



EFFECTS OF HAEMODIALYSIS AND CONTINUOUS AMBULATORY PERITONEAL DIALYSIS ON NITRIC OXIDE SERUM CONCENTRATION IN PATIENTS WITH CHRONIC RENAL FAILURE

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ABSTRACT

Introduction: Nitric oxide (NO) plays an important role in a wide range of physiologic and pathophysiological processes. A major mediator of endothelial function, NO regulates vasodilatory and antithrombotic actions in the vasculature and plays a role in reproductive functions, bronchodilation, bone formation, memory, insulin sensitivity, and gastrointestinal relaxation. Impaired NO bioactivity is strongly associated with endothelial dysfunction. NO, an L-arginine derivative, also exerts a variety of renal and extrarenal physiological and pathophysiological effects. It seems that NO synthetic pathway could have a key role in mediating the complex hemodynamic and hemostatic disorders associated to the progression of renal disease. It remains unclear whether endogenous NO production is increased or decreased in patients with chronic renal failure. The objective of this study was to present the effect of different dialysis treatment on NO serum concentration in patients with chronic renal failure.

Patients and Methods: To evaluate endogenous NO production in these patients we studied plasma NO₂ and NO₃ levels (determined with the Griess method) in patients who underwent regular continuous ambulatory peritoneal dialysis or repeated haemodialysis and in healthy subjects. The study included 51 patients suffering from chronic renal failure and 30 healthy subjects.

Results: Our results show that patients with chronic renal failure had a significantly higher NO serum concentration than controls. These values did not differ between patients on haemodialysis and those on continuous ambulatory peritoneal dialysis. NO serum concentration did not differ between female and male independently of the patient's treatment.

Discussion and Conclusion: From obtained results we can concluded that uremia is associated with excessive systemic NO release independently of the patient's treatment. Alter (increase) NO synthesis may help to explain some pathological changes seen in uraemia such as bleeding tendency, a well-known complication of uremia and hemodialysis hypotension.

Key words: Nitric oxide, chronic renal failure, continuous ambulatory peritoneal dialysis, haemodialysis

INTRODUCTION

Nitric oxide (NO), a gaseous free radical derived from L-arginine, is a potent modulator of vascular tone. It has platelet antiaggregation and anti-adhesion properties. NO is also involved in the immune response and exerts a variety of renal and extrarenal physiological and pathophysiological effects¹. NO is generated by three isoforms of nitric oxide synthases (NOS): two acutely responsive, constitutive isoforms, neuronal NOS (nNOS)

and endothelial NOS (ecNOS), and the slower, more persistent, inducible NOS (iNOS)². Inhibition of this enzyme would lead to reduced NO levels and hence vasoconstriction. It has therefore been proposed that NO synthase insufficiency may play a key role in hypertension. Nitric oxide seems to be protective of atherosclerosis progression when produced at lower concentrations and to facilitate it at high rates of synthesis³. In this

context, it has been suggested that a diminished availability of L-arginine, the precursor for NO synthesis, is a common alteration of diseases such as hypercholesterolaemia, chronic renal failure (CRF) and heart failure^{4,5}.

NO regulates glomerular ultrafiltration; tubular reabsorption, and intrarenal renin secretion². Many of these renal effects are mediated by interactions with angiotensin II and adrenergic (alpha 2) activity⁶. A number of studies, both in the experimental model of renal mass reduction in rats and in uremic patients, have raised the hypothesis that abnormalities of NO synthetic pathway could have a key role in mediating the complex hemodynamic and hemostatic disorders associated to the progression of renal disease⁷. It seems that an inhibition of NO synthesis at the glomerular level is involved in the genesis of chronic renal failure, whereas a systemic activation of the L-arginine-NO pathway is a feature of established uraemia⁸. Uremia is associated with excessive systemic NO release, both in experimental model and in human beings. In the systemic circulation of uremic rats, as well as uremic patients, NO is formed in excessive amounts^{2,7,9}. Possible cause of the increased NO levels is higher release from systemic vessels due to the augmented expression of both iNOS and endothelial NOS. A putative cause for excessive NO production in uremia can be guanidinosuccinate, an uremic toxin that accumulates in the circulation of uremic patients and upregulates NO synthesis from cultured endothelial cells. Upregulation of systemic NO synthesis might be a defense mechanism against hypertension of uremia. On the other hand, more NO available to circulating cells may sustain the bleeding tendency, a well-known complication of uremia⁷. Since N-monomethyl-L-arginine (L-NMMA), an inhibitor of NO synthesis, normalizes the prolonged bleeding time of uremic rats, it has been suggested that bleeding associated with uremia was due to an excessive NO formation¹⁰. Drugs capable of enhancing renal NO activity may be renoprotective in a variety of experimental renal diseases, particularly those characterized by derangements of glomerular hemodynamics². There is ample evidence that in chronic renal failure there is an abnormal regulation of the L-arginine-NO pathway both in the kidney and at the systemic level^{11,12,13,14}. NO is a potent inhibitor of platelet adhesion and aggregation. It has been demonstrated that both the transport of L-arginine and NO production are enhanced in platelets taken from uraemic patients on haemodialysis, which participates in the prolonged bleeding time observed in uraemia^{10,15,16}. The renal proximal tubule is the major site of L-arginine synthesis and most L-arginine produced by the kidney enters

the systemic circulation with only a small portion being used and metabolised to urea in the kidney. Thus, the kidney plays an important role in maintaining a constant supply of L-arginine for use by other organs^{17,18}.

In this study we evaluate plasma NO₂ and NO₃ levels in patients with CRF who underwent regular continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis (HD) and in healthy subjects.

MATERIAL AND METHODS

Patients and methods

The study included 51 patients suffering from chronic renal failure who were treated with CAPD (*Group A*), repeated HD (*Group B*) and in healthy subjects (*Group C*). This study had the approval of the our institutional clinical research ethic review board and consent was obtained from each patient.

Patients from *group A* (total 23 patients; 13 female, 10 male) exchanged dialytic fluid from peritoneal cavity three time per day. The average age was 55.8 and average period of CAPD duration in these patients was 3.4 year.

Patients from *group B* (total 28 patients; 13 female, 15 male). The average age was 55.9. The mean duration of haemodialysis was from 180 to 240 minutes (individual approach), three times a week. The dialysers used were produced by Gambro and Fresenius companies with controlled ultrafiltration, and bicarbonate module were applied. Haemodialysis was performed on the following dialysers: E₄H, F₆, F₆₀, F_{60s}. Heparinisation was continuous with 4000-5000 i.u. of heparin per patient. No patients had primary pulmonary disease nor had haemodynamic instability during haemodialysis. The average period of haemodialysis duration in these patients was 3.4 year.

Thirty healthy volunteers (*Group C*) matched for age were used as controls. Exclusion criteria were infection, diabetes mellitus, heart failure and recent blood transfusion. All patients treated at Department for Nephrology and dialysis University hospital of Niš.

Serum sampling

Blood samples from all observed patients were taken from *cubital vein*. This procedure from patients of *group B* (patients treated with regular haemodialysis) were performed immediately before of the following haemodialysis. From the patients of *group A* (patients treated with continuous ambulatory peritoneal dialysis) blood samples were collected immediately before of emptying of

peritoneal cavity. From the control group (group C) blood were collected in basal conditions. After coagulation and centrifugation at 2.000 g for 5 min, the serum was frozen at -20°C until the determination of ACE activity. Blood samples for the determination of NO concentration were diluted 1:1 (vol/vol) with 0.9% saline, protein-precipitated (30% ZnSO₄, 0.05 ml per ml of blood), centrifuged at 2.000 g for 10 minutes and frozen at -20°C until the determination of NO level.

Measurement of NO concentration

The NO level in the serum was determined by measuring nitrite concentrations, a stable metabolic product of NO with oxygen. Conversion of NO₃²⁻ into NO₂²⁻ was done with nitrate reductase elementary zinc. NO₂²⁻ concentration in serum was determined by classic colorimetric Griess reaction. Briefly, equal volumes of samples and Griess reagent (sulfanilamide and naphthalene-ethylene diamine dihydrochloride) were mixed at room temperature. After 5 min, the absorbance was measured at 546 nm using spectrophotometer. The concentration of nitrite was determined by a standard curve prepared with sodium nitrite (1-200 OM).

Statistics

The results of measurement was expressed as a mean ± SEM. Differences between the means were statistically compared by Student's t-test; Cochran and Cox modification, and differences at $P < .05$ were considered significant.

RESULTS

The results of measurements NO serum concentration in patients with chronic renal failure who were treated with CAPD (Group A), repeated HD (Group B) and in healthy subjects (Group C) were shown in Figure 1.

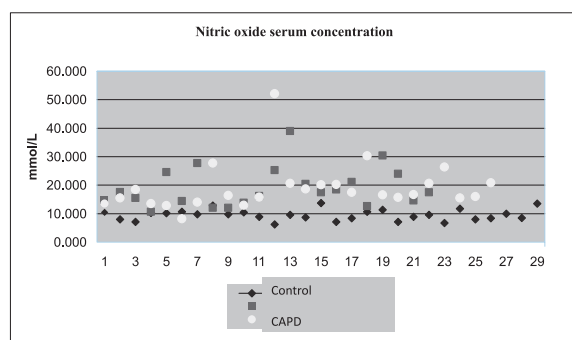


Figure 1. NO serum concentration in patients on CAPD, HD and in healthy subjects

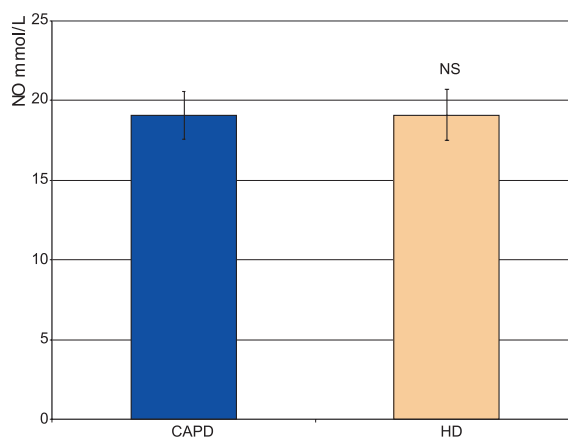


Figure 2. Relation between NO serum concentration in patients on CAPD (A) and patients on HD (B). *NS not significant

Figure 2. presents means (X) of NO serum concentration in patients on CAPD (Group A) and repeated HD (Group B). Statistic analysis by means of Student's t-test for small independent samples (Cochran and Cox modification) showed that these values did not differ (N.S.) between patients on HD and those on CAPD.

Figure 3. presents means (X) of NO serum concentration in patients on CAPD (Group A), repeated HD (Group B) and in healthy subjects (Group C). Statistic analysis by means of Student's t-test for small independent samples (Cochran and Cox modification) showed that patients with chronic renal failure (those on CAPD and those on HD) had a significant ($P < .05$) higher NO serum concentration than controls (figure 3).

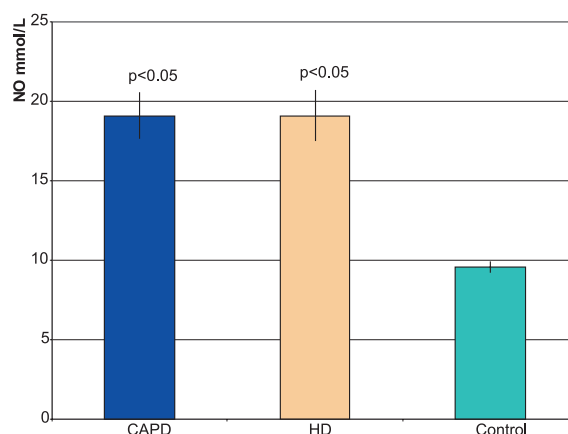


Figure 3. Relation between NO serum concentration in patients on CAPD, HD and in healthy subjects (C).

Also, we tested difference between NO serum concentration in female (F) and male (M) patients with chronic renal failure who underwent CAPD (Group A), or repeated HD (Group B) (figure 4). Statistic

analysis showed that NO serum concentration did not differ (NS) between female (F) and male (M) patients independently of the patient's treatment.

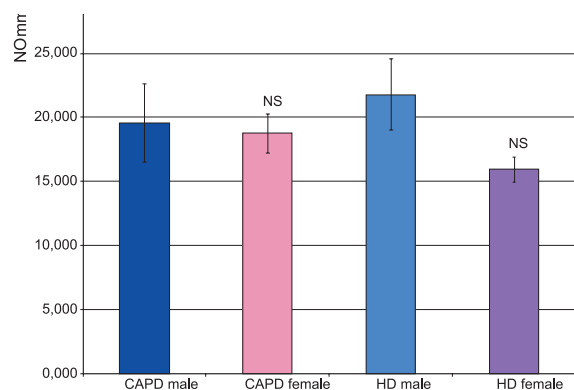


Figure 4. Relation between NO serum concentration according to sex in patients on CAPD and on HD*NS not significant

DISCUSSION

CRF is a pathological state with high morbidity and mortality, and a full understanding and adequate treatment of this disease remain a challenge¹⁹. The progression of renal failure results in a complex syndrome referred to as uraemia. Until kidney transplantation becomes widely available, patients with end-stage renal disease (ESRD) requiring renal replacement treatment (RRT) will have to be maintained on either HD or CAPD.

The uraemic syndrome is a complex condition that results from an accumulation of multiple waste compounds, combined with failure of the endocrine and homeostatic functions of the kidney in end-stage CRF patients²⁰. Treatment with HD and CAPD presents different pathophysiological profiles and it has been suggested that clinical outcome in chronic renal failure may depend on the mode of dialysis⁸.

Nitric oxide exerts multiple effects on renal function. It remains unclear whether endogenous nitric oxide production is increased or decreased in patients with chronic renal failure. To evaluate endogenous nitric oxide production in these patients we studied plasma NO₂ and NO₃ levels in patients with CRF who underwent CAPD or HD and in healthy subjects.

Plasma NO₂ and NO₃ concentration did not differ between patients on HD and those on CAPD. Our results are comparable with the literature data^{8,9}. Uraemia *per se*, independently of treatment conditions, activates L-arginine transport, physiological precursor for NO synthesis. This mechanism seems to be activated as renal failure progresses, independently of the patient's treatment⁸.

Although there is controversy as to whether systemic NO levels are increased or decreased in renal failure²¹, our results show clearly that patients with CRF (those on HD and those on CAPD) had a higher plasma NO₂ and NO₃ concentration than controls. The obtained results are in compliance with the results obtained by other authors^{2,7,8,9}. Uremia is associated with excessive systemic NO release, both in experimental model and in human beings. In the systemic circulation of uremic rats, as well as uremic patients, NO is formed in excessive amounts^{2,7,9}. In CAPD patients much attention has been paid to endocrine dysfunction occurring in uraemia. Glucose intolerance is a common finding in uraemia and results primarily from peripheral tissue insensitivity to insulin²². Continuous absorption of 100–200 g/day glucose causes hyperglycaemic stress and accentuates hyperinsulinaemia in CAPD patients²³. Elevated glucose and insulin are known to increase L-arginine uptake via the transport system y⁺ (CAT-1) and NO production²⁴. Another possible explanation for increase NO production in CAPD patients gave Devenport et al.²⁵. As peritoneal mesothelial cells have a common embryological derivation with endothelial cells, then mesothelial cells could potentially be a major source of locally produced NO. But also the increased NO production during episodes of acute bacterial peritonitis is more likely due to a combination of increased NO production by peritoneal endothelial cells and transmigrating macrophages^{25,26}.

Chronic hypotension, which affects 5–10% of HD patients in the interdialytic period, is characterized hemodynamically by preserved cardiac index, heart rate or stroke volume, but reduced total peripheral vascular resistances. Although its pathophysiology is not well defined, an increased production of vasodilators, such as nitric oxide or adrenomedullin, are possibly involved^{27,28}. Thus, the increased production of NO seems to be involved in the pathophysiology of chronic hypotension in dialysis patients. Although the mechanism of this increased production of vasodilators is unknown, it is likely that the inflammatory state of uremia plays a role²⁹. In fact, both nitric oxide and adrenomedullin production are induced by cytokines. Nishimura et al.³⁰ observed that serum levels of hepatocyte growth factor (HGF), a cytokine which induces endothelial proliferation and nitric oxide-mediated vasodilation, was increased in hypotensive hemodialysis patients. Taking these observations together, it appears that the chronic microinflammatory state of uremia can play a role in chronic hypotension of dialysis patients, through the induction of the synthesis of several vasodilator substances²⁷.

The possible explanation for controversial results - whether endogenous NO production is increased

or decreased in patients with CRF - maybe found da Silva et al³¹. They reported NO synthesis are only stimulated in platelets from well-nourished CRF patients, leading to impaired platelet aggregation. The absence of this adaptive response in the L-arginine-NO pathway in platelets from malnourished CRF patients may account for the enhanced occurrence of thrombotic events in these patients³¹. Malnutrition is a common feature in CRF and adversely affects patient morbidity and mortality. Inadequate diet and a state of persistent catabolism play major roles in uraemic malnutrition, yet the underlying mechanisms have not been completely clarified. It has been suggested that abnormalities in NO bioactivity, coupled with malnutrition and inflammation, may contribute to increased incidence of atherothrombotic events in uraemia²⁰. Amongst the earliest indications of nutritional deficiency are low concentrations of plasma amino acids, including L-arginine, the precursor for NO synthesis. The enhancement of L-arginine transport is essential to maintain increased NO synthesis in platelets taken from these patients²⁰.

Brunini et al.³² have established that reduced plasma L-arginine and NO production and increased tumour necrosis factor- α (TNF- α), fibrinogen, and C-reactive protein levels in malnourished uremic patients are associated with increased aggregability of platelets. Their findings may explain the increased cardiovascular mortality in patients with deficient nutritional status, leading to inflammation, oxidative stress, impaired L-arginine-NO signalling, and platelet activation. Those investigators also assumed the potential benefits of L-arginine supplementation and platelet function in malnourished uremic patients.

Also, we tested difference between plasma NO₂ and NO₃ levels in female and male patients with CRF who underwent CAPD or repeated HD. NO serum concentration did not differ between female and male independently of the patient's treatment. We couldn't compare these findings because of no literature data about NO serum concentration in patients with CRF who underwent two different dialysis treatment according to sex.

CONCLUSIONS

- On the basis of our results, it may be concluded that endogenous NO production in patients with CRF is increased.
- There is no difference between Nitric oxide concentration in serum of patients who underwent CAPD or repeated HD.
- NO serum concentration did not differ between female and male patients independently of the patient's treatment.

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EFEKTI HEMODIJALIZE I KONTINUIRANE AMBULANTNE PERITONEALNE DIJALIZE NA SERUMSKE KONCENTRACIJE AZOTNOG OKSIDA U PACIJENATA SA HRONIČNOM RENALNOM INSUFICIJENCIJOM

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APSTRAKT

Uvod: Azotni oksid (NO) ima važnu ulogu u brojnim fiziološkim procesima. Kao glavni medijator u funkciji endotela reguliše vazodilataciju i antitrombinsku aktivnost u krvnim sudovima, te učestvuje u reproduktivnim funkcijama, bronhodilataciji, formiranju kosti, memoriji, osjetljivosti na insulin i gastrointestinalnoj relaksaciji. Poremećaj bioaktivnosti NO snažno je povezan sa disfunkcijom endotela. NO, derivat L-arginina, takođe ispoljava različite bubrežne fiziološke i patofiziološke efekte. Čini se da bi put sinteze NO mogao imati ključnu ulogu u posredovanju kompleksnih hemodinamskih i hemostatskih poremećaja koji prate napredovanje bubrežne bolesti. Ostaje nejasno da li je kod bolesnika sa hroničnom renalnom insuficijencijom povećano ili smanjeno endogeno stvaranje NO. Cilj ovog rada je bio da se pokaže efekt primjene različitih dijaliznih tretmana na serumsku koncentraciju NO kod bolesnika sa hroničnom bubrežnom insuficijencijom.

Pacijenti i metode: Da bismo odredili nivo endogenog stvaranja NO kod ovih bolesnika mjerili smo nivo NO_2 i NO_3 (određivan Griess-ovom metodom) u plazmi bolesnika koji su liječeni kontinuiranom ambulatornom peritoneumskom dijalizom, ponavljanim hemodijalizama, te u grupi zdravih pojedinaca. U studiju su bili uključeni 51 bolesnik sa hroničnom bubrežnom insuficijencijom i 30 zdravih pojedinaca.

Rezultati i Diskusija: Naši rezultati pokazuju da je koncentracija NO u serumu bolesnika sa hroničnom bubrežnom insuficijencijom bila statistički značajno veća nego kod kontrolne grupe. Ove vrijednosti se nisu razlikovale između bolesnika liječenih kontinuiranom ambulatornom peritoneumskom dijalizom i onih liječenih ponavljanim hemodijalizama. Koncentracija NO u serumu nije se razlikovala između ženskih i muških bolesnika, bez obzira na primijenjeni tretman.

Zaključak: Iz dobijenih rezultata možemo zaključiti da je uremija praćena povećanim sistemskim otpuštanjem NO, nezavisno od vrste primijenjenog tretmana. Promjena (povećanje) sinteze NO mogla bi pomoći u razjašnjavanju nekih patoloških promjena koje se mogu vidjeti u uremiji kao što su sklonost krvarenju, dobro poznata komplikacija uremije i hemodijalizna hipotenzija.

Ključne riječi: Nitrični monoksid, hronična bubrežna insuficijencija, kontinuirana ambulatorna peritonealna dijaliza, hemodijaliza

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