



# PLASMA LEVELS OF BRAIN NATRIURETIC PEPTIDES AND CARDIAC TROPONIN IN HEMODIALYSIS PATIENTS

HALIMA RESIĆ\*, SELMA AJANOVIĆ, NIHAD KUKAVICA,  
FAHRUDIN MAŠNIĆ, AIDA ĆORIĆ

Haemodialysis Clinic, University of Sarajevo Clinics Centre,  
Bolnička 25, 71 000 Sarajevo, Bosnia and Herzegovina

\* Corresponding author

## ABSTRACT

Patients with End-Stage Renal Disease (ESRD) are at high risk of death as a result of the cardiovascular disease (CVD), which cannot be explained by the conventional risk factors only. Haemodialysis patients frequently have elevated serum concentrations of the cardiac troponins T, specific markers of myocardial injury. Plasma levels of brain natriuretic peptide (BNP) are elevated in fluid volume overload and heart failure, and decreased during dialysis. Currently, LV hypertrophy and LV dysfunction are considered the strongest predictors of cardiovascular mortality in dialysis population, and the synthesis of cardiac natriuretic peptides is high in the presence of alterations in the left ventricular (LV) mass and function. The aim of this study was to investigate the factors associated with the increased serum levels of BNP and CTN in haemodialysis patients, and their impact on cardiovascular morbidity.

In this cross-sectional study we included 30 patients with ESRD, without coronary symptoms, who were subjected to regular dialysis treatment three times a week for the duration of four hours. Heart failure was defined as an ejection fraction (EF) of < 35%, and dyspnoea associated with either elevated jugular pressure or interstitial oedema evidenced in chest X-ray. All patients were in sinus rhythm at the time of the study. Twenty-five patients were on erythropoietin treatment. Blood samples were taken before and after the dialysis session.

Our study included 30 patients (17 males, 13 females). The average age was 53,8 years (total range 31-74) divided into two groups: euvolemic and hypervolemic. The average dialysis time was 70,3±46,95 months. All haemodialysis patients had excessively high levels of BNP 2196,66±4553,86 ng/cm<sup>3</sup>. Plasma cTnT was found to be increased in 33,3% of patients.

Patients with hypervolemia had significantly higher cTnT levels (0,0577±0,0436), as compared to the euvolemic patients 0,0184±0,0259 p<0,05. The elevated cTnT significantly correlated with the level of BNP (p<0,01), while average post-dialysis BNP was not significantly lower (1698,06±3499,15; R=0,191; p-ns.) as compared to the pre-dialysis BNP (1839,13±3691,55; R=432; p<0,01). The pre-dialysis cTnT was lower (0,0315±0,0372) as compared to the post-dialysis cTnT (average 0,0399). Euvolemic patients had BMI 24,28±3,15, as compared to the hypervolemic patients BMI 25,71±4,20 (p-n.s.). Increased BNP was not

in correlation with older age ( $R=0,271$  p-ns.) and duration of dialysis ( $R=0,198$ ). The hematocrit level increases significantly during haemodialysis (39,9%;  $p<0,05$ ). Patients with higher BNP and cTnT have significantly higher indexed left ventricular mass, as compared to the patients with normal ventricular function.

Our study shows that 33,3% of asymptomatic patients on haemodialysis have elevated cTnT while all patients have elevated BNP. Measuring the plasma concentration of brain natriuretic hormones may be useful for identification of the dialysis patients with LVH.

KEY WORDS: haemodialysis, troponin, brain-natriuretic peptide, cardiovascular disease.

## INTRODUCTION

Determination of the plasma concentrations of cardiovascular peptides in haemodialysis (HD) patients has potential clinical value in:

1. Determination of volume status
2. Assessing and improving cardiovascular stability
3. Determination of degree of heart failure
4. Survival prognosis

The haemodialysis patients frequently have elevated cardiac natriuretic peptide levels. Cardiac troponin (cTnT) is exclusively expressed in cardiomyocytes, and is released into circulation after irreversible damage of cardiac muscle (1). Release of cardiac markers in ischemia is influenced by different factors, the most important being the compartmentation. There are several other reasons for appearance of cTnT, including myocardial damage due to the increased LV wall tension from hypertrophy, or acute or chronic volume overload, a condition that is frequently found in haemodialysis patients. In some studies, cTnT was associated with left ventricular mass and cardiovascular congestion (2,3). Possible reasons include impaired cardiac haemodynamics or underlying musculature in uraemia. Increased myocardial dilatation in the state of acute or chronic hyperhydration may lead to secretion of cTnT and BNP, and the dialysis procedure influences their levels by haemoconcentration. Patients with renal insufficiency have increased BNP, and that is an indicator of coronary artery disease and LVH (4,5).

## MATERIALS AND METHODS

### Patients

In our study we included patients with ESRD, treated by chronic intermittent haemodialysis for a period longer than 6 months. The study design was cross-sectional, with one year follow-up period. The exclusion criteria were the following: age  $>75$  years, acute myocardial ischaemia, acute infections, and malignancy. The evaluation entailed the following: demographic data, BMI, blood pressure, haematocrit (HTC), assessment of the hydration status. At the time of the

inclusion, blood samples for cTnT, BNP, and HTC were drawn prior to dialysis (after weekend) and after.

### Methods

HD patients were treated three times a week with the standard bicarbonate dialyses (Na 138 mmol/L,  $\text{HCO}_3^-$  35 mmol/dm<sup>3</sup>, K-2,0 mmol/dm<sup>3</sup>, Ca -1,5 mmol/dm<sup>3</sup>, Mg- 0,5 mmol/dm<sup>3</sup>). Blood flow rate varied between 250-350 cm<sup>3</sup>/min, and standard dialysate flow was 500 cm<sup>3</sup>/min. All HD patients were anuric (24 h urine volume  $<500$  cm<sup>3</sup>, while a minority of patients (N=5) had 24 h diuresis  $>500$  cm<sup>3</sup>/24 h. Left ventricular function was assessed by 2-D and Doppler echocardiography. The thickness of ventricular walls and intraventricular septum, and the diameter of LV, were measured by M-mode echocardiography. Hypervolemia was assessed according to clinical score system which included the following parameters: difference to dry weight  $>3,5$  kg, peripheral oedema, radiological signs of pulmonary congestion in the chest X-ray.

### Statistical analysis

Data were expressed as means and standard deviations. Categorical variables were expressed as absolute numbers and percentages. Statistical significance was assumed at values  $p<0,05$ .

## RESULTS

Thirty patients with ESRD, treated by haemodialysis, were included in our study. The main demographic and clinical characteristic of the patients included in the study are presented in Table 1.

Patient characteristics	N=30	p
Age (years)	53 (range 32-75)	
Gender M/F	17/13	
Period of dialysis treatment (months)	70,3±46,95	
Oligoanuric ( $<500$ cm <sup>3</sup> /day)	25	
BMI (Kg/m <sup>2</sup> )	24,76±3,47	
Systolic blood pressure (mmHg) pre-dialysis	130,33±21,09	$<0,01$
Diastolic blood pressure (mmHg) pre-dialysis	78±6,64	$<0,01$
Systolic blood pressure (mmHg) post-dialysis	111,33±21,29	$<0,01$
Diastolic blood pressure (mmHg) post-dialysis	72±9,96	$<0,01$

TABLE 1. Characteristics of patients

Average age of patients was  $53,8 \pm 15,68$  years and average period of dialysis treatment was  $70,3 \pm 46,95$  months. The primary renal diseases were nephroangiosclerosis (44%), glomerulonephritis 24%, polycystic kidney disease 20%, pyelonephritis 9%, and diabetic nephropathy 3%.

Hypervolemia was found in 10 out of 30 patients. Average pre-dialysis serum levels of BNP was elevated  $1839,13 \pm 3691,55$  pg/cm<sup>3</sup> and post-dialysis level of BNP decreased to  $1698,06 \pm 3499,15$  (R=0,191, p=ns.). Pre-dialysis and post-dialysis plasma BNP was higher in patients with left ventricular dysfunction and hypervolemia (BNP  $4619,5 \pm 5509,3$ ) as compared to euvolemic patients (BNP  $448,77 \pm 563,85$ ) (Table 2).

Gender	Euvolemic N=20	Hypervolemic N=10	P
Age	<b>10F/10M</b>	4F/6M	n.s
Time on dialysis	<b>71,4±52,51</b>	68,1±35,68	n.s
BMI	<b>24,28±3,15</b>	25,71±4,20	p<0,05
BNP	<b>448,77±563,85</b>	4619±5509,3	p<0,01
cTnT	<b>0,0184±0,0259</b>	0,0577±0,0436	
LV mass index (g/m <sup>2</sup> )	<b>120,05±29,6</b>	170,35±42,20	p<0,05
Interventricular septum (mm)	<b>8,1±2,1</b>	1,217±0,280	

TABLE 2. Characteristics of euvolemic and hypervolemic patients

Increased BNP was not related to age (p=ns.) and duration of dialysis, but rather to hypervolemia and LV mass index (p<0,01) (Table 2).

Elevation of cTnT correlated significantly with the level of BNP R=0,432 (p<0,01). Average pre-dialysis cTnT in 10 patients was  $0,0315 \pm 0,0372$  ng/cm<sup>3</sup> and post-dialysis cTnT was significantly higher ( $0,0318 \pm 0,0399$ ) (R=0,403, p<0,01). Average difference between pre and post-dialysis body weight was 2,5-4,5 kg, and BMI (body mass index (kg/m<sup>2</sup>) was  $24,76 \pm 3,47$  /m<sup>2</sup> (Table 3).

<b>BNP (ng/cm<sup>3</sup>) pre-dialysis</b>	<b>1839±3691,55</b>	<b>p</b>
<b>BNP (ng/cm<sup>3</sup>) post-dialysis</b>	1698,06±3499,15	n.s.
<b>cTPN (pg/cm<sup>3</sup>) pre-dialysis</b>	0,0315±0,0372	
<b>cTPN (pg/cm<sup>3</sup>) post-dialysis</b>	0,0318±0,0399	<0,05
<b>HTC (%) pre-dialysis</b>	35,44±3,50	<0,05
<b>HTC (%) post-dialysis</b>	39,9±3,59	<0,05
<b>LV mass index (g/m<sup>2</sup>)</b>	120,05±29,6	170,35±42,20
<b>Interventricular septum (mm)</b>	8,1±2,1	1,217±0,280

TABLE 3. Laboratory parameters

The haematocrit level increased significantly during haemodialysis, 35,44% vs. 39,9% (p<0,05). Hypervolemia signs were as follows: dry weight >3,5 kg, clinical signs of hypervolemia (oedema, dyspnoea), and radiological signs of pulmonary congestion. Patients

with signs of hypervolemia (n=10) had significantly higher cTnT (prior to haemodialysis) in comparison to haemodialysis patients without hypervolemia ( $0,0577$  ng/cm<sup>3</sup> vs.  $0,0184$  mg /cm<sup>3</sup> p<0,05) and the same results were found for BNP. Twenty-five out of 30 patients were oligoanuric while 5 were not. High levels of cTnT and BNP were found in oligoanuric patients.

Systolic blood pressure was  $130,33 \pm 21,09$  mmHg during pre-dialysis, and significantly decreased at the end of dialysis ( $111,33 \pm 21,09$  p<0,01). The same was observed for diastolic blood pressure ( $78 \pm 6,64$  vs.  $72 \pm 9,96$ , p<0,01). There was a significant linear correlation between the BNP and LV mass index in pre-dialysis ( $4619,5$  BNP; LVMI  $170,35$  g/m<sup>2</sup>) (p<0,01) vs. post-dialysis level BNP  $1698,06$ , but there was no correlation between BNP and EF (48,4) (p=ns).

Echocardiography showed left ventricular hypertrophy in 55,8% patients. None of the patients had significant heart valve disease. LV dysfunction was found in 18 patients, with an average left ventricular ejection fraction of  $48,64 \pm 9,496$ . Fifteen of patients with LV dysfunction also had right ventricular enlargement.

## DISCUSSION

Cardiac troponin is released from cardiomyocytes into circulation after irreversible damage of cardiac muscle. High levels of troponin may be caused not only by major coronary artery stenosis, but also by microvascular lesions, silent plaque, rupture or subclinical myocardial fibrosis and necrosis (6, 7). The reason for cTnT elevation in haemodialysis patients is undetermined. Possible reasons include periodical hemodynamics or underlying cardiac disease with specific alterations of cardiac musculature in uraemia (8, 9, 10). The dialysis membrane may also alter cTnT and BNP concentrations. In our study we found an upper limit of cTnT levels in 10 hypervolemic patients out of the total of 30 patients examined. In previous studies, cTnT was associated with left ventricular mass and cardiovascular congestion in chronic haemodialysis patients (12, 13). Different studies have reported 20-53% frequency of cTnT upper limit (14). Our study showed that the period of dialysis treatment and patients' age were not associated with high cTnT. Another study showed that age, duration of dialysis, and initial kidney disease, were associated with high cTnT (15, 16). Actually, little is known about the route of degradation of cTnT; furthermore, the kinetics of decreases and the catabolic path-

ways of cTnT in haemodialysed patients are not known. In our study, serum concentrations of cTnT were significantly higher in oligoanuric patients than in patients with diuresis. Willging et al. (13) reported rates of urinary clearance of less than 0,01 cm<sup>3</sup>/min. in patients without renal impairment following acute myocardial infarctus. In chronic renal failure patients, before haemodialysis, there was a positive correlation between serum concentrations of creatinine and cTnT (18). In the Lowebeer et al. study a negative correlation between the serum levels of cTnT and creatinine was found in haemodialysis patients (15). The cardiovascular status in older patients with decreased muscle proved to be worse. In the early 1990 a research was conducted into the application of cardiac natriuretic peptides for the diagnosis of LVH and systolic dysfunction. High plasma level of BNP in dialysis patients is multifactorial and depends on extra cellular volume expansion. Nita et al. reported that BNP may be a possible indicator of reduced ventricular function in HD patients (22).

Different studies reported that plasma BNP has high specificity and sensitivity in diagnosis of left ventricular dysfunction in patients with normal renal function (22, 24). Determination of BNP in diagnosing ventricular dysfunction in patients with end stage renal failure has not been thoroughly explored. In our study we found that the brain natriuretic peptide was, to a high degree, correlated with several echocardiographic parameters, including LV mass index and thickness of the left ventricular walls, especially in hypervolemic patients. BNP was elevated in all haemodialysis patients, but significant elevation was found in hypervolemic patients. Possible explanation for high increase of BNP in this group of patients could be that the left ventricular hypertrophy is potentially important cause of elevated natriuretic peptides in dialysis patients. Our data suggest a significant impact of declining residual diuresis on the level of BNP. Numerous studies showed that measurements of BNP could be helpful for identification of the LVH and left ventricular dysfunction (25).

## CONCLUSION

This study shows that BNP was 20 times higher in our dialysis patients. Determining plasma levels of BNP is useful in diagnosing the impaired left ventricular function in HD patients. Continued high plasma level of BNP may indicate the need for further pharmacological treatment with ACE inhibitors in the application of extended or daily haemodialysis. The magnitude of cTnT was particularly apparent in patients with fluid overload. We confirmed that plasma cTnT is elevated in about 33% of asymptomatic haemodialysis patients.

## REFERENCES

- (1) Heeschen C., Deu A., Langenbrink L., Goldmann B., Hamm C. Analytical and diagnostic performance of troponin assays in patients suspicious for acute coronary syndromes. *Clin. Biochem.* 2000; 33: 359–368
- (2) Jaffe A., Ritter C., Meltzer V., Harter H., Roberts H. Unmasking artefactual increases in creatine kinase isoenzymes in patients with renal failure. *J. Lab. Clin. Med.* 1984; 104: 193–202
- (3) McLaurin M., Apple F., Voss E., Herzog C., Sharkey S. Cardiac troponin I, cardiac troponin T and creatine kinase-MB in dialysis patients without ischemic heart disease: evidence of cardiac troponin T expression in skeletal muscle. *Clin. Chem.* 1997; 46: 976–982
- (4) Haller C., Zehelein J., Remppis A., Müller-Bardorff M., Katus H. Cardiac troponin T in patients with end-stage renal disease: absence of expression in truncal skeletal muscle. *Clin. Chem.* 1998; 44: 930–938
- (5) Ooi D., House A. Cardiac troponin T in hemodialysed patients. *Clin. Chem.* 1998; 44: 1410–1416
- (6) Roppolo L., Fitzgerald R., Dillow J., Ziegler T., Rice M., Maisel A. A comparison of troponin T and troponin I as predictors of cardiac events in patients undergoing chronic dialysis at Veteran's Hospital: a pilot study. *J. Am. Coll. Cardiol.* 1999; 34: 448–454
- (7) Stolar JC., Georges B., Shita A., Verbeelen D. The predictive value of cardiac troponin T measurements in subjects on regular haemodialysis. *Nephrologie Dialysis and Transplantation* 1999; 14: 1961–1967
- (8) Katus H., Remppis A., Scheffold T., Diederich K., Kueber W. Intracellular compartmentation of cardiac troponin T its release kinetics in patients with reperfused and non-reperfused myocardial infarction. *Am. J. Cardiol.* 1991; 67: 1360–1367

- (9) Adams J., Bodor G., Davila-Roman V. et al. Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993; 88: 101–106
- (10) Ricchiuti V., Apple F. RNA expression of cardiac troponin T isoforms in diseased human skeletal muscle. *Clin. Chem.* 1999; 45: 2129–2135
- (11) Frankel W., Herold D., Ziegler T., Fitzgerald R. Cardiac troponin T is elevated in asymptomatic patients with chronic renal failure. *Am. J. Clin. Pathol.* 1996; 106: 118–123
- (12) Apple F., Sharkey S., Hoefft P. et al. Prognostic value of serum cardiac troponin I and T in chronic dialysis patients: a 1-year outcomes analysis. *Am J Kidney Dis* 1997; 29: 399–403
- (13) Willging S., Keller F., Seimbach G. Specificity of cardiac troponins I and T in renal disease. *Clin. Chem. Lab. Med.* 1998; 36: 87–92
- (14) Collinson P., Hadcocks L., Foo Y. et al. Cardiac troponins in patients in renal dysfunction. *Ann. Clin. Biochem.* 1998; 35: 380–386
- (15) Löwbeer C., Ottosson-Seeberger A., Gustafson S., Norrman R., Hulting J., Gutierrez A. Increased cardiac troponin T and endothelin-1 concentrations in dialysis patients may indicate heart disease. *Nephrol. Dial. Transplant.* 1999; 14: 1948–1955
- (16) Tun A., Khan I., Win M. et al. Specificity of cardiac troponin I and creatine kinase-MB isoenzyme in asymptomatic long-term hemodialysis patients and effect of hemodialysis on these cardiac markers. *Cardiology* 1998; 90: 280–285
- (17) Solaro R. Troponin I, stunning, hypertrophy and failure of the heart. *Circ. Res.* 1999; 84: 122–124
- (18) Martin G., Becker B., Schulman G. Cardiac troponin-I accurately predicts myocardial injury in renal failure. *Nephrol. Dial. Transplant.* 1998; 13: 1709–1712
- (19) deFilippi C., Tiblier E., Sperger H. et al. Angiographic correlates of cardiac troponin T and I elevation in chronic hemodialysis patients (Abstract). *Circulation* 1999; 100 [Supplement 1]: I-291
- (20) Wessels S., Atmann K., Törnig J., Ritz E. Cardiovascular structural changes in uremia: implications for cardiovascular function. *Semin. Dial.* 1999; 12: 288–292
- (21) Sagnella G.A. Measurement and significance of circulating natriuretic peptides in cardiovascular disease. *Clin. Sci* 1998; 95: 519–529.
- (22) Nitta K., Kawashima A., Yumura W., Naruse M., Oba T., Kabaya T., Nihei H. Plasma concentration of brain natriuretic peptide as an indicator of cardiac ventricular function in patients on hemodialysis. *Am. J. Nephrol.* 1988; 18: 411–415.
- (23) Goto T., Takase H., Toriyama T., Sugiura T., Kurita Y., Tsuru N., Masuda H., Hayashi K., Ueda R., Dohi Y. Increased circulating levels of natriuretic peptides predict future cardiac event in patients with chronic hemodialysis. *Nephron.* 2002; 92(3): 610–615.
- (24) Wei T.M., Zeng C.L., Chen L.P., Chen Q.Y., Zhao R.Y., Lu G.X. et al. Bedside tests B-type natriuretic peptide in the diagnosis of left ventricular diastolic dysfunction in hypertensive patients. *Eur. J. Heart failure* 2005; 7: 75–79.
- (25) Clerico A., Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: a review. *Clin. Chem.* 2004; 50: 33–50.