The Journal of International Medical Research
2004; 32: 109 – 117

Effects of Dopexamine on Rat Cardiorenal Functions During Lipopolysaccharide-induced Experimental Sepsis

BB Yelken[1], ES Görenek[1], K Uzuner[2], Y Aydin[2] and C Elmas[3]

[1]Department of Anesthesiology and ICU, [2]Department of Physiology, Medical Faculty, Osmangazi University, Eskisehir, Turkey; [3]Department of Anaesthesiology, Hospital of Horgen, Switzerland

We aimed to test the protective effect of dopexamine on renal function and systemic haemodynamics in rats with induced sepsis. Female Sprague-Dawley rats were randomized into three equal groups: group 1 (control, received 3% creatinine throughout the experiment); group 2 (sepsis, received 3% creatinine and *Escherichia coli* lipopolysaccharide [LPS] endotoxin [8 mg/kg per h]); and group 3 (sepsis plus dopexamine, received 3% creatinine, *E. coli* LPS and dopexamine [1 µg/kg per min]). Time-adjusted heart rate, systolic, diastolic and mean arterial pressures, urine volume and glomerular filtration rate (from creatinine clearance) were recorded. After bacterial infusion heart rate increased and mean arterial pressure decreased; the fall in mean arterial pressure was less pronounced with dopexamine (group 3) than without (group 2). Dopexamine also induced significant and moderate increases in urine volume and heart rate, respectively. We concluded that dopexamine has some positive inotropic–chronotropic effects and induces favourable responses in renal function.

KEY WORDS: Dopexamine; Sepsis; Acute renal failure; Urinary volume; Glomerular filtration rate; Blood pressure

Introduction

Sepsis, especially septic shock, is one of the main causes of acute renal failure (ARF). The prevalence of ARF in sepsis ranges from 9% to 40%.[1] Hypotension, decreased renal blood flow, nephrotoxic effects of endotoxins and the cellular mediators and elevated efferent sympathetic nerve activity may contribute to renal excretory function failure during sepsis.[2,3] Thus the maintenance of renal perfusion and function is also an important goal in septic shock therapy.

Dopaminergic stimulation can produce renal vasodilation and enhances renal blood flow and glomerular filtration rate, inducing an increase in diuresis and natriuresis.[4] The renal vasodilatory properties of dopamine have long been known and the drug has been used frequently to preserve renal function in patients at an increased risk of developing ARF.[5] The effects of dopamine on

renal haemodynamics and excretory function seem obvious, but its effects on renal blood flow have been questioned in sepsis.[6,7] Dobutamine, a heart stimulating drug with similarities to dopamine, has no significant effects on renal blood flow in humans and experimental animals.[8 – 10]

Dopexamine is a synthetic catecholamine, which has a unique combination of marked β-adrenergic and dopaminergic effects without any α-adrenergic effects. Dopexamine stimulates β_2-adrenoreceptors and DA_1 and DA_2 receptors and may restore blood flow to an organ because of its vasodilating properties.[10] It is theorized that dopexamine may increase hepatosplanchnic perfusion and potentially mitigate some of the untoward sequelae of sepsis and septic shock, but data concerning effects of dopaminergic agents on renal function in septic states remain controversial. Palsson *et al.*[3] studied renal effects of dopexamine in an experimental model of sepsis in rats and concluded that the renal excretory function was improved with dopexamine. In contrast, Levy *et al.*[11] demonstrated in human septic shock that 1 µg/kg per min of dopexamine had no impact on renal function.

The aims of the present study were:

(i) To study the effects of an infusion of *Escherichia coli* lipopolysaccharide (LPS) endotoxin on systemic haemodynamics and renal function in rats;
(ii) To investigate the effects of dopexamine on haemodynamics and renal function in this sepsis model.

Materials and methods

The institution's Animal Studies Committee gave approval for the study.

ANIMALS

Thirty female Sprague-Dawley rats (250 – 300 g) were maintained on standard rat food and water *ad libitum*. The rats were deprived of food overnight before the experiment.

EXPERIMENTAL DESIGN

The rats were divided into three groups. Rats in group 1 (n = 10) were time-adjusted controls and only received 3% creatinine in saline. They received an equivalent volume of saline in the endotoxin and dopexamine periods. In group 2 (n = 10), the rats received a solution of 3% creatinine and *E. coli* endotoxin suspended in saline to determine changes in renal function. An equivalent volume of saline in the dopexamine period was given. Experiments in group 3 (n = 10) were designed to determine the effect of dopexamine on *E. coli*-induced changes in blood pressure, heart rate, urine volume and glomerular filtration. The rats received a solution of 3% creatinine plus infusions of *E. coli* endotoxin and dopexamine in subsequent time periods (Fig. 1).

SURGICAL PROCEDURE

The rats were anaesthetized intraperitoneally with ketamine hydrochloride 50 mg/kg (50 mg/ml Ketalar®, Parke-Davis, Istanbul, Turkey) and xylazine hydrochloride 10 mg/kg (23.32 mg/ml Rompun® 2%, Bayer, Istanbul, Turkey). Rectal temperature was maintained at 37 ± 0.5 °C with a radiant heat lamp connected to a temperature controller. The left femoral vein and artery were cannulated with polyethylene (PE)-50 tubing. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured with a pressure transducer (Biopac Systems, Inc., Santa Barbara, CA, USA) and monitored, along with heart rate, using a data acquisition system (MP 100 Biopac Systems, Inc., Santa Barbara, CA, USA). Mean arterial pressure (MAP) was calculated using the formula (SBP + [2 × DBP])/3. Immediately after catheterizing the femoral vein, 3% creatinine in saline was infused at a rate of 25 µl/min and maintained

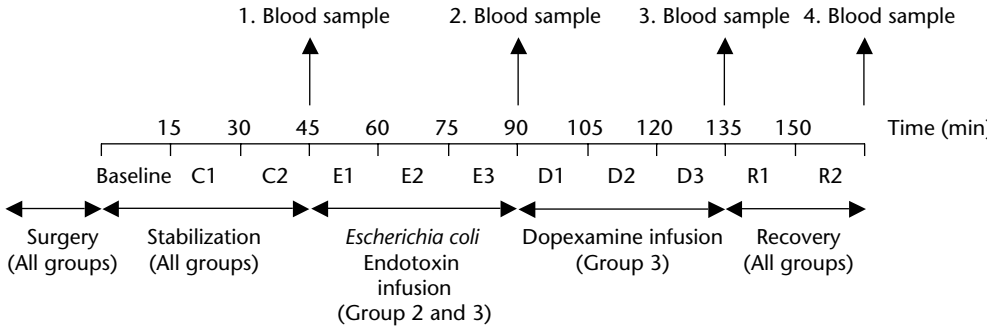


FIGURE 1: Schematic representation of study protocol, indicating the different treatments the groups received and the samples taken during the different time periods

throughout the experiment. The total infusion rate was adjusted to give a urine flow rate plus insensible fluid loss of around 25 µl/min. The bladder was cannulated with PE-100 tubing via an abdominal incision. The rat was positioned on its side and urine allowed to flow, by gravity, into collection vials located below the level of the animal.

POST-SURGICAL EXPERIMENTAL PROCEDURES

After surgery and a 30-min stabilization period, there were two 15-min baseline clearance periods (C1 and C2, Fig. 1). During this period, urine volume was measured over the 15-min period, blood pressures measured every 15 min and a 0.2 ml arterial blood sample was taken between C1 and C2 from all rats. In group 1, a saline infusion was continued until the time-adjusted protocols in groups 2 and 3 were completed. In groups 2 and 3, an intravenous infusion of *E. coli* LPS endotoxin (serotype 0127:B8, 100 mg, Sigma, St. Louis, MO, USA) was initiated following the stabilization period and baseline clearances for 45 min at a rate of 8 mg/kg per h. During the infusion of *E. coli* endotoxin, three 15-min clearance periods (E1, E2 and E3) occurred and a 0.2 ml arterial blood sample collected after E3. In group 2, the rats then received saline to allow for time adjustment with group 3. In group 3, dopexamine (1 µg/kg per min) was infused for 30 min after the *E. coli* endotoxin infusion. During infusion of dopexamine two 15-min clearances were collected (D1 and D2) and a 0.2 ml arterial blood sample taken after D2. After dopexamine infusion was completed, saline infusion was continued for 30 min and two 15-min clearances (recovery periods R1 and R2) and a 0.2 ml arterial blood sample were collected (Fig. 1).

On completion of the clearance periods, the rats were killed with a lethal injection of thiopental sodium.

MEASUREMENTS AND CALCULATIONS

Urine volumes were determined gravimetrically. Creatinine concentrations in urine and plasma were determined by the method of Folin and Wu.[12] Glomerular filtration rate (ml/min) was calculated from creatinine clearance as: (urine concentration/plasma concentration) × urine volume.

STATISTICAL ANALYSIS

Data were expressed as mean ± SE. We used analysis of variance (ANOVA) for between and within group comparisons. Duncan's multiple range test was used for *post-hoc* analysis when appropriate. $P < 0.05$ was considered significant.

Results

HAEMODYNAMIC EFFECTS

Baseline values for heart rate, and the effects of *E. coli* infusion (induction of sepsis) and dopexamine after sepsis are shown in Table 1. Heart rate before *E. coli* infusion was not statistically different between groups. In group 2 and group 3, heart rate increased significantly ($P < 0.05$) after *E. coli* LPS infusion compared with group 1 and baseline values.

In the post-*E. coli* LPS-treatment period systolic, diastolic and mean arterial pressure were significantly ($P < 0.05$) decreased in groups 2 and 3 compared with baseline and controls (group 1). This decrease was significantly ($P < 0.05$) less in group 3 compared with group 2 (Table 1; Fig. 2).

RENAL EFFECTS

In all three groups, urine volume decreased significantly ($P < 0.05$) from baseline values (15 min). Within 30 – 45 min of endotoxin administration, urine volume further decreased significantly ($P < 0.05$) in groups 2 and 3 compared with baseline and controls (group 1). An increase in urine volume occurred in group 2 and 3 rats 30 – 45 min after saline or dopexamine infusion, respectively, and urine volume did not differ significantly between groups at the end of the experiment (Fig. 3).

In group 1, glomerular filtration rate remained unchanged throughout the study. During the first 15 min of endotoxin infusion in groups 2 and 3, the glomerular filtration rate decreased significantly ($P < 0.05$). The

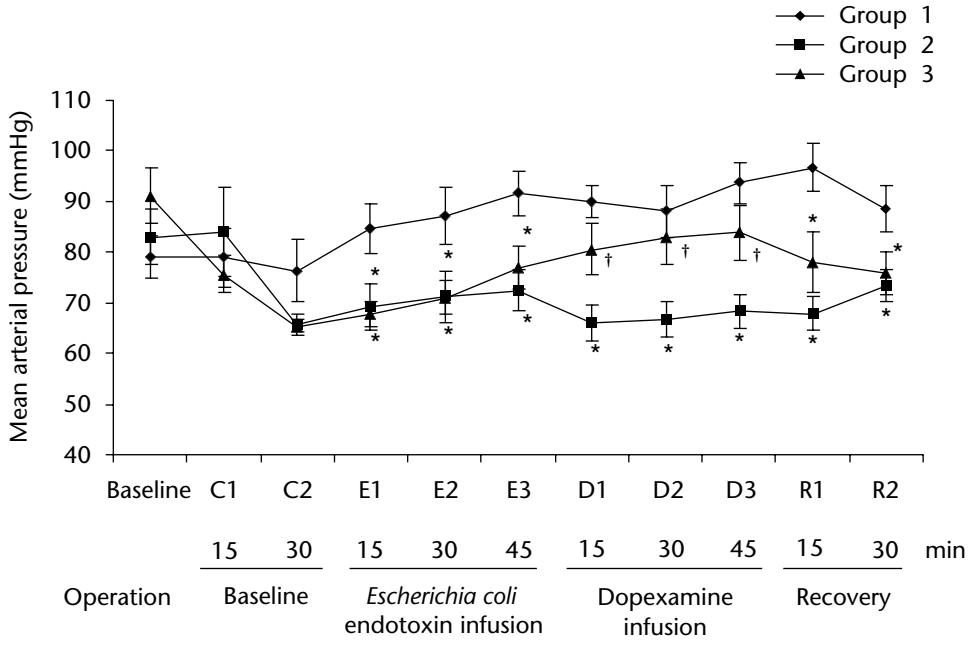


FIGURE 2: Mean arterial pressure (± SE) in the three groups of rats ($n = 10$ each). Group 1 (control group) only received 3% creatinine and saline infusions; group 2 (sepsis group) received an *Escherichia coli* lipopolysaccharide (LPS) endotoxin infusion followed by a saline infusion; group 3 (sepsis + dopexamine group) received an *E. coli* LPS endotoxin infusion followed by a dopexamine infusion. *$P < 0.05$ compared with baseline values and control group; †$P < 0.05$ group 3 compared with group 2

TABLE 1:
Heart rate and systolic and diastolic blood pressure before, during and after infusion of *Escherichia coli* endotoxin and during treatment with dopexamine or saline in groups 1 (control), 2 (sepsis) and 3 (dopexamine)

	Heart rate (beats/min)			Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Baseline	244 ± 8.84	246 ± 15.79	250 ± 10.00	103.9 ± 6.9	112.3 ± 5.8	116.4 ± 6.7	66.7 ± 3.9	68.6 ± 4.2	74.8 ± 4.6
C1	256 ± 12.22	260 ± 10.74	266 ± 9.91	98.8 ± 6.0	109.0 ± 9.9	99.5 ± 3.9	70.7 ± 3.6	70.5 ± 7.6	61.4 ± 3.2
C2	262 ± 11.33	266 ± 7.91	278 ± 10.51	95.3 ± 6.5	91.7 ± 1.7	89.6 ± 1.5	62.0 ± 4.6	54.3 ± 2.2	52.4 ± 1.3
E1	266 ± 9.91	266 ± 11.17	289 ± 11.40	104.8 ± 4.1	94.0 ± 5.7[a,b]	89.5 ± 3.0[a,b]	66.7 ± 3.9	56.2 ± 3.6[a,b]	55.3 ± 1.9[a,b]
E2	269 ± 9.48	278 ± 8.66[a,b]	304 ± 11.47[a,b]	110.5 ± 6.1	94.9 ± 6.6[a,b]	92.5 ± 4.2[a,b]	70.1 ± 3.1	57.1 ± 4.1[a,b]	57.9 ± 2.9[a,b]
E3	268 ± 13.72	280 ± 5.96[a,b]	308 ± 12.00[a,b]	112.5 ± 4.9	99.4 ± 5.1[a,b]	102.0 ± 5.8[a,b]	74.3 ± 3.1	57.3 ± 3.3[a,b]	61.5 ± 2.9[a,b]
D1	270 ± 10.85	294 ± 7.91[a,b]	310 ± 10.85[a,b]	111.5 ± 3.7	94.4 ± 5.27[a,b]	111.0 ± 7.1	75.9 ± 3.1	53.1 ± 1.7[a,b]	61.8 ± 4.2
D2	274 ± 9.45	304 ± 7.18[a,b]	326 ± 11.56[a,b]	110.8 ± 4.7	95.8 ± 4.9[a,b]	115.7 ± 3.6	74.5 ± 3.5	54.4 ± 2.2[a,b]	61.7 ± 4.1
D3	280 ± 10.74	312 ± 7.42[a,b]	336 ± 11.85[a,b]	115.9 ± 3.8	99.9 ± 4.75[a,b]	113.8 ± 6.8	74.6 ± 3.3	55.3 ± 2.2[a,b]	62.9 ± 4.1
R1	274 ± 11.56	316 ± 5.81[a,b]	334 ± 8.96[a,b]	118.8 ± 5.2	102.0 ± 4.0[a,b]	109.6 ± 7.2[a]	76.3 ± 4.2	54.3 ± 2.6[a,b]	59.9 ± 5.2[a]
R2	284 ± 11.85	318 ± 4.66[a,b]	336 ± 10.24[a,b]	115.9 ± 4.1	106.0 ± 4.2[a,b]	106.8 ± 5.8[a]	72.1 ± 3.1	56.7 ± 2.8[a,b]	60.5 ± 4.5[a]

Values are mean ± SE.
[a] $P < 0.05$ versus control group.
[b] $P < 0.05$ versus baseline.
C, baseline clearance period (all groups); E, period of infusion of *E. coli* lipopolysaccharide endotoxin (groups 2 and 3, group 1 received saline during this period); D, period of infusion of dopexamine (group 3, groups 1 and 2 received saline during this period); R, recovery period (all groups received saline).

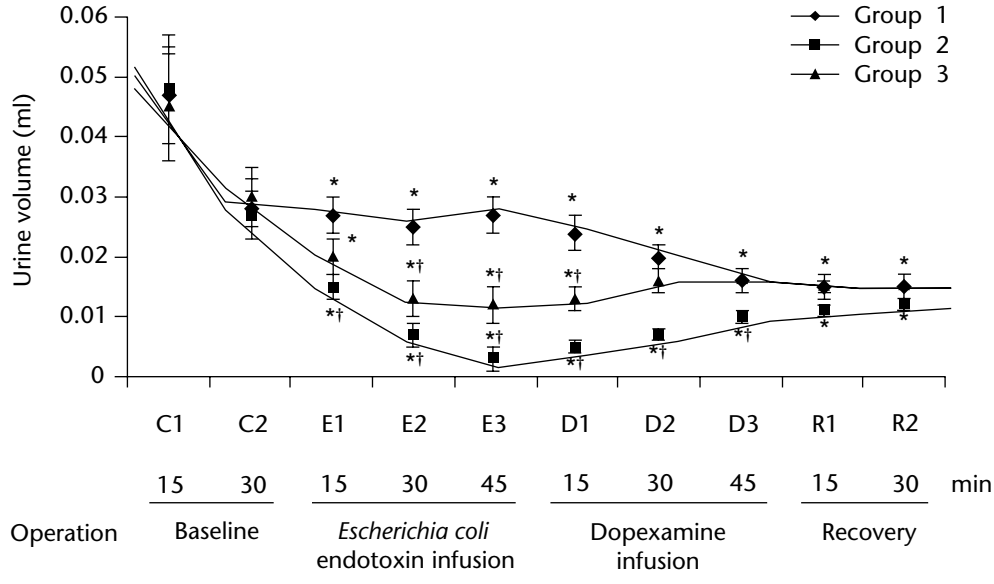


FIGURE 3: Mean ± SE of urine volume in the three groups of rats ($n = 10$ each). Group 1, (control group) only received 3% creatinine and saline infusions; group 2 (sepsis group) received an *Escherichia coli* lipopolysaccharide (LPS) endotoxin infusion followed by a saline infusion; group 3 (sepsis + dopexamine group) received an *E. coli* LPS endotoxin infusion followed by a dopexamine infusion. *$P < 0.05$ compared with baseline value; †$P < 0.05$ compared with control group

increase in glomerular filtration rate prompted by dopexamine in group 3 rats 15 – 30 min after dopexamine infusion was significantly different from group 2 (Fig. 4).

Discussion

This study demonstrates that a 45-min intravenous infusion of *E. coli* LPS endotoxin induced a pronounced impairment of renal excretory function, as shown by decrease in urine output and glomerular filtration rate. Dopexamine improves renal function after infusion of *E. coli* endotoxin.

Sepsis, especially septic shock, is one of the main causes of ARF.[1 – 3] The mechanism by which sepsis with endotoxaemia induces ARF may be via impaired renal blood flow, reduced glomerular filtration rate or acute tubular damage. Renal blood flow can decrease as a result of hypotension due to hypovolaemia, cardiac depression, systemic vasodilation or a combination of these.[3,13] The primary mediators of the sepsis syndrome and its potentially fatal complications are the endotoxins. Endotoxins are lipopolysaccharides associated with the outer cell membrane of Gram-negative bacteria. The effects of endotoxins depend on the equilibrium between the cellular mediators released and their natural antagonists. *E. coli* LPS is the most common and important endotoxin studied.[14]

Kikeri *et al.*[2] demonstrated that *E. coli* endotoxin decreased glomerular filtration rate and renal blood flow with no changes in mean arterial pressure, cardiac output and total peripheral resistance in awake rats. The absence of hypotension was explained by the relative resistance of rats to endotoxin. Using animals that were awake avoided the

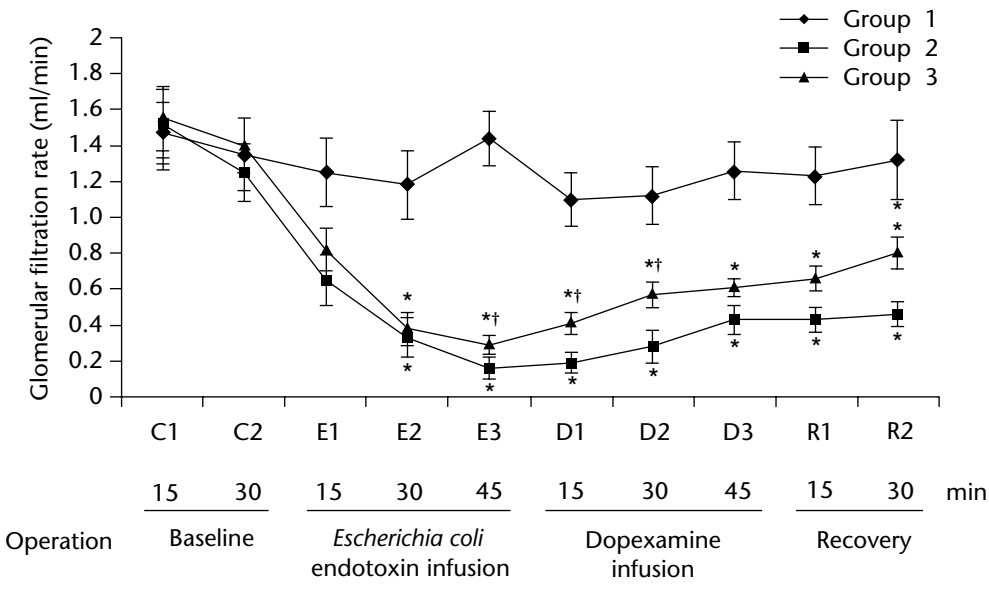


FIGURE 4: Mean ± SE of glomerular filtration rate in the three groups of rats (n = 10 each). Group 1 (control group) only received 3% creatinine and saline infusions; group 2 (sepsis group) received an *Escherichia coli* lipopolysaccharide (LPS) endotoxin infusion followed by a saline infusion; group 3 (sepsis + dopexamine group) received an *E. coli* LPS endotoxin infusion followed by a dopexamine infusion. *$P < 0.05$ compared with baseline values and control group; †$P < 0.05$ group 3 compared with group 2

influence of anaesthesia on systemic haemodynamics after endotoxin administration. They also indicated that the duration of ARF induced by endotoxin was dose dependent. The immediate renal response is comparable when low doses of endotoxin (0.1 – 1 mg/kg) are used but the decrease in glomerular filtration rate is more transient.[15] We therefore used an experimental rat model in which septic shock was induced by 8 mg/kg per h dose of *E. coli* and we observed decreased systolic, diastolic and mean pressures, urine volume and glomerular filtration rate. During the recovery period all these parameters remained stable and returned to the normal range in group 2 (without treatment). This observation may be explained by the resistance of rats to endotoxin.

Inotropic agents have been used to treat sepsis by improving systemic circulation and preventing the deterioration of renal function. The effects of dopamine on renal haemodynamic and excretory functions seem obvious, but the protective role of dopamine on renal function has been questioned.[6,7,16] Dobutamine has no significant effects on renal blood flow when infused at increasing infusion rates in healthy volunteers or experimental animals.[8 – 10] This is probably due to the fact that dobutamine does not possess dopaminergic properties.[17]

Dopexamine hydrochloride has interesting vasodilator properties, with marked intrinsic agonist activity at β_2-adrenoreceptors and lesser agonist activity at dopaminergic receptors (DA_1 and DA_2). Dopexamine improves cardiac performance by a marked vasodilation and a mild inotropic activity. Its effects on the dopaminergic receptors

increases cerebral, myocardial, splanchnic and renal blood flow. These haemodynamic effects are associated with an increase in diuresis and natriuresis.[18] Dopexamine has been shown to increase renal blood flow and glomerular filtration rate in animal experiments and healthy volunteers.[2,3,8,9,19]

The infusion rate for effective doses of dopexamine range from 0.5 – 5 µg/kg per min depending on the pathology. In several studies, a dose-dependent increase in heart rate and arrhythmia has been demonstrated with dopexamine.[20 – 22] We therefore used a low dose of dopexamine (1 µg/kg per min) to avoid such cardiac complications.

Dopexamine has been evaluated in several animal experiments and human trials in septic shock. Palsson *et al.*[3] compared the renal effects of dopexamine with both dopamine and dobutamine in an experimental model of induced sepsis in conscious rats. They concluded that renal excretory function was improved to a greater extent with dopexamine than with the other two agents. Dopexamine maintained blood pressure better than dobutamine, although no differences were noted in mean arterial pressure between dopexamine and dopamine.[3] Colardyn *et al.*[20] evaluated dopexamine use in patients with septic shock and observed a short-term increase in cardiac index and heart rate and a dose-dependent decrease in systemic vascular resistance, although urine output increased with the lower dose of 1 µg/kg per min dopexamine. In the long-term, tolerance may have developed as these effects gradually diminished.[20] In contrast, van Lambalgen *et al.*[23] observed no significant changes in renal perfusion with dopexamine in endotoxaemic rats.

Like others we found an increase in urine volume with 1 µg/kg per min dopexamine, but could not demonstrate a significant change in glomerular filtration rate. This may be explained by a number of factors other than a lack of renal effect, i.e. too small sample size and low baseline creatinine clearance. Further studies are required to determine whether these effects, and different doses of dopexamine, will benefit renal outcome in sepsis.

• Received for publication 21 August 2003 • Accepted subject to revision 5 September 2003
• Revised accepted 4 November 2003

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Address for correspondence
BB Yelken
Universite Evleri 19 sk D-7, 26040 Eskisehir, Turkey.
E-mail: bbyelken@ogu.edu.tr