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# Effect of nitric oxide on exercise-induced proteinuria in rats

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**Gündüz, Filiz, Oktay Kuru, and Ümit Kemal Şentürk.** Effect of nitric oxide on exercise-induced proteinuria in rats. *J Appl Physiol* 95: 1867–1872, 2003. First published July 18, 2003; 10.1152/japplphysiol.00599.2003.—Temporary proteinuria occurring after exercise is a common finding, and it is explained predominantly by alterations in renal hemodynamics. In this study, we investigated whether nitric oxide (NO), which is known to have an effect on renal hemodynamics and to increase during exercise, has a role in postexercise proteinuria. In the first step of this study, the effect of acute NO synthase blockage on exercise proteinuria was evaluated. The urinary protein levels in animals that performed acute exhaustive treadmill running exercise were considerably elevated compared with the control animals. Significantly elevated urinary protein levels were also detected in animals that received $N^{\omega}$-nitro-L-arginine methyl ester before exhaustion, compared with both control and exhausted groups, and mixed-type proteinuria was detected in electrophoresis, as in all exhausted animals. In the second step of the study, a NO donor (isosorbide mononitrate) was given to rats 1 h before exhaustive exercise. Mixed-type proteinuria and the elevation in urinary protein levels that occur as a consequence of exhaustive exercise were prevented by NO donor treatment. Finally, in the third step of our study, a calcium channel blocker (diltiazem), another vasodilator, was applied to the rats 1 h before exhaustive exercise. Urinary protein levels were not different in exhausted rats with or without calcium channel blocker treatment. On the other hand, in both groups, urinary protein levels were higher than in the control group. The tail-cuff blood pressure alterations caused by vasodilator drug applications before exercise were not different for NO donor and calcium channel blocker groups. These results suggest that endogenous NO might prevent the postexercise proteinuria from becoming more severe by affecting hemodynamic changes that occur during exercise.

nitric oxide synthase; nitric oxide synthase blockage; isosorbide mononitrate; diltiazem

NITRIC OXIDE (NO) has an important role in regulation of kidney functions, as well as in the regulation of many other tissues and organs. NO is effective in regulation of glomerular and medullary hemodynamics through vascular resistance, tubuloglomerular feedback response, renin release, and regulation of extracellular fluid volume (16, 17). It was demonstrated that acute systemic NO synthase (NOS) blockage causes a prominent increase in resistance of efferent and afferent arterioles and decreases renal blood flow besides increasing the systemic blood pressure (BP) (1). However, glomerular filtration rate either is not affected or is decreased less compared with the renal blood flow, because of the increased filtration fraction after NOS blockade (15, 16). In addition, it was shown that NOS blockage affects proximal tubular functions, and decreases total (absolute) and fractional tubular reabsorption (8, 9).

NO also contributes to the blood flow redistribution occurring during exercise. Increased NO production during exercise induces a vasodilatation in heart and skeletal muscles, and it prevents excessive vasoconstriction in the renal and splachnic region (18, 33). It was demonstrated that the vasoconstriction response in kidney, especially in the renal cortex, increased prominently when NOS blockage was applied before exercise (15). On the other hand, much is unknown about the effect of NO on kidney blood flow and functions, which are altered during exercise. Nor has the effect of NO on proteinuria occurring after exercise been investigated either.

Exercise proteinuria is common in athletes. It is described as a "temporary increase in protein excretion by urine in healthy individuals after exercise" (27) and was shown to occur in various exercising laboratory animals as well as in humans (5, 14, 27). The basic mechanisms of postexcercise proteinuria are increased glomerular permeability and/or exceeding the maximum tubular reabsorption capacity for proteins (6, 29). The permeability of the glomerular capillary membrane, which does not allow the filtration of macromolecules under normal circumstances, increases because of the renal hemodynamic alterations occurring during exercise. It is known that a considerable decrease in renal blood flow and an increase in filtration fraction occur during exercise and that this facilitates the passage of macromolecules/proteins to the ultrafiltrate (13, 23). Although the roles of many factors, such as prostaglandin, renin-angiotensin system, sympathetic stimulation, and negative charge loss from the glomerular membrane, are accounted for in the glomerular permeability change occurring during exercise (25, 26,

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28), the effect of NO on exercise proteinuria is not yet known.

It is possible that NO, which is increased during exercise, may have a role on relevance of exercise proteinuria because of either exercise or NO having an effect on renal hemodynamics. The aim of this study was to demonstrate whether NO has an effect on the occurrence of exercise-induced proteinuria. To test this hypothesis, we evaluated exercise proteinuria in rats under conditions of both NOS inhibition and increased NO availability.

## MATERIALS AND METHODS

### *Animals*

Eighty, 3-mo-old male Wistar rats weighing 200–280 g were used in this experimental study. All rats were given standard rat chow and tap water ad libitum and housed at 23 ± 2°C on a 12:12-h dark-light cycle. All procedures were approved by the Akdeniz University Animal Care and Usage Committee and followed the guidelines established by American Physiological Society. We randomly divided animals into 10 groups, and we tested our hypothesis in three steps of experiments.

### *Experimental Procedure*

*Step I.* In this step, the effect of acute NOS blockage on exercise proteinuria was evaluated. $N^{\omega}$-nitro-L-arginine methyl ester (L-NAME) was used for NOS blockage, and it was administered 2 h before exercise in a dose of 10 mg/kg ip. Control (C; $n = 8$), exhaustive exercise (Exer; $n = 8$), NOS blockage (L-NAME; $n = 8$), and exhaustive exercise + NOS blockage (L-NAME-Exer; $n = 8$) groups were involved in this step. C and Exer groups received 0.5 ml of sterile saline solution (vehicle) intraperitoneally. BP measurements were made in all groups. Basal (pretreatment of L-NAME) and posttreatment (just before exercise or 2 h after L-NAME administration) BP values were measured by a noninvasive tail-cuff method, and data were obtained with the MAY-BPHR200 unit and MP 100A-CE data acquisition system (BIOPAC Systems, Santa Barbara, CA) connected to a personal computer.

*Step II.* Isosorbide mononitrate (Ismn) was used as the NO donor in this step in which the effect of exogenously applied NO on exercise-induced proteinuria was examined. C animals ($n = 8$) received 0.5 ml of sterile saline solution intragastrically. The NO donor was administered in one group of animals (Ismn; 2 mg/kg po, $n = 8$), whereas the other group was subjected to additional exercise protocol 1 h after Ismn treatment (Ismn-Exer; 2 mg/kg po, $n = 8$). Basal (pretreatment of Ismn) and posttreatment (just before exercise or 1 h after Ismn administration) BP values were measured by a noninvasive tail-cuff method.

*Step III.* In this step, the effect of diltiazem (Dilti; a calcium channel blocker), another vasodilator agent, on exercise proteinuria was tested to reveal whether the effect of NO on exercise proteinuria is specific. For this purpose, one group received the calcium channel blocker without exercise (Dilti; $n = 8$), whereas another received it 1 h before acute exhaustive exercise (Dilti-Exer; $n = 8$) in a dose of 0.3 mg/kg. Sterile saline solution (0.5 ml ip) was administrated via intraperitoneal injection in C rats ($n = 8$). Basal (pretreatment of Dilti) and posttreatment (just before exercise or 1 h after Dilti administration) BP were measured by a noninvasive tail-cuff method.

### *Exercise Protocol and Sampling*

Acute exhaustive exercise was performed on a motor-driven treadmill (MAY-TME 9805, Commat, Ankara, Turkey). All the rats performing exercise were familiarized to treadmill running 5 days before actual experiment day. For the first 2 days, they were put on the treadmill just so that they would recognize it. They walked very slowly on treadmill for 5 min during subsequent 2 days, and finally they rested on the last day. The treadmill was equipped with an electric shock grid on the rear barrier to provide exercise motivation to the animals. The protocol was started at a speed of 20 m/min and no incline. The grade was gradually increased and reached 15% in 20 min. Running was continued until exhaustion. The point of exhaustion was determined by animal's loss of righting reflex when turned on its back.

Twenty-four-hour urine samples were collected from all animals while they were in metabolic cages and were used for protein and creatinine measurements. All animals in the exhausted groups were placed in metabolic cages immediately after treadmill running. The animals that received only drug treatment were placed in metabolic cages after drug administrations (2 h later for L-NAME group and 1 h later for Ismn and Dilti groups).

### *Proteinuria Assessment*

Total urinary protein levels were measured by spectrophotometric technique as described by Lowry et al. (19) and values are expressed as milligrams per milligram creatinine. Creatinine was measured by kinetic-spectrophotometric methods (BioSystems).

To determine the type of proteinuria, we used the Sebia Hydragel Proteinurie kit. After diluting the urine sample with saline to obtain ~0.2 g/dl protein, we applied a 5-μl urine sample to each well of the gel and let the samples diffuse into the gel for 10 min. The gel plate was placed in a Sebia K20 chamber at 8–10 mA, −60 V, for 60 min during migration. At the end of the migration time, the gel plate was stained with acid violet for 30 min and destained for 45 min with destaining solution. The gel was dried in a hot 80°C airstream for at least 15 min and was used to determine proteinuria type. The 16-, 32-, 48-, and 64-kDa molecular mass markers were used for determining the protein fraction. The band for 64 kDa indicated albumin.

### *Statistical Analyses*

Data are presented as means ± SE. Statistical analyses were performed with two-way analysis of variance test, and the Newman-Keuls post hoc test was used to compare intergroup differences when a significant $F$ ratio was found. A value of $P \leq 0.05$ was considered as statistically significant.

## RESULTS

BP values of all groups are shown in Tables 1–3. No difference for basal BP values was detected between the groups. BP levels after 2 h in L-NAME groups were considerably higher compared with the basal levels (Table 1). Significantly decreased BP levels were obtained in groups that received Ismn (Table 2) or diltiazem (Table 3). No statistically significant difference between the BP-lowering effects of Dilti and Ismn was detected. Exhaustion times were not different between all groups (data not shown).



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Table 1. *Basal and posttreatment blood pressure measurements (mean arterial pressures) of step I groups*

| | Control | L-NAME | Exercise | L-NAME-Exercise |
|---|---|---|---|---|
| Basal | 102.8 ± 4.5 | 102.4 ± 6.8 | 101.8 ± 4.2 | 98.6 ± 4.8 |
| Posttreatment | 103.2 ± 3.4 | 116.4 ± 8.2* | 102.8 ± 5.1 | 115.4 ± 4.1* |

Values are means ± SE given in mmHg. L-NAME, $N^{\omega}$-nitro-L-arginine methyl ester. *$P < 0.05$, difference from basal blood pressure.

Urinary protein levels are presented in Fig. 1. Although urinary protein levels increased after acute exhaustive exercise (Exer) compared with the C group, the urinary protein levels of animals that performed acute exhaustive exercise 2 h after L-NAME injection (L-NAME-Exer) were found to be significantly higher compared with both the C and Exer groups (Fig. 1*A*). The urinary protein levels of the rats that received L-NAME treatment without exercise were not different from those of the C group. The urinary protein levels of the rats that received NO donor without exercise (Ismn) were not different from those of the C group, whereas treatment with the NO donor prevented exercise-induced proteinuria in the Ismn-Exer group (Fig. 1*B*). There was no difference in urinary protein levels between the group that received Dilti treatment only (Dilti) and the C group. However, the urinary protein levels in the group which performed exercise 1 h after diltiazem treatment (Dilti-Exer) was found to be significantly higher compared with the other two groups (Fig. 1*C*).

The results obtained from urinary protein electrophoresis are shown in Fig. 2. Acute exhaustive exercise (Exer) caused mixed-type proteinuria, which is characterized by an increase in both light and heavy protein chain bands. Although band pattern of L-NAME group was similar to that of the C group, mixed-type proteinuria was detected in L-NAME-Exer group (Fig. 2*A*). The urinary protein electrophoresis patterns of Ismn and Ismn-Exer groups were similar to that of the C group (Fig. 2*B*). Mixed-type proteinuria was also detected in the Dilti-Exer group, whereas the results were similar in Dilti and C groups (Fig. 2*C*).

## DISCUSSION

The renal vasculature is under continuous and strong influence of NO (15–17). Although it has been demonstrated that NO plays an important role in blood redistribution during exercise, the effect of NO on exercise-induced proteinuria had not been investigated until now. In this study, it was shown that NOS inhibition increases exercise proteinuria in rats and that the urinary protein levels return to control values with use of a NO donor. The results suggests that NO prevents a further increase in the proteinuria arising during exercise.

Table 2. *Basal and posttreatment blood pressure measurements (mean arterial pressures) of step II groups*

| | Control | Ismn | Ismn-Exercise |
|---|---|---|---|
| Basal | 103.1 ± 2.5 | 93.8 ± 2.4 | 101.4 ± 1.8 |
| Posttreatment | 102.3 ± 1.6 | 83.7 ± 3.3* | 88.0 ± 4.4* |

Values are means ± SE given in mmHg. Ismn, isosorbide mononitrate. *$P < 0.05$, difference from basal blood pressure.

Table 3. *Basal and posttreatment blood pressure measurements (mean arterial pressures) of step III groups*

| | Control | Dilti | Dilti-Exercise |
|---|---|---|---|
| Basal | 101.9 ± 7.5 | 98.5 ± 2.3 | 103.4 ± 4.1 |
| Posttreatment | 100.8 ± 4.2 | 87.5 ± 1.5* | 96.0 ± 5.3* |

Values are means ± SE given in mmHg. Dilti, diltiazem. *$P < 0.05$, difference from basal blood pressure.

The factors primarily responsible for the induction of exercise proteinuria are changes in renal hemodynamics during exercise, the loss of negative charges in glomerular barrier, exceeding the proximal tubular reabsorption capacity, and exercise-induced oxidative stress (2, 11, 29). The increase in glomerular permeability during and immediately after exercise is also explained generally by the increase in filtration fraction (31). Renal blood flow decreases as a consequence of the increase in the renal symphatetic nerve activity and elevated level of catecholamines in circulation during exercise (2, 25, 30). Furthermore, an increase in resistance of afferent and efferent arterioles and in renin release are achieved by symphatetic stimulation during exercise. Angiotensin II, another possible effective vasoconstrictor agent in renal hemodynamics, has been investigated extensively. Angiotensin II production after renin release has been shown to cause an increase in transglomerular pressure and filtration fraction via a more prominent constriction of efferent arteriole (3, 6). On the other hand, some authors did not observe an involvement of renin-angiotensin system in postexercise proteinuria (24). In addition, it has been indicated that sympathetic neurotransmitters, such as dopamine and neuropeptide Y, could increase and that these may contribute to the splachnic and renal vasoconstriction during exercise (21). Involvement of vasoconstrictor agents in induction of postexercise proteinuria have been well studied compared with vasodilators, with the exception of prostaglandin (2, 26).

In the first step of this study, we investigated whether NO, which is one of the major vasodilator agents in kidney, has an effect on exercise proteinuria. We aimed to demonstrate the effect of acute NOS inhibition on proteinuria arising after exercise. Low-dose (10 mg/kg) L-NAME was used for NOS blockage. Previously used high doses, in a wide range of 30–300 mg/kg, have been shown to cause reluctance for running in rats (33). In addition, low-dose L-NAME treatment would influence the systemic hemodynamic parameters less compared with a high dose. In this study,



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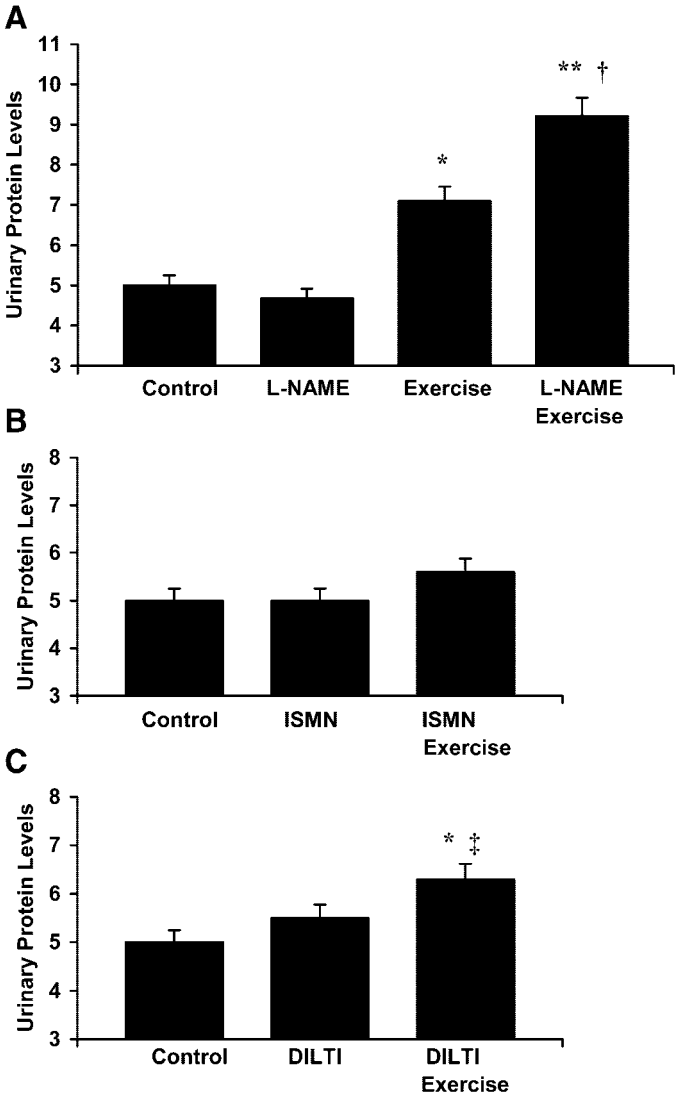


Fig. 1. Urinary protein levels of all groups. Values are means ± SE given in mg/mg creatinine. *A*: effect of nitric oxide synthase blockage on exercise-induced proteinuria (*step I* groups). *B*: effect of nitric oxide donor on exercise-induced proteinuria (*step II* groups). *C*: effect of calcium channel blocker on exercise-induced proteinuria (*step III* groups). L-NAME, $N^{\omega}$-nitro-L-arginine methyl ester; Ismn, isosorbide mononitrate; Dilti, diltiazem. *$P < 0.05$; **$P < 0.01$, difference from control group. †$P < 0.05$, difference from exercise group. ‡$P < 0.05$, difference from Dilti group.

BP increased ~15% as a result of L-NAME treatment. Exercise-induced proteinuria was significantly higher in the L-NAME-treated group before exhaustion (L-NAME-Exer) compared with the C and Exerc groups. Elevated NO production due to increased shear stress during exercise increases blood flow in heart and skeletal muscles (10, 22). However, NO also prevents excessive decrease in the renal and splachnic blood flow that occurs in renal-splanchnic region during exercise (33). As stated before, either sympathetic activation or increased angiotensin II production decrease renal blood flow during exercise (25, 28). Therefore, because NO in particular plays the balancing role against these vasoconstrictor agents, inhibition of NO production by NOS blockage might have induced an excessive proteinuria after exercise as a result of the increase in effectiveness of angiotensin II on efferent arteriole resistance.

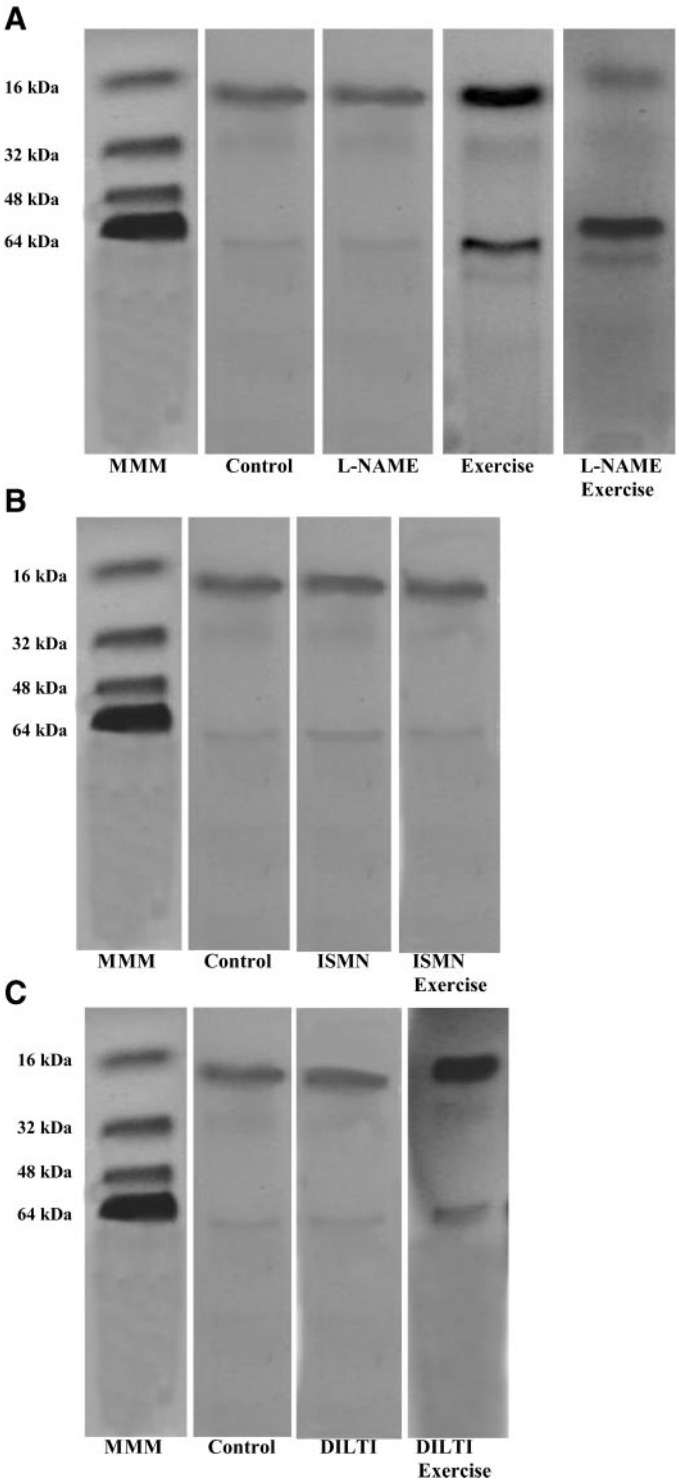


Fig. 2. Urinary protein electrophoresis of all groups. *A*: effect of nitric oxide-blockage on exercise-induced proteinuria (*step I* groups). *B*: effect of nitric oxide donor on exercise-induced proteinuria (*step II* groups). *C*: effect of calcium channel blocker on exercise-induced proteinuria (*step III* groups). MMM, molecular mass markers.



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We planned the second step of our study to investigate whether the exogenously given NO (Ismn) has an effect on exercise proteinuria. In addition, we investigated whether this effect is specific to NO by giving a nonspecific vasodilator agent (calcium channel blocker, Dilti) to another group in the third step of our study. In preliminary studies, doses of both drugs that caused similar hypotensive effects were determined. Agents that were given 1 h before exercise caused an ~7–13% decrease in BP. These agents did not affect urinary protein concentration and electrophoretic pattern when administered alone. The level of proteinuria after exercise in the group that received NO donor before exercise (Ismn-Exer) was not different from that of the C group. Furthermore, the urinary protein electrophoresis was similar to that of the C group. However, the effect of the calcium channel blocker was different from that of the NO donor. The amount of protein in Dilti-Exer group rats' urine after exercise was significantly higher compared with the C group, and mixed-type proteinuria was detected in electrophoresis. Because NO plays a major role in maintanace of renal blood flow (17), the decrease in renal blood flow that occur during exercise might have been prevented by addition of exogenous NO to endogenously produced NO. Thus the occurrence of postexercise proteinuria might be reduced.

Proteinuria induced by exercise is more prominent in diabetic and hypertensive patients (12, 34). In particular, physical exercise can be used as a provocative test to detect the silent stage of the kidney disorder in both types of diabetes (7). The renin-angiotensin system was the focus of most in the studies performed to explain the severe proteinuria occurring after exercise in diabetic patients (12, 32). The results of our study may indicate that one of the reasons for exercise-induced proteinuria in diabetic and hypertensive patients could be decreased NO production, because decreased NO production due to endothelial damage was reported in diabetes and hypertension (20). These findings may lead to the suggestion that one of the reasons for severe proteinuria after exercise in diabetic and hypertensive patients is NO deficiency.

In conclusion, proteinuria occurring after exercise becomes more prominent by NOS blockage and is prevented with exogenous NO treatment. Besides sympathetic activation and increased angiotensin II levels, which seem to be the most investigated factors in pathogenesis of exercise-induced proteinuria, the effect of NO on renal hemodynamics should be considered to be one of the primary reasons for postexercise proteinuria.

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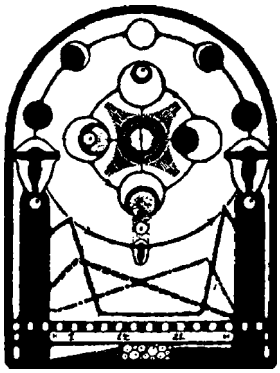



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