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Renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines

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Abstract *Objective:* To evaluate the renal effects of low-dose dopamine in patients with sepsis syndrome or septic shock treated with catecholamines.
Design: Prospective, clinical study using sequential periods.
Setting: A 12-bed surgical intensive care unit in a university hospital.
Patients: 14 patients with sepsis syndrome and 15 patients with septic shock treated with exogenous catecholamines were studied. They had no diuretic treatment.
Intervention: Two periods of 2 h each with and without $2\ \mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine infusion. Hemodynamic and renal data were obtained at the end of each period. Measurements were repeated after 48 h of dopamine infusion in patients with sepsis syndrome. All data were evaluated by the Wilcoxon rank test.
Measurements and results: In patients with sepsis syndrome, diuresis and creatinine clearance increased significantly by 100% and 60%, respectively, during low-dose dopamine infusion without any change in systemic hemodynamics. The renal response to dopamine decreased significantly after 48 h of dopamine infusion ($P < 0.01$). In patients with septic shock treated with catecholamines, no variation of either systemic hemodynamics or renal function was noted during low-dose dopamine infusion.
Conclusion: The renal effects of low-dose dopamine in patients with sepsis syndrome decrease with time. No renal effect of low-dose dopamine was observed in patients with septic shock treated with catecholamines. These findings suggest a desensitization of renal dopaminergic receptors.

Key words Low dose dopamine · Catecholamines · Sepsis syndrome · Septic shock · Renal function · Dopaminergic receptors · Desensitization

Introduction

Sepsis and septic shock are a major cause of multiple organ failure in critically ill patients frequently associated with acute renal failure [1]. Sodium and water retention are often present [2] in the early phase of severe sepsis before multiple organ failure, which itself closely predicts mortality [3].

Dopamine is an endogenous catecholamine, an immediate precursor of norepinephrine, which is widely used for its hemodynamic [4] and renal effects [5]. The renal properties of low-dose dopamine were first

demonstrated by Goldberg and coworkers who showed that systemic hemodynamics, diuresis, sodium excretion and renal blood flow were improved in both cardiac patients and healthy volunteers [6, 7]. Elsewhere, low-dose dopamine seems to be effective in improving renal function in critically ill patients [8, 9]. However, little is known about the renal effects of dopamine during severe sepsis [10]. Experimental studies have shown that infusion of low-dose dopamine improves renal hemodynamics in healthy dogs treated with norepinephrine [11] and in dogs with septic shock pretreated with ibuprofen [12]. Furthermore, Orme observed that in hypertensive patients, during long-term administration of dopamine, renal response was abolished [13].

The aim of this study was to evaluate the renal effects of short- and long-term infusion of low-dose dopamine in patients with sepsis syndrome [14] or septic shock treated with high doses of catecholamines.

Materials and methods

Patients

The patients eligible for this study were critically ill with sepsis syndrome as defined by Bone [14] (group 1) or septic shock treated with catecholamines (epinephrine or norepinephrine, group 2). Patients were included in the study if: (1) they were in stable hemodynamic condition for at least 4 h before the beginning of the study; (2) they presented clinical signs of sodium and water retention (clinical edema or increase in body weight > 0.5 kg day^{-1}); (3) they received neither diuretics 8 h prior to the study [15] nor dopamine 24 h prior to the study [13]. The exclusion criteria were anuria (diuresis < 500 ml day^{-1}), hemodialysis-hemofiltration or a history of chronic renal failure.

The study was approved by the institutional review board of the hospital, and informed consent was obtained from each patient or, when appropriate, from the family. For each patient, the following data were recorded: weight, height, simplified acute physiologic score [16], sepsis score at inclusion [17], serum lactate at inclusion, number of organ failure at inclusion [3], the underlying medical and surgical pathology and the sepsis focus.

Protocol

In both groups of patients, the study started on the day of inclusion (D0) and consisted of two periods of 2-h duration. The first period was a baseline period without infusion of dopamine. Then dopamine hydrochloride, diluted in 5% dextrose was given intravenously via an independent catheter [18] with a volumetric infusion pump at an infusion rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The second period was 2 h long and was the dopamine period (see Fig. 1).

In group 1, low-dose dopamine infusion was continued for at least 48 h. The study was repeated on day 2 (D2) and the procedure was reversed. The dopamine period (dopamine D2) was followed by the baseline period (baseline D2) just after interruption of the dopamine infusion.

In group 2, the study was stopped on the day of inclusion (D0) after the dopamine period (Fig. 1).

Physiologic measurements

At the end of each period, the following data were collected.

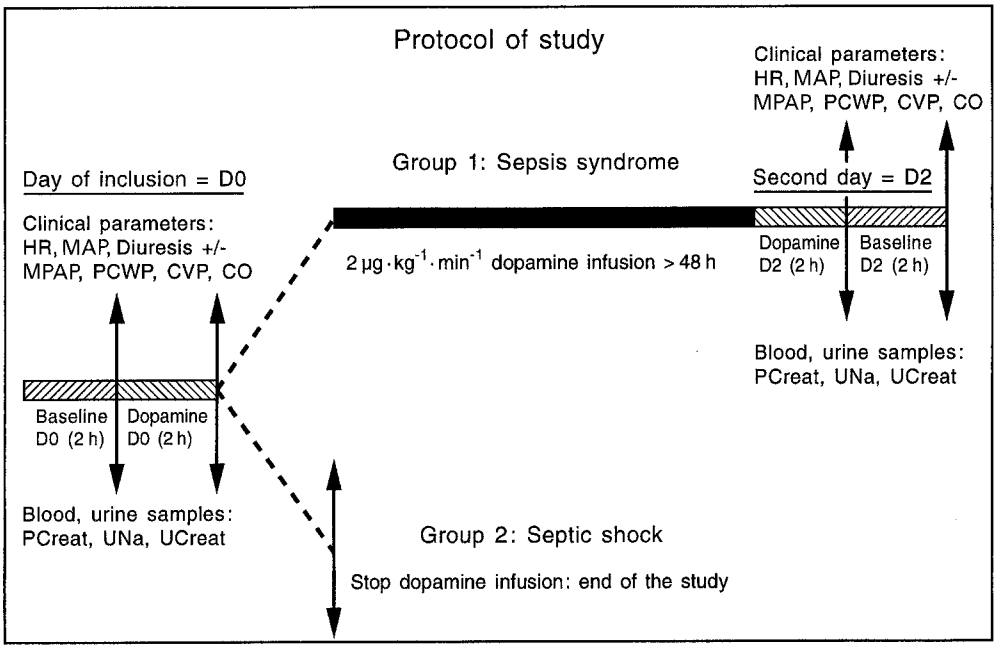

Fig. 1 Description of the different periods and phases of the protocol and timing of the physiologic measurements performed in the two groups of patients: group 1 with sepsis syndrome ad group 2 with septic shock treated with exogenous catecholamines

Hemodynamic data

Heart rate (HR) and mean arterial pressure (MAP) were monitored continuously via an arterial catheter if present, or a noninvasive device (at least one measurement was taken every 10 min). When a pulmonary artery catheter (Baxter-Edwards Swan-Ganz 93-131-7F, Irvine, Calif.) was in place, mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) were measured at the end-expiratory phase. Cardiac output (CO) was measured in triplicate by the thermodilution technique using 10 ml of ice-chilled (< 2 °C) 5%-dextrose injections.

During the study, MAP was maintained within 20% of the baseline values by additional fluids in patients with sepsis syndrome or by modifying the rate of infusion of exogenous catecholamines.

Renal parameters

Two-hour diuresis (V) (ml $2\,h^{-1}$) was measured with a precision of 10 cc via a small graduated container. Urine and blood samples were collected for measurement of urine sodium concentration (UNa) ($mmol \cdot l^{-1}$), urine creatinine concentration (UCreat) ($\mu mol \cdot l^{-1}$) and plasma creatinine concentration (PCreat) ($\mu mol \cdot l^{-1}$) and plasma creatinine concentration (PCreat) ($\mu mol \cdot l^{-1}$) (IL 508 Instrument Laboratory, Delhomme, France). Creatinine clearance (CreatCl) ($ml \cdot min^{-1}$) and sodium excretion (UNaV) ($mmol \cdot min^{-1}$) were respectively calculated during a period of 2 h [19, 20] with standard formulas: $CreatCl = (UCreat \times V)/(PCreat \times 120)$ and $UNaV = (UNa \times V)/120$.

Statistical analysis

Data are reported as mean ± SD. Based on a previous study in critically ill patients [9], we have considered a 40% difference in diuresis to be of clinical significance. To demonstrate this, the α risk was set at 5% and the β risk was set at 10%. A minimum sample sizes of 13 patients should show statistical significance if one exists [21]. Statistical analysis was performed using a non-parametric Wilcoxon signed rank test for small groups and physiologic parameters. A P value < 0.05 was considered statistically significant.

Results

Fourteen patients were included in group 1 (Table 1) and 15 in group 2 (Table 2). All patients in group 2 and 10/14 in group 1 were under positive pressure ventilation during the study. Five patients in group 1 and 12 patients in group 2 had a pulmonary artery catheter. Most of them had severe post operative sepsis and had one or more signs of organ dysfunction, especially in group 2 (11 MOF 2, 4 MOF 3). The mean serum lactate level in group 2 was 2.7 ± 2.5 $mmol \cdot l^{-1}$ during the study. The mean SAPS score and the mortality predicted were respectively 13 ± 3.3 with a 20% death rate in group 1 and 14 ± 3 with a 35% death rate in group 2 [16].

Systemic hemodynamics did not change significantly in the two groups during infusion of low-dose dopamine versus baseline (Table 3). There were no significant variations in MAP, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO).

In group 1, diuresis significantly increased during dopamine infusion on day 0 (112 ± 48 vs 226 ± 134 $ml \cdot 2h^{-1}$, $P = 0.0002$) and on D2 (142 ± 90 vs 166 ± 80 $ml \cdot 2h^{-1}$, $P = 0.02$) (Fig. 2). However, dopamine induced diuresis significantly decreased ($P = 0.004$) after 48 h of dopamine infusion. The significant increase in both UNaV and CreatCl during the dopamine period was

Table 1 Clinical data on the patients with sepsis syndrome (group 1) included in the study (*SAPS* simplified acute physiologic score, *MOF* multiple organ failure)

Patients	Age	Saps score	Sepsis score	MOF	Pathology/sepsis	Outcome[a]
1	82	17	15	2	Fat embolism/pneumonia	Dead
2	28	12	12	1	Multiple trauma/pneumonia	Alive
3	93	14	14	1	Intestinal obstruction/ pneumonia	Dead
4	78	12	20	1	Peritonitis/ulcus	Dead
5	93	14	7	1	Pneumonia	Dead
6	65	11	16	1	Gastrectomy/peritonitis	Alive
7	75	13	14	1	Aspiration/ARDS	Dead
8	26	7	9	1	Multiple trauma/pneumonia	Alive
9	23	12	13	1	Multiple trauma/pneumonia	Alive
10	20	13	14	1	Septicemia	Alive
11	85	19	17	2	Peritonitis/angiocholitis	Alive
12	27	7	15	1	Cellulitis	Alive
13	60	16	20	1	Gastrectomy/pneumonia	Dead
14	72	14	7	1	Gastrectomy/septicemia	Alive
Mean ± SD	59 ± 28	13 ± 3.3	13 ± 4.7			7 Dead 7 Alive

[a] Patients were considered alive if they were discharged from the ICU

Table 2 Clinical data on the patients with septic shock (group 2) included in the study. Catecholamines (*NE* Norepinephrine, *E* Epinephrine, *Dobu* Dobutamine)

Patients	Age	Saps score	Sepsis score	MOF	Pathology/sepsis	Catecholamines (μg/kg per mn)	Lactates (mmol/l)	Outcome[a]
1	60	16	17	2	Gastrectomy/pneumonia	NE:0.5	1.7	Dead
2	82	13	11	2	Peritonitis	NE:0.12	2	Alive
3	71	13	21	2	Biliary peritonitis	NE:1	3.4	Dead
4	75	13	14	2	Pancreatitis	NE:0.4	1	Dead
5	54	15	13	2	Oesophagectomy	NE:0.2	0.9	Dead
6	58	14	17	2	Multiple trauma/pneumonia	NE:0.5	1.7	Alive
7	78	17	23	3	Pancreatitis	NE:0.2	1.8	Dead
8	80	15	14	2	Peritonitis/ulcus	NE:0.7	1.8	Alive
9	76	12	13	2	Arthritis/shock	E:0.1 Dobu:10	1	Dead
10	71	10	20	3	CPR/aspiration/ARDS	E:0.8 Dobu:10	1.8	Dead
11	74	10	13	3	Peritonitis/ARDS	NE:0.2	1.9	Alive
12	73	12	14	2	Pneumonia	NE:1.1	8.6	Dead
13	58	12	12	2	Hip prosthesis sepsis	NE:0.7	0.8	Alive
14	70	21	17	3	Necrosis colitis	NE:2/E:2 Dobu:10	8.9	Dead
15	69	17	14	2	Multiple trauma/pneumonia	E:0.2 Dobu:5	2.6	Dead
Mean ± SD	70 8.6	14 3	15.5 3.5				2.7 +/− 2.5	10 Dead 5 Alive

[a] Patients were considered as alive if they were discharged from the surgical intensive care unit

Table 3 Comparison of hemodynamic and renal parameters between low-dose dopamine infusion and baseline period at the day of inclusion (D0) in patients with sepsis syndrome (group 1) or with septic shock (group 2). *HR* heart rate, *MAP* mean arterial pressure, *MPAP* mean pulmonary arterial pressure, *PCWP* capillary wedge pressure, *CVP* central venous pressure, *CO* cardiac output, *UNa* urine sodium concentration, *UNaV* sodium excretion, *PCreat* plasma creatinine concentration, *UCreat* urine creatinine concentration, *CreatCl* creatinine clearance

(n = patients with Swan-Ganz catheter/ all patients of the group)	Group 1: Sepsis (n = 5/14) syndrome		Group 2: Septic (n = 12/15) shock	
	Baseline period	Dopamine infusion	Baseline period	Dopamine infusion
Hemodynamic data:				
HR ($b \cdot min^{-1}$)	104 ± 10	109 ± 15	101 ± 18	106 ± 17
MAP (mmHg)	81 ± 20	83 ± 17	78 ± 10	76 ± 11
MPAP (mmHg)	26 ± 5	25 ± 8	27 ± 8	22 ± 6
PCWP (mmHg)	12 ± 4	13 ± 5	13 ± 5	13 ± 5
CVP (mmHg)	10 ± 4	10 ± 3	10 ± 4	10 ± 4
CO ($l \cdot min^{-1}$)	6.5 ± 2	6.5 ± 2	7.9 ± 2	8.1 ± 2
Renal data:				
Diuresis ($ml \cdot 2h^{-1}$)	113 ± 54	216 ± 145*	201 ± 131	184 ± 111
UNa ($mmol \cdot l^{-1}$)	37 ± 31	36 ± 35	56 ± 35	60 ± 37
UNaV ($mmol \cdot 2h^{-1}$)	4 ± 4	7 ± 7*	11 ± 5	11 ± 4
PCreat ($mmol \cdot l^{-1}$)	142 ± 130	137 ± 133	154 ± 100	156 ± 101
Ucreat ($mmol \cdot l^{-1}$)	7.8 ± 5	7.6 ± 6	4.4 ± 2	4.8 ± 2
CreatCl ($ml \cdot min^{-1}$)	76 ± 68	120 ± 116*	60 ± 35	52 ± 31

*$P < 0.05$ vs baseline period in the same group of patients

essentially related to the increase in diuresis since dopamine infusion did not influence significantly UNa, UCreat and PCreat (Table 3).

In group 2, there was no significant change in diuresis, renal sodium excretion and creatinine clearance during infusion of low-dose dopamine (Table 3).

Discussion

The main findings of this study are (1) an important increase in diuresis and creatinine clearance with a very low dose of dopamine in severe septic patients with

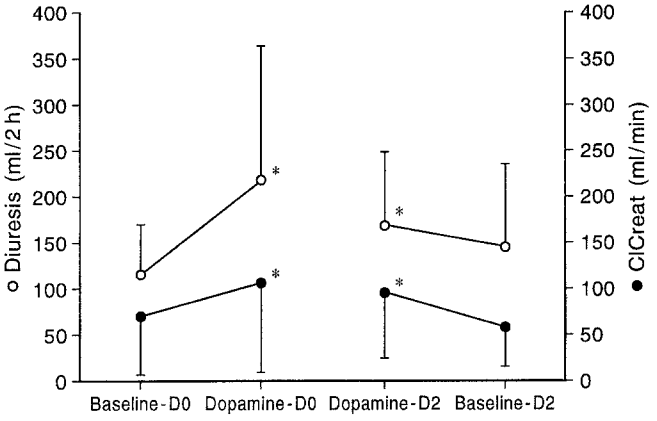

Fig. 2 Variation of diuresis (ml/2 h) and creatinine clearance ClCreat (ml/min) in patients with sepsis syndrome (group1) (mean ± SD) during baseline period and dopamine infusion at the day of inclusion (D0) and after 48 h of dopamine infusion (D2). * $P < 0.05$ vs baseline on the same day

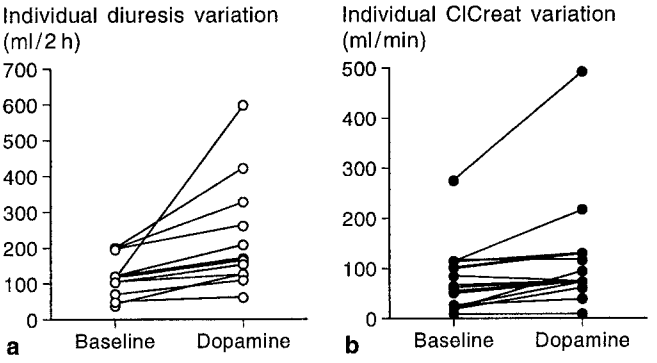

Fig. 3 Individual variation of renal parameters during low-dose dopamine infusion versus baseline period at the day of inclusion (D0). **a** 2-h diuresis (ml/2 h) and **b** Creatinine clearance (ClCreat; ml/min)

normal kidney function and (2) a lack of renal effect of low-dose dopamine in patients with septic shock and without renal failure. In these two groups, systemic hemodynamics remained essentially unchanged during dopamine infusion versus baseline period.

In our patients, we did not find any systemic effect of low-dose dopamine. No significant variation of systemic arterial pressure or CO were found in either group. In septic shock patients, Martin et al. showed that norepinephrine had beneficial effects on renal function by increasing arterial pressure and CO [22]. In our study, low-dose dopamine was added to high-dose catecholamines for improving renal function without variation of systemic hemodynamic. Two $\mu g \cdot kg^{-1} \cdot min^{-1}$ stimulates dopaminergic receptors without stimulation of other adrenergic receptors (α and β), as is observed at higher doses [8]. In another study, the same authors showed that a high dose of norepinephrine was more effective than a high dose of dopamine to reverse abnormalities of hyperdynamic septic shock [23].

Renal effects of low-dose dopamine have been described by Goldberg and coworkers in cardiac patients and healthy volunteers [6, 7]. Low-dose dopamine is currently being used in many intensive care units when patients become oliguric [8–9]. However, little is known about the renal effects of low-dose dopamine in critically ill patients with sodium and water retention and without renal failure.

Concerning the patients with sepsis syndrome (group 1), without renal failure, we observed a significant increase in diuresis and creatinine clearance (100% and 60% respectively) at the initiation of $2\ \mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine infusion. There is also a significant increase of renal sodium excretion (about 75%) during low-dose dopamine infusion versus the baseline period (Table 3).

In patients with oliguria or renal failure, Parker et al. showed that $1.5–2.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine infusion increased the diuresis 42% and improved renal function [9], but their patients were very heterogeneous and 18/52 of these patients received furosemide the effects of which is known to be potentiated by dopamine [15]. In surgical intensive care patients, Flancbaum noted that low-dose dopamine improves renal function immediately and drastically in patients with oliguria and without diuretic treatment [24]. However, they did not study long-term renal effects of low-dose dopamine in these patients. In our study, we note a significant improvement of creatinine clearance during low-dose dopamine infusion without a significant change in urinary sodium or creatinine concentration (Fig. 2). Consequently, we can expect that the improvement of renal function observed is more related to an increase of the glomerular filtration rate by an activation of dopaminergic receptor located on the afferent arteriole of the glomerulus [25] than an inhibition of the Na + /K + /ATPase pump located on the cell membrane by the tubular dopaminergic receptors [26, 27].

One limitation of our study is the lack of baseline measurements because of discontinuation of dopamine infusion on the first day of the study. Thus, the increase in diuresis might have been independent of the infusion of dopamine. However, for patients in group 1, the test was repeated on the second day, and a statistical difference of diuresis was still present. In these patients, the dopamine-diuresis gain was significantly less after more than 48 h of low-dose

dopamine infusion. Orme found similar results in hypertensive patients [13]. This diminution of the renal effect of dopamine might be explained by sodium and water depletion or hemodynamic changes over 2 days. However, we did not find any significant difference in weight (74 ± 12 vs 77 ± 9 kg, $P = 0.42$), baseline diuresis (113 ± 48 vs 142 ± 90 ml · $2h^{-1}$, $P = 0.7$) or baseline MAP (81 ± 20 vs 83 ± 15 mmHg, $P = 0.69$) between D0 and D2. Another hypothesis is related to the molecular action of dopamine on specific receptors. Renal receptors of dopamine are essentially of type 1 (DA 1) [27] coupling with adenylate-cyclase and cAMP as are β-adrenergic receptors [28]. A decrease in the response to β-agonists with time in the failing human heart [29] and in asthma [30] has been described and may be related to a down-regulation of the β-adrenergic receptors [31]. A similar mechanism may also occur for DA 1 receptors and may explain the decrease in the renal response after long-term infusion of low-dose dopamine.

Concerning the lack of renal effects of low-dose dopamine in patients with septic shock treated with catecholamines (group 2), our results are in opposition to most previous experimental studies. In two dog studies, 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of dopamine infusion improved renal hemodynamics when added to an infusion of norepinephrine [11] or when administered during septic shock and after pretreatment by ibuprofen [12]. However, in these two experimental studies, the renal function was not examined. In a recent experimental study, Strigle found no difference in creatinine clearance and renal blood flow with or without renal range dopamine in dogs with endotoxinic shock treated by fluid resuscitation and norepinephrine [32].

In patients with septic shock, catecholamines were used to maintain temporarily the hemodynamic status for several hours and days before the recovery of the sepsis by surgical procedure and/or antibiotics. A decrease in the vascular/cardiac effects of the vasoactive/inotropic drugs is often observed which suggests a "desensitization" of adrenergic receptors. Three mechanisms of desensitization are discussed for adrenergic receptors [33]: (1) an uncoupling receptor with protein G; (2) internalization of the receptor in the cell membrane (these two mechanisms may occur in minutes to hours); (3) destruction with a decrease in the number of receptors. This long-term desensitization may occur over hours to days and may also involve a decrease in the receptor synthesis [34].

Exogenous catecholamines could interact with renal dopaminergic receptors DA 1. Finally, a heterogenous desensitization of renal dopaminergic receptors by prior infusion of catecholamines might explain the lack of renal effect of low-dose dopamine in our patients.

The desensitization of renal dopaminergic receptors in our two groups remains an hypothesis and is worth confirming in further studies.

Conclusion

In severe septic patients, renal effects of low-dose dopamine are variable despite no significant change in systemic hemodynamics. In patients with sepsis syndrome, diuresis and creatinine clearance increase by 100% and 60% respectively with a very low dose of dopamine, but the renal response to dopamine decreases with long-term infusion (> 48 h). In patients with septic shock treated with high doses of catecholamines, low-dose dopamine infusion does not improve renal function.

These results suggests an autologous desensitization of renal dopaminergic receptors in patients of group 1 and heterologous desensitization in patients of group 2 pretreated by exogenous catecholamines. This hypothesis must be confirmed in other studies.

This phenomenon may decrease the renal effect of a prophylactic infusion of low-dose dopamine in patients with salt and water retention. Moreover, it seems unnecessary to use a low-dose dopamine infusion to improve renal function in patients with severe septic shock treated with high doses of exogenous catecholamines.

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