# The protective effect of low-dose dopamine on renal functions in hypotensive rats: an experimental study

## Hipotansif sıçan modelinde düşük doz dopamin infüzyonunun böbrek koruyucu etkisi: Deneysel çalışma

Hatice KAYA,[1] Hale TUFAN,[2] Mehmet ÖZDOĞAN,[3] Gülnaz ARSLAN[1]

*BACKGROUND*

The aim of this study was to investigate the effect of low-dose dopamine on markers of the renal functions in a rat model of hypotension.

*METHODS*

Forty Wistar rats were divided into control, hypotension, dopamine, and hypotension+dopamine groups. Hypotension was achieved by sodium-nitroprusside infusion. Samples were drawn for analysis during the two-hour study period.

*RESULTS*

Blood urea nitrogen levels were significantly increased in hypotension group during the early phase but this difference disappeared at the end of the second hour. Dopamine infusion had no effect on creatinine and potassium clearance. Despite the significance of improved sodium clearance in the hypotensive rats treated with dopamine, natriuresis did not occurred in the dopamine-only group.

*CONCLUSION*

It can be stated that low dose dopamine infusion at a rate of 0.5 μg $kg^{-1}$ $min^{-1}$ has a short-term preventive action against the increase of blood urea nitrogen during the early phase of pharmacologically induced hypotension.

***Key Words:*** Blood urea nitrogen; creatinine; low-dose dopamine; receptors, dopamine; renal function.

*AMAÇ*

Bu çalışmada hipotansif sıçan modelinde düşük doz dopamin infüzyonunun böbrek koruyucu etkisi araştırıldı.

*GEREÇ VE YÖNTEM*

Çalışmada kontrol, hipotansiyon, dopamin ve dopamin+hipotansiyon gruplarına ayrılan Wistar cinsi 40 sıçan kullanıldı. Hipotansiyon yaratmak için sodium nitroprussid infüzyonu kullanıldı ve iki saatlik çalışma süresince kan ve idrar örnekleri toplandı.

*BULGULAR*

Hipotansiyon grubunda kan üre nitrojen düzeyinin çalışmanın birinci saatinde anlamlı derecede yükseldiği, fakat çalışma süresinin sonunda bu farkın kaybolduğu gözlendi. Dopamin infüzyonunun kreatinin ve potasyum klirensine etkisi gözlenmedi. Sadece dopamin verilen sıçanlarda natriürez gözlenmezken, dopamin verilen hipotansif sıçanlarda idrar sodyum atılımının anlamlı derecede arttığı saptandı.

*SONUÇ*

Düşük doz dopamin infüzyonunun farmakolojik olarak oluşturulan hipotansiyonun erken safhasındaki kan üre nitrojen yükselmesine karşı engelleyici etki gösterdiği saptandı.

***Anahtar Sözcükler:*** Kan üre nitrojen; kreatin; düşük doz dopamin; reseptör, dopamin; böbrek fonksiyonu.

[1]Departments of Anesthesiology and Reanimation and [2]Pharmacology, Medicine Faculty of Başkent University, [3]Department of General Surgery, Medicine Faculty of Hacettepe University, Ankara, Turkey.

[1]Başkent Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, [2]Farmakoloji Anabilim Dalı, [3]Hacettepe Üniversitesi Tıp Fakültesi Genel Cerrahi Anabilim Dalı, Ankara.

Correspondence *(İletişim)*: Mehmet Özdoğan, M.D. Mertler Sok., No: 41 / 7, 06510 Beştepe, Ankara, Turkey.
Tel: +90 - 312 - 213 02 08 Fax (*Faks*): +90 - 312 - 291 27 05 e-mail (*e-posta*): mehmetozdogan01@superonline.com

Acute renal failure is a common medical problem. Hypotension during the pre-, intra- or postoperative period is one of the most commonly observed etiological factors in the development of acute renal failure. Despite the lack of significant evidence, low-dose dopamine infusion is commonly used in order to protect or improve renal functions during hypotensive periods.

Dopamine has variable dose dependent effects on $D_{1-5}$, $\alpha_1$, $\alpha_2$ and $\beta_1$ receptors. It preserves renal functions by selectively stimulating $D_1$ and $D_2$ receptors at lower doses. This stimulation causes an increase in renal blood flow, urinary output and electrolyte excretion by decreasing vascular resistance.[1] Studies in rats, dogs and humans have shown that dopamine reverses and improves the effects of vasoconstrictors on renal functions.[2-5] It also causes diuresis, natriuresis and kaliuresis in isolated rat kidney.[6] Low-dose dopamine significantly increases glomerular filtration rate, electrolyte clearance and urinary flow without systemic hemodynamic effects in normotensive humans.[5]

In this study, our aim was to investigate the effect of low-dose dopamine on markers of the renal function in a rat model of hypotension below the auto-regulatory range, induced by the infusion of sodium nitroprusside.

## MATERIALS AND METHODS

Forty male Wistar rats weighing between 200-300 g were used throughout the study. This study complies with the European Community guidelines for the use of experimental animals. The Committee of Ethics in Animal Experiments of Başkent University approved the investigation.

*Study groups*: Rats were divided into four groups: Control (C), hypotension (H), dopamine (D) and hypotension + dopamine (H+D) groups (n=10 per group). Blood and urinary samples were drawn for analysis during the two-hour study period. All rats were catheterized by femoral and carotid route for invasive monitoring and blood sampling.

*Anesthesia*: Anesthesia was maintained with 70 mg $kg^{-1}$ Ketamine and 10 mg $kg^{-1}$ Xylasine by intraperitoneal route. The animals were allowed spontaneously to breath room air, without tracheal cannulation.

*Monitorization*: After induction, rats were catheterized through the carotid artery for monitorization of blood pressure and through the femoral vein for volume and drug infusion and sampling. Electrodes and rectal heat probe were placed. A physiological recorder (Biopac®, Model MPIOOA) was used for monitorization and recordings.

Venous blood samples were drawn at the beginning and at the 1st and 2nd hours of the experiment, and processed in a Hitachi 717 automatic analyzer (Boehringer; Mannheim, Indianapolis, USA) for the measurement of serum BUN, creatinine, and sodium and potassium levels. Urinary samples were collected via suprapubic catheterization at the second hour of the experiment and pH, density, sodium and potassium of urine were studied. Volume loss due to the blood sampling was replaced with 5% dextrose of the two times the volume of the blood drawn in the control group. The volumes of drug infusions in the other groups were adjusted to be equal to that of the control group.

*Hypotension*: A fresh solution of sodium nitroprusside was infused at a rate of 40 μg $kg^{-1}min^{-1}$ using an infusion pump during 2-hour study period. This amount of sodium nitroprusside decreases the mean arterial pressure (MAP) to 50 mmHg in rats.[7,8]

*Dopamine*: A fresh solution of dopamine was in fused at a rate of 0,5 μg $kg^{-1}min^{-1}$ using an infusion pump.

*Statistical methods*: Non-parametric Kruskall-Wallis test was used to evaluate the difference between the groups. Mann-Whitney U-test was used as post hoc test.

## RESULTS

*Hemodynamic measurements*: Mean arterial pressure measurements were lower in group H than in group C ($p<0.05$). There were not any significant differences in hemodynamic measurements between groups C and D. Similarly; hemodynamic parameters of groups H and H+D were not statistically different (Fig. 1). Dopamine infusion at the rate of 0,5 μg $kg^{-1}min^{-1}$ did not affect hemodynamic parameters in neither hypotensive nor normotensive rats.

*Blood and urinary chemistry*: Serum urea, creatinine, sodium and potassium levels in each group

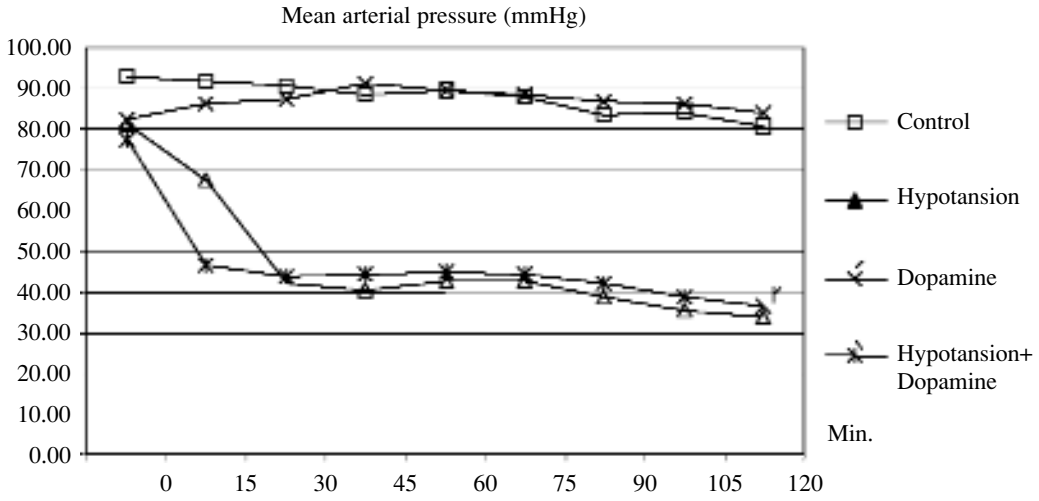


**Fig. 1.** Mean arterial pressure measurements during the study period.

at time 0, first and second hours were given in Table 1-4.

There were no changes in BUN levels in groups D and C during the study period. It, however, raised in both groups H and H+D. Compared between these two groups; the rise in group H+D was significantly lower than that of the group H at first hour ($p<0.05$). This difference was not observed at second hour of the study. BUN levels were not different between group C and group D. Creatinine levels did not show any statistical differences between the groups during the study period.

Serum sodium levels decreased in all groups during the study period ($p<0.01$), however there was not any difference between the groups. Similarly, serum potassium levels increased significantly ($p<0.05$) within but not between the groups.

Sodium clearance was found to be significantly higher in group H+D than in the other three groups ($p<0.01$). There was not any difference in sodium clearance between the other groups (Table 5). Values of the potassium clearance, urinary pH, density and volume did not also show any difference between the groups.

**Table 1.** Blood urea measurements (mg/dl) (mean±SD)

| | 0 | 1. hour | 2. hour |
|---|---|---|---|
| C | 19.50±2.84 | 19.30±2.87 | 20.70±2.91 |
| D | 21.70±5.42 | 21.30±3.89 | 22.00±5.37 |
| H | 19.70±4.60 | 25.10±4.23 | 26.90±5.51 |
| H+D | 21.90±4.07 | 23.40±4.86* | 27.40±6.96 |

*The increase in group H+D was significantly lower than that of the group H at first hour ($p<0.05$).

**Table 2.** Serum creatinine measurements (mg/dl) (mean±SD)

| | 0 | 1. hour | 2. hour |
|---|---|---|---|
| C | 0.41±0.17 | 1.13±2.07 | 0.54±0.25 |
| D | 0.40±0.09 | 0.42±0.12 | 0.50±0.17 |
| H | 0.39±0.17 | 0.59±0.18 | 0.69±0.16 |
| H+D | 0.51±0.15 | 0.49±0.31 | 0.65±0.30 |

**Table 3.** Serum sodium measurements (mmol/L) (mean±SD)

| | 0 | 1. hour | 2. hour |
|---|---|---|---|
| C | 139.40±10.12 | 132.90±13.08 | 127.90±13.19 |
| D | 140.10±7.62 | 133.20±8.68 | 127.10±8.14 |
| H | 131.17±15.07 | 123.07±14.87 | 119.80±15.56 |
| H+D | 142.30±6.85 | 129.10±11.12 | 130.30±5.31 |

**Table 4.** Serum potassium measurements (mmol/L) (mean±SD)

| | 0 | 1.hour | 2. hour |
|---|---|---|---|
| C | 4.51±0.87 | 4.76±0.50 | 4.62±0.63 |
| D | 4.32±0.62 | 4.28±0.62 | 4.92±0.37 |
| H | 4.60±0.61 | 4.72±0.60 | 4.84±0.73 |
| H+D | 4.90±0.60 | 5.12±0.50 | 5.32±0.58 |

**Table 5.** Urinary sodium and potassium measurements (mean±SD)

| | Sodium (mmol/l) | Potassium (mmol/l) | Sodium clearance (ml/min) | Potassium clearance (ml/min) |
|---|---|---|---|---|
| C | 67.4±34.20 | 41.33±19.89 | 4.31±2.38 | 73.80±36.20 |
| D | 62.60±35.90 | 46.84±14.22 | 4.57±1.73 | 92.40±34.90 |
| H | 74.20±37.80 | 39.75±17.62 | 4.94±2.40 | 71.80±32.10 |
| H+D | 120.20±17.47* | 39.13±14.36 | 7.80±1.20* | 64.42±26.35 |

* Urinary sodium and sodium clearance were found to be significantly higher in group H+D than in the other three groups ($p<0.01$).

## DISCUSSION

Hypotension is one of the most common etiological factors in acute renal failure and has well-known negative effects on renal functions.[9] Despite the lack of significant clinical evidence,[10-12] renal dose dopamine is commonly used in an attempt to protect or to improve renal function. Recent clinical data suggests that administration of low-dose dopamine by continuous infusion to critically ill patients at risk of renal failure does not provide significant protection.[13] Our aim in this study was to investigate the effect of low-dose dopamine on renal function in hypotensive rats.

It is known that low-dose dopamine has no significant hemodynamic effect in humans.[5,14,15] It has also previously been shown that dopamine infusion at a rate of 0,5 μg $kg^{-1}min^{-1}$ had no hemodynamic effect in rats.[2,4] We have chosen to infuse dopamine at this dose to investigate its renal effects without influencing hemodynamic parameters. Dopamine infusion at a rate of 0,5 μg $kg^{-1}min^{-1}$ showed no hemodynamic affect, and sodium nitroprusside induced hypotension did not cause a reflex tachycardia in our study

The increase in BUN level is a non-specific marker of renal functions. In several clinical studies with surgical patients, low-dose dopamine was found not to affect the BUN level.[16-18] Two recent experimental studies suggested beneficial effects of selective $D_1$ receptor agonists in preventing acute renal failure and BUN increase in streptozotocine-induced diabetic rats[19] and in rats with cisplatin-induced acute renal failure.[20] BUN levels increased in both hypotensive and dopamine treated hypotensive rats in our study. This rise was significantly lower in group H+D than in the group H at the first hour ($p<0.05$). The difference disappeared at the second hour of the experiment. The increase in renal blood flow caused by dopamine at pressures lower than the auto-regulatory threshold might have led this short-term prevention against the rise in BUN levels in our study. Low-dose dopamine can be stated to have a short-term preventive effect on renal functions as the BUN level is considered as a marker of prerenal azothemia.

Serum creatinine level and creatinine clearance is not affected by low-dose dopamine treatment in surgical and intensive care patients.[16-18,21,22] Similarly, we could not found any effect of low-dose dopamine on creatinine clearance. However, it can be criticized that two-hour period of our experiment is very short for creatinine elevation.

One of the most significant effects of low-dose dopamine is the increase in sodium excretion[15,23,24] and it was reported that this effect is independent of its hemodynamic action.[25] The potassium excretion was reported to increase by low-dose dopamine in rats[6] and healthy volunteers but this increase in humans has not been statistically significant.[25,26] Potassium clearance was not affected by low-dose dopamine infusion in our study. We could reach a significant increase in sodium clearance in hypotensive rats treated with low-dose dopamine. This increase, interestingly, was not observed in normotensive low-dose dopamine treated rats. This finding may be due to more significant increase in renal blood flow caused by dopamine at lower blood pressures - pressures lower than the auto-regulatory threshold - as the other investigators stated.[27]

## CONCLUSION

Despite its theoretical appeal, there is a few clinical data in the literature to support the use of

low-dose dopamine as a reno-protective agent. Several reviews, indeed, condemn its use for prophylactic purposes. Clinical studies with low-dose dopamine have usually been conducted in insufficient and heterogeneous intensive care patient population. The dosages administrated and parameters studied have not been standardized, and the statistical power of these studies has been poor. It seems that experimental studies on this subject will continue in this respect.

In conclusion, it can be stated that dopamine infusion at a rate of 0,5 μg $kg^{-1}min^{-1}$ has a short-term preventive action against the increase of BUN during the early phase of pharmacologically induced hypotension and it possessed a significant natriuretic effect in hypotensive but not normotensive rats.

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