catecholamines, vasopressin, and thromboxane, is enhanced, the renin-angiotensin system is activated, and renal perfusion is compromised (9). Moreover, cardiopulmonary bypass also induces tubular damage, as suggested by the persistence of microalbuminuria and of elevated urinary *N*-acetyl-β-D-glucosaminidase up to 6 d after cardiac surgery (10).

Although the concept of low-dose dopamine in the prevention of ARF remains controversial (11), "renal-dose" dopamine is still one of the most frequently used prophylactic measures to prevent renal dysfunction in postoperative patients. Clearly, the effects of dopamine on renal function are well documented, both in healthy subjects and in patients with various diseases. Potentially advantageous effects include an increase in renal blood flow via activation of dopaminergic receptors in the renal vasculature (12,13), an increase in GFR, and an increase in sodium and water excretion. Dopamine inhibits sodium reabsorption in the proximal tubule, in the medullary thick ascending limp of the loop of Henle, and in the cortical

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collecting duct, thus reducing renal oxygen consumption (14–17). In addition, dopamine increases the formation and the release of prostaglandin E_2, which dilates medullary vessels and also inhibits oxygen consumption in tubular cells (17). Whether a benefit can be derived from these effects on renal function in the prevention of postoperative ARF in the clinical situation has not been convincingly demonstrated.

An alternative approach to renal protection is the use of loop diuretics such as furosemide. Loop diuretics are clearly ineffective in established ARF (18,19) but, at least in the experimental situation, can exert a protective effect if given before a potential renal insult (20–22). Furosemide inhibits sodium reabsorption in the thick ascending limp of the loop of Henle, thus inducing a reduction in tubular oxygen consumption and improving renal tolerance to hypoxia (21). An increased excretion of renal vasodilatory prostaglandin E has been reported after intravenous administration of furosemide (23). By increasing tubular flow, dopamine and loop diuretics can both decrease the concentration of toxins such as myoglobin or hemoglobin in the tubular fluid and prevent the development of tubular obstruction (2). On the other hand, a renoprotective effect was not confirmed in other clinical situations, and renal vasodilation induced by furosemide might cause a maldistribution of blood flow within the kidney (24,25).

Despite this ongoing debate about the protective effects of low-dose dopamine and loop diuretics in the prevention of ARF, both substances continue to be broadly used in many institutions throughout the world. In a recent survey of the members of the European Workgroup of Cardiothoracic Intensivists, nine of 38 centers used low-dose dopamine perioperatively, 11 of 38 used furosemide continuously for renoprotection, and 34 of 38 used furosemide bolus injections when diuresis decreased to <0.5 ml/kg per h (39,000 cases of cardiac surgery per year).

Unfortunately, only a few placebo-controlled studies have been performed to resolve this ongoing controversy. Thus, in a placebo-controlled double-blind trial, we investigated whether continuous infusion of dopamine or furosemide can exert a renoprotective effect in the early postoperative period in patients after cardiac surgery.

Materials and Methods

Patients

In a placebo-controlled randomized double-blind trial, 132 adult patients who underwent elective cardiac surgery were screened. Six patients were excluded because of problems with urine collection. Thus, 126 patients (87 men and 39 women) with normal renal function (baseline serum creatinine value <2.0 mg/dl) were enrolled in the study. After randomization, three patients who required reoperation for bleeding complications were excluded from analysis. Figure 1 depicts the structure of the study trial. Patients' demographic data are given in Table 1. The study was approved by the ethics committee of the Medical Faculty of the University of Vienna. Written informed consent was obtained from each patient before inclusion. Patients were assigned by block randomization (sealed envelopes) to one of three groups on the morning of surgery (Figure 1).

Intervention

The study medications and placebo were provided in uniformly appearing 50-ml syringes blinded to attending physicians and nurses

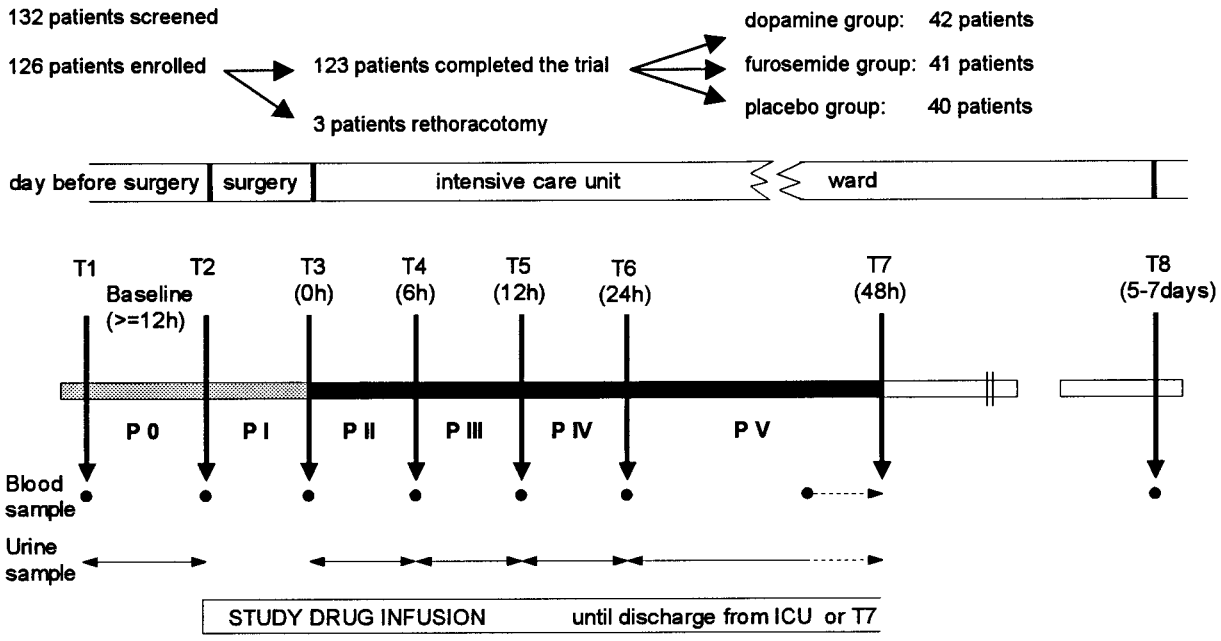

Figure 1. Trial profile and study protocol. T, sampling points; P, measurement periods. Blood samples were collected 1 d before surgery (T1), on the morning of surgery (T2), on admission (T3), at 6 h (T4), 12 h (T5), 24 h (T6), and 48 h after admission to the intensive care unit (ICU) or at discharge (T7), and at 5 to 7 d after surgery (T8). During P0 to PV, urine was collected simultaneously with blood samples. After induction of anesthesia (PI), infusion of the study drug was started via a central venous line. The study medication was continued until discharge of the patient from the ICU or until 48 h after surgery (T7), whichever came first.

Table 1. Patients' demographic data[a]

Characteristic	Dopamine	Furosemide	Placebo
No. of patients	42/(1)	41/(6)	40/(0)
Female/male	12/30	14/27	13/27
Age (yr)	63 ± 10	63 ± 10	65 ± 10
Weight (kg)	78 ± 10	75 ± 14	76 ± 12
Height (cm)	167 ± 28	169 ± 8	169 ± 9
Reoperation	1	2	2
Diabetes mellitus	5	12/(2)	10
Hypertension (RRsyst > 140 mmHg)	18	21/(3)	16
Parsonnet score (% predicted mortality)	8 ± 7	11 ± 9	10 ± 8
Left ventricular function			
LVF >50%	32	28/(4)	31
LVF <50%	10 /(1)	13/(2)	9
CABG	28	21/(3)	23
Aortic valve repair	6	4	7
Mitral valve repair	2	6	4
Combined CABG and valve repair	5 /(1)	6/(3)	4
Combined aortic and mitral valve repair	0	0	2
Other procedures	1	4	0

[a] Values are expressed as mean ± SD. ANOVA with Newman-Keuls test was used for multiple comparison. None of the variables were significantly different. Values in parentheses indicate the number of patients with acute renal injury. RRsyst, systolic arterial pressure; LVF, left ventricular function; CABG, coronary artery bypass graft.

involved in intra- and postoperative care. The syringes, labeled "renal protection," contained one of the following:

- Dopamine (Dopamine Giulini; Solvay Pharma, Hannover, Germany): 200 mg in 50 ml of 0.9% sodium chloride (group D);
- Furosemide (Lasix; Hoechst AG, Frankfurt am Main, Germany): 50 mg in 50 ml of 0.9% sodium chloride (group F); or
- Placebo: 50 ml of 0.9% sodium chloride (Fresenius Pharma, Graz, Austria) (group P).

The infusion rate was 1.5 to 3 ml/h, depending on body weight, to yield 2 μg/kg per min dopamine or 0.5 μg/kg per min furosemide. After induction of anesthesia, infusion of the study drug was started via a central venous line using a motor-driven syringe (Perfusor Secura FT; Braun Medical, Germany). The study medication was continued until discharge of the patient from the intensive care unit (ICU) or 48 h after surgery, whichever came first. Study drug infusion was discontinued when urine output was >2000 ml in 4 h.

Data Acquisition

The primary end point was the change in serum creatinine values over time (2). Secondary end points were the occurrence of acute renal injury (ARI), changes in creatinine clearance over time, urine output per hour, volume intake per hour, serum sodium, serum potassium, other parameters of renal function (see below), necessity for hemodialysis or hemofiltration, and hospital mortality rate. ARI was defined as an increase in serum creatinine values of >0.5 mg/dl between baseline value and the maximum value within 48 h ($\Delta Crea_{max}$) (24).

Perioperative Management

Patients were premedicated with midazolam. All patients received standard general anesthesia with midazolam, etomidate, fentanyl, and pancuronium. In all patients a central venous catheter, and in two-thirds of the patients a Swan-Ganz catheter, was inserted for monitoring of hydration state. Ringer's aspartate (Fresenius Pharma) was infused during induction of anesthesia, and Ringer's lactate or 6% hydroxy-ethyl-starch (Fresenius Pharma) was infused if required thereafter. Patients were ventilated with oxygen in air; ventilation was set to a tidal volume of 8 ml/kg, a respiratory rate of 12/min, and a positive end-expiratory pressure of 5 mmHg.

The cardiopulmonary bypass circuit consisted of a hollow-fiber oxygenator (Bard HF 5701; C. R. Bard, Inc., Havorhill, MA) primed with Ringer's lactate (2000 ml), mannitol (20 g), heparin (8000 IU) (Immuno, Vienna, Austria), and aprotinin (1,000,000 KIU) (Trasylol; Bayer Pharma, Leverkusen, Germany). Flow during cardiopulmonary bypass was maintained at 2.5 L/min per m^2, and mild hypothermia (30 to 32°C) was employed. Myocardial protection consisted of cold, intermittent blood cardioplegia administered via a combination anterograde and retrograde technique. Hematocrit was kept at >20%, with donor blood if necessary. BP was maintained at >50 mmHg by intermittent administration of phenylephrine. After weaning from cardiopulmonary bypass, mean arterial pressure was maintained above 60 mmHg with fluid loading and appropriate vasoactive drugs (epinephrine). Treatment in the ICU was defined by institutional standards.

Blood and Urine Samples

The flow chart of the study protocol is shown in Figure 1. After preoperative urine collection (period P0) and urine volume measurement, 10 ml of urine was collected for analysis. Urine sodium, urine potassium, urine creatinine, urine urea nitrogen, and urine osmolarity were determined. After inclusion of the patient in the study, blood was sampled simultaneously with the preoperative urine (time points T1 and T2) to determine blood urea nitrogen, serum creatinine, serum sodium, serum potassium, and serum osmolarity. After surgery, blood samples were collected in the ICU at five time points (T3 to T7), and urine was collected during four periods (PII to PV). At 5 to 7 d after

surgery (T8), only blood urea nitrogen, serum creatinine, serum sodium, and serum potassium levels were determined. Creatinine clearance, osmolar clearance, free-water clearance, and fractional excretion of sodium (FE_{Na}) were calculated by standard formulas:

$$\text{Creatinine clearance (ml/min)} = \text{Urine creatinine} \times \text{Urine output/Serum creatinine}$$

$$\text{Osmolar clearance (ml/h)} = \text{Urine osmolarity} \times \text{Urine output/Serum osmolarity}$$

$$\text{Free-water clearance (ml/h)} = \text{Osmolar clearance} - \text{Urine output}$$

$$FE_{Na}\ (\%) = \text{Urine sodium} \times \text{Serum creatinine/Serum sodium} \times \text{Urine creatinine}$$

Statistical Analyses

Data are expressed as mean ± SD. Statistical analysis was performed based on intention to treat, with the use of a commercial package (SAS 6.12, 1996, Cary, NC). Continuous demographic data were analyzed using one-way ANOVA with the Newman-Keuls test for multiple comparisons. Categorical data were analyzed using χ^2 analysis. $\Delta Crea_{max}$ was analyzed by ANOVA with one grouping factor, the three randomized treatments; covariates were creatinine value during the baseline period, duration of extracorporeal circulation time and aortic cross-clamping time, furosemide bolus injection, left ventricular function, diabetes, hypertension, the need for inotropic support, and age over 70 yr. We used a backward elimination technique, and only covariates with an $F > 2$ remained in the final model. The study power was 80% with a P value <0.05 to detect a difference of 0.14 mg/dl in $\Delta Crea_{max}$ between treatment groups. Comparisons between the three treatments were performed only when the treatment factor was significant in the ANOVA (SAS 6.12, GLM, Type III SS). Changes of study variables over time were analyzed by a similar technique. A P value <0.05 was considered statistically significant.

Results

A total of 126 patients, 42 patients in each group, were initially enrolled in the study. Left ventricular function and indications for surgery were similar in all three study groups. Three patients were excluded after randomization. One patient in group F and two in group P required reoperation because of bleeding, leaving 42 patients in group D, 41 in group F, and 40 in group P. None of the three patients who were excluded developed ARI. Demographic perioperative data and outcome in the three study groups are given in Table 2.

The study drug was discontinued in two patients in group D and in three patients in group F because urinary output exceeded 2000 ml within the first 4 h. Furosemide bolus injections (20 mg) within 48 h were considered clinically necessary (decrease in urine output to <0.5 ml/kg per h) in 16 of 42 patients in group D, eight of 41 in group F, and 20 of 40 in group P ($P < 0.02$) (Table 2). In group F, two patients died of myocardial infarction, and two patients died of a mesenteric artery thrombosis. In group P, one patient died from severe sepsis. There were no deaths in group D.

The time course of changes in serum creatinine (Table 3) showed a significant increase in group F that started in PII and was significant during PIII and PIV. $\Delta Crea_{max}$ was more pronounced in group F than in both of the other groups ($P < 0.001$) (Figure 2), and creatinine clearance was lower in group F than in both of the other groups during PII to PIV ($P < 0.05$ for PIV). The frequency of ARI was significantly higher in group F (six of 41) than in group D (one of 42) and group P (zero of 40) ($P < 0.01$). Renal replacement therapy became necessary in two patients, both in group F.

The rise in serum creatinine in group F was preceded by an increase in FE_{Na} and an increase in urine output during PII and PIII (Table 3). During PV, an increase in serum creatinine occurred in all groups. Urinary output was compensated by intravenous fluids during all periods.

In a regression analysis to identify factors contributing to the change of serum creatinine, the duration of cardiopulmonary

Table 2. Patients' perioperative characteristics[a]

Parameter	Dopamine	Furosemide	Placebo	*P* Value
No. of patients	42/(1)	41/(6)	40/(0)	
CPB time (min)	109 ± 36	119 ± 70	103 ± 30	
Aortic cross-clamp time (min)	71 ± 31	72 ± 33	63 ± 21	
Urine output during surgery (ml)	1220 ± 620	1390 ± 810	920 ± 550	<0.01[b]
Fluids during surgery (ml)	6100 ± 1750	6160 ± 1930	6050 ± 1580	
Catecholamines	9/(1)	10/(3)	5	
Furosemide injection	16/(1)	8/(4)	20	<0.02[b,c]
Total length of ICU stay (days)	2.2 ± 5.2	1.7 ± 2	2.4 ± 6	
Total length of hospital stay (days)	13.9 ± 11.3	16.8 ± 34	11.9 ± 7	
Hospital mortality rate	0	4/(2)	1	

[a] Values are expressed as mean ± SD. ANOVA with Newman-Keuls test was used for multiple comparison. Values in parentheses indicate the number of patients with acute renal injury. CPB, cardiopulmonary bypass; ICU, intensive care unit.
[b] Furosemide compared with placebo.
[c] Furosemide compared with dopamine.

Table 3. Renal function, hemodynamic measures, and fluid intake/output during the perioperative study periods[a]

Period/ Timepoint and Group[b]	Serum Creatinine (mg/dl)	Serum BUN (mg/dl)	FE_{Na} (%)	Creatinine Clearance (ml/min)	Urine (ml/h)	Fluid Intake (ml/h)	MAP (mmHg)	PCWP (mmHg)	CVP (mmHg)
P0									
D	0.98 ± 0.23	16.2 ± 6.1	0.80 ± 0.56	101 ± 35	72 ± 36		89 ± 22		
F	1.00 ± 0.22	18.2 ± 8.1	0.96 ± 0.67	88 ± 38	67 ± 33		90 ± 24		
P	0.96 ± 0.23	17.3 ± 5.9	0.95 ± 0.53	99 ± 47	74 ± 43		86 ± 20		
PII									
D	0.95 ± 0.22	15.3 ± 6.2	3.91 ± 2.38	91 ± 31	260 ± 157	277 ± 195	77 ± 7	13 ± 2	10 ± 3
F	1.07 ± 0.24[c]	17.1 ± 6.9	6.85 ± 4.35[c,d]	76 ± 41	335 ± 151[d]	326 ± 203	81 ± 11	13 ± 2	10 ± 3
P	0.97 ± 0.21	15.8 ± 6.0	3.48 ± 3.24	106 ± 64	224 ± 154	314 ± 208	81 ± 10	12 ± 1	10 ± 3
PIII									
D	1.01 ± 0.24	15.8 ± 5.8	1.46 ± 1.24	98 ± 40	108 ± 61	142 ± 106	74 ± 10	12 ± 2	10 ± 3
F	1.13 ± 0.30[c,d]	17.7 ± 7.8	2.96 ± 1.92[c,d]	81 ± 50	150 ± 59[c,d]	173 ± 106	75 ± 10	12 ± 5	10 ± 3
P	1.02 ± 0.25	15.9 ± 5.7	1.78 ± 1.42	109 ± 55	116 ± 80	197 ± 171	78 ± 12	11 ± 1	10 ± 3
PIV									
D	1.02 ± 0.25	19.8 ± 15.4	1.18 ± 0.99	119 ± 64	94 ± 49	116 ± 83	78 ± 9	13 ± 2	11 ± 3
F	1.25 ± 0.36[c,d]	20.9 ± 9.2	2.46 ± 2.08	70 ± 40[c,d]	99 ± 44	117 ± 62	77 ± 9	12 ± 5	10 ± 3
P	1.01 ± 0.25	16.1 ± 7.4	1.52 ± 1.33	112 ± 56	97 ± 52	111 ± 60	80 ± 10	11 ± 2	10 ± 3
PV									
D	1.21 ± 0.45	25.7 ± 8.1	0.82 ± 0.48	72 ± 35	94 ± 12	143 ± 12	69 ± 2	12 ± 2	7 ± 8
F	1.40 ± 0.75	23.7 ± 10.0	2.33 ± 1.54	96 ± 70	120 ± 75	168 ± 82	82 ± 14	12 ± 5	12 ± 3
P	1.10 ± 0.36	23.7 ± 10.7	1.49 ± 1.13	95 ± 54	104 ± 19	121 ± 19	65 ± 0	12 ± 2	10 ± 0
T8									
D	1.01 ± 0.23	21.3 ± 9.5							
F	1.04 ± 0.38	23.0 ± 11.3							
P	1.03 ± 0.32	22.8 ± 10.5							

[a] Values are expressed as mean ± SD. ANOVA with Newman-Keuls test was used for multiple comparisons. BUN, blood urea nitrogen; CVP, central venous pressure; FE_{Na}, fractional excretion of sodium; MAP, mean arterial pressure; PCWP, pulmonary artery wedge pressure.

[b] P0, perioperative; PII, 0 to 6 h in intensive care unit (ICU); PIII, 6 to 12 h in ICU; PIV, 12 to 24 h in ICU; PV, 24 to 48 h in ICU; T8, 1 wk after surgery. D, dopamine; F, furosemide; P, placebo.

[c] $P < 0.05$, furosemide compared with dopamine.

[d] $P < 0.05$, furosemide compared with placebo.

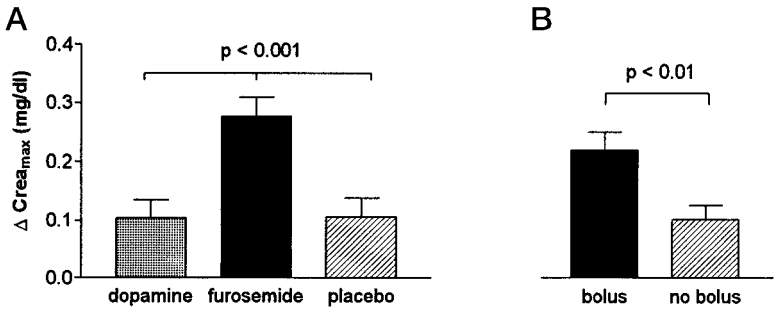

Figure 2. (A) Maximal increase of serum creatinine above baseline value within 48 h ($\Delta Crea_{max}$) in the three study groups receiving either dopamine, furosemide, or placebo. (B) $\Delta Crea_{max}$ in patients receiving additional bolus injections of furosemide. Values are expressed as mean ± SD. ANOVA with Newman-Keuls test was used for multiple comparisons.

bypass was significant during PII, and the use of additional furosemide bolus injections became significant in PV.

$\Delta Crea_{max}$ was increased in patients who received additional furosemide injections, regardless of the treatment group ($P <$ 0.01). $\Delta Crea_{max}$ was directly correlated with duration of cardiopulmonary bypass (coefficient ± SEM; 0.22 ± 0.04 mg · dl^{-1} · h^{-1}) ($P < 0.001$), but was negatively correlated with duration of aortic cross-clamp time (−0.19 ± 0.07 mg · dl^{-1} ·

h^{-1}) ($P < 0.01$). For the average of our study population, the effect of cardiopulmonary bypass and aortic cross-clamp time on $\Delta Crea_{max}$ was about 0.02 mg/dl.

To assess any potential effect of cardiopulmonary bypass time on these findings, we separately analyzed all patients with a cardiopulmonary bypass time greater than 2 h. The distribution was comparable between groups: group D, 14 of 42; group F, 14 of 41; and group P, 10 of 40. Restricting the analysis to the patients with prolonged cardiopulmonary bypass, results were similar to those for the whole study population, significant factors being the study drug ($P < 0.01$), duration of cardiopulmonary bypass ($P < 0.001$), and furosemide bolus injection ($P < 0.01$). However, $\Delta Crea_{max}$ was not dependent on the use of catecholamines, left ventricular function, history of hypertension, diabetes mellitus, or age.

The only additional measured parameters that showed a significant difference between groups were FE_{Na} and urinary output (Table 3). During all periods, there were no differences between the groups with regard to volume intake per hour, serum sodium, serum potassium, blood urea nitrogen, or osmolar- and free-water clearance (Table 3).

Discussion

Continuous infusion of renal-dose dopamine failed to exert any advantage over placebo for renal protection in well hydrated patients after cardiac surgery. Continuous infusion of furosemide not only was ineffective, but was even detrimental and induced renal dysfunction. Thus, these two widely used pharmacologic interventions for preventing ARF are no longer indicated in the perioperative management of patients undergoing cardiac surgery.

The controversy surrounding the effectiveness of dopamine and/or furosemide in the prevention of postoperative ARF is not new (18,24,26–30). Nevertheless, both substances continue to be widely used in the prevention of perioperative renal injury (12,13,21,26,31). The main effects of furosemide include inhibition of sodium reabsorption and promotion of diuresis, but also vasodilation of cortical vessels. Inhibition of sodium reabsorption mitigates tubular oxygen consumption and thus might enhance renal tolerance to hypoperfusion (21). Augmentation of tubular flow is also considered to be advantageous in several types of ARF by decreasing the tubular concentration of toxins and preventing tubular obstruction (2).

As expected, furosemide significantly augmented diuresis during the perioperative period. Although the overall incidence of renal dysfunction observed in our study was similar to that in other series (1,3,5), plasma creatinine was higher, creatinine clearance was lower, and ARI occurred predominantly in the group receiving furosemide. The simultaneous increase in FE_{Na} suggests that sodium reabsorption was effectively inhibited. The negative effects of furosemide on renal function are illustrated by the fact that in subjects in whom additional injections of furosemide were necessary, a significant increase in serum creatinine became apparent in all patient groups.

Thus, in contrast to findings from several animal experiments in which furosemide prevented the development of tubular lesions in isolated rat kidneys during a pulsatile flow perfusion (21), we not only failed to demonstrate a renoprotective effect of furosemide, but even observed the contrary, an impairment of renal function by this loop diuretic. Similar conclusions were drawn in a study in patients undergoing cardiac angiography who received furosemide or mannitol, compared with placebo, to prevent radiocontrast-induced renal damage (24). In that study, as in ours, an increase in serum creatinine values was most pronounced in the group receiving furosemide, and it was concluded that adequate hydration is more effective than pharmacologic interventions in preventing ARF. Moreover, in the case of established ARF, it is well documented that furosemide does not exert any beneficial effects (19).

The negative effect of furosemide on renal function cannot be explained by induction of hypovolemia and a concomitant decrease in renal perfusion as a consequence of high urinary volume. All of our patients were well hydrated and had continuously monitored volume status and filling pressures. Alternatively, neurohumoral activation has been reported with furosemide, and transient rises in BP have been shown to result from activation of the sympathetic and renin-angiotensin systems (32). This can increase peripheral vascular resistance, left ventricular afterload, and cardiac work and can mediate a fall in cardiac output, thus at least potentially aggravating myocardial ischemia (33–35). Moreover, induction of maldistribution of renal blood flow with diversion of medullary perfusion by a decrease in cortical vascular resistance might promote tubular dysfunction (24).

Dopamine exerts well characterized effects on renal functions mediated by both vascular and tubular mechanisms (36–38), resulting in an increase in renal plasma flow and creatinine clearance and a stimulation of natriuresis and urinary flow. These at least potentially advantageous actions have been documented both in healthy subjects and in patients with various disease processes such as cardiac failure, septicemia, or liver disease (36,37,39). In several controlled trials with dopamine, improvement of several parameters of renal function (although not improved survival) has been reported (40–43). Even recently, dopamine administration was recommended for surgery patients (44).

Nevertheless, at least for the perioperative period, few data supporting the use of dopamine are available. Low-dose dopamine has been shown to reverse periods of oliguria after cardiopulmonary bypass in an uncontrolled study (36) and to induce diuresis and natriuresis in well hydrated patients compared with a group in whom fluids were restricted (16). However, in patients with normal renal function undergoing coronary revascularization, low-dose dopamine had no beneficial effect on urine flow, creatinine clearance, or incidence of transient renal impairment (45). After major vascular surgery, dopamine (3 μg/kg per min) was administered to 15 patients with a postoperative urinary output of $<$0.5 ml/kg per h (44). Three of these patients did not increase urinary output after dopamine infusion, and two of the three were treated with additional furosemide bolus injections and developed renal insufficiency.

In our study, the increase in urine output and FE_{Na} after

cardiopulmonary bypass was nearly identical in group D and group P, as were the changes in renal function; thus, we could not identify a protective effect of dopamine on renal function. Our results are in accordance with several recent reports arguing against the routine use of dopamine for renal protection (2,11,46).

At least potentially, the beneficial effects of dopamine might be masked by untoward actions, such as the blockade of the tubuloglomerular feedback mechanism or maldistribution of intrarenal blood flow (26). Moreover, in the absence of clinically advantageous actions, undesired side effects such as induction of tachyarrhythmia (47), increase in myocardial oxygen consumption (48), inhibitory effects on minute ventilation and oxygen saturation (49,50), and suppression of circulating pituitary-dependent hormones should be taken into consideration (51).

In conclusion, this prospective randomized placebo-controlled trial evaluating the renal protective effect of dopamine or furosemide in cardiac surgery patients did not demonstrate any benefit in favor of these widely used drugs. Our results rather suggest an increased risk for renal impairment in patients receiving furosemide. Neither of these pharmacologic agents should be used in the prevention of development of perioperative ARF in cardiac surgery patients. These results again underscore the importance of maintaining adequate hydration for the prevention of ARF (24).

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