Circulating N-Terminal Pro-Brain Natriuretic Peptide and Cardiac Troponin T in Chronic Dialysis Patients

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Abstract

In the general population, plasma concentrations of cardiac troponin T (cTnT) and N-terminal pro-brain natriuretic peptides (NT-proBNP) are useful as markers of cardiac ischemia and heart failure respectively. Whether these cardiac markers have similar diagnostic potential in chronic dialysis patients are not known. The authors studied the diagnostic value of cTnT and NT-proBNP correlated with the clinical status of 63 chronic renal failure (CRF) patients with chronic dialysis (30 males and 33 females), aged 26 to 77 years (mean ± SD, 55.9 ± 12.6 years). Plasma cTnT and NT-proBNP were determined by using Elecsys 2010 (Roche, Switzerland). The authors found that 23.8 per cent of the chronic dialysis patients had cTnT concentrations more than the cut-off (≥ 0.1 ng/ml) and 100 per cent of these patients had NT-proBNP concentrations over the cut-off (> 334 pg/ml). The authors could not demonstrate the statistical difference between males and females for NT-proBNP concentrations as reported in the general population. But cTnT concentrations in females were significantly less than males. The authors also found a weak correlation between the two markers, when the circulating cTnT was correlated with NT-proBNP. These results suggested that plasma cTnT in chronic dialysis patients should be a prognostic marker for cardiac ischemia by using the same cut-off as the normal population. However, plasma NT-proBNP concentrations could not be used as a heart failure marker in this group of patients and needed another cut-off value for specific use in chronic dialysis patients. Moreover, the combination of cTnT and NT-proBNP concentrations in these patients may be another choice for detection of both cardiac ischemia and heart failure in the same situation. These combination markers should improve mortality in chronic dialysis patients.

Key word : Chronic Dialysis, Chronic Renal Failure, NT-proBNP, cTnT

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Chronic renal failure (CRF) is the classical clinical situation in which the cardiac natriuretic peptides are almost universally raised. Extracellular volume expansion, concomitant heart disease, and severely reduced or abolished renal clearance are the main factors responsible for the high plasma concentration of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)[1-4]. The increasing incidence of CRF has prompted investigation into its etiology and natural history. Studies have recently reported that the increasing mortality in chronic dialysis patients is most frequently caused by congestive heart failure (CHF), coronary artery disease (CAD), or both[5-7]. A noninvasive biochemical testing method for early detection and monitoring the condition of cardiac complications in chronic dialysis patients would be useful and might lead to improved survival[8-14]. N-terminal pro-brain natriuretic peptide (NT-proBNP) may be reliable and a less time consuming assay for the detection of CHF and left ventricular dysfunction (LVD) particularly in chronic dialysis patients. Cardiac Troponin T (cTnT) also demonstrated that its plasma or serum concentrations should be an important predictor of long-term, all-cause mortality and cardiovascular mortality in patients with chronic dialysis.

The purpose of this present study was to evaluate the concentrations of NT-proBNP and cTnT in chronic dialysis patients in Thailand compared with other countries. Another objective was to demonstrate the correlation between NT-proBNP and cTnT in this group of patients.

MATERIAL AND METHOD

Patient population

The Ethical Committee for Human Study at Siriraj Hospital, Mahidol University, approved the study. Informed consent was obtained from each participant. Sixty-three CRF patients with chronic dialysis (30 males and 33 females), aged 26 to 77 years (mean ± SD, 55.9 ± 12.6 years) were enrolled in the study. All participants were without history of clinical evidence of circulatory congestion or myocardial infarction.

NT-proBNP assay

Blood samples were collected in EDTA tubes and centrifuged within 30 min and the plasma was stored at -85°C before assay. NT-proBNP concentrations were determined with an electrochemiluminescence immunoassay (ECLIA) by using Elecsys 2010 (Roche Diagnostics, Switzerland). The intra- and interassay variation coefficient was 3 per cent and 5 per cent respectively.

Cardiac troponin T assays

Cardiac troponin T was measured on the 3rd generation Roche Elecsys 2010 analyzer. The manufacturer's stated detection limit is < 0.01 ng/ml, with an imprecision of 10 per cent coefficient of variation (CV) at 0.03 ng/ml. Total imprecision was 7.0 per cent at 0.07 ng/ml.

Statistical analysis

The data were processed using the SPSS for Window software (SPSS Inc, Chicago, IL). All data were presented as mean with standard deviation. The Wilcoxon test for unpaired observations was used to compare the means of the 2 sets of data. The null hypothesis was rejected at the 95 per cent confidence interval, considering $p < 0.05$ as significant.

RESULTS

The main demographic and biochemical data of the patients included in the studies are shown in Table 1. When the authors compared plasma NT-proBNP concentrations between males and females, no statistical difference was found as shown in Fig. 1. Fig. 2 shows the box-plot of cTnT from male and female patients with chronic dialysis. There was a statistically significant difference between this group

Table 1. Baseline characteristics, renal function tests, lipid profiles, NT-proBNP and cTnT of chronic renal failure patients with chronic dialysis.

Number	63
Male/female	30/33
Age (years)	55.9 ± 12.6
Glucose (mg/dl)	114.1 ± 50.5
BUN (mg/dl)	84.1 ± 18.8
Creatinine (mg/dl)	12.6 ± 3.3
Uric acid (mg/dl)	9.1 ± 1.7
Cholesterol (mg/dl)	182.6 ± 39.7
Triglyceride (mg/dl)	116.0 ± 56.7
HDL-C (mg/dl)	45.8 ± 14.1
Calcium (mg/dl)	9.5 ± 0.9
Phosphate (mg/dl)	6.2 ± 2.0
Magnesium (mg/dl)	3.0 ± 0.5
NT-proBNP (pg/ml)	33,688 ± 50,035
(range)	(996-215,790)
cTnT (ng/ml)	0.089 ± 0.088
(range)	(0.001-0.348)

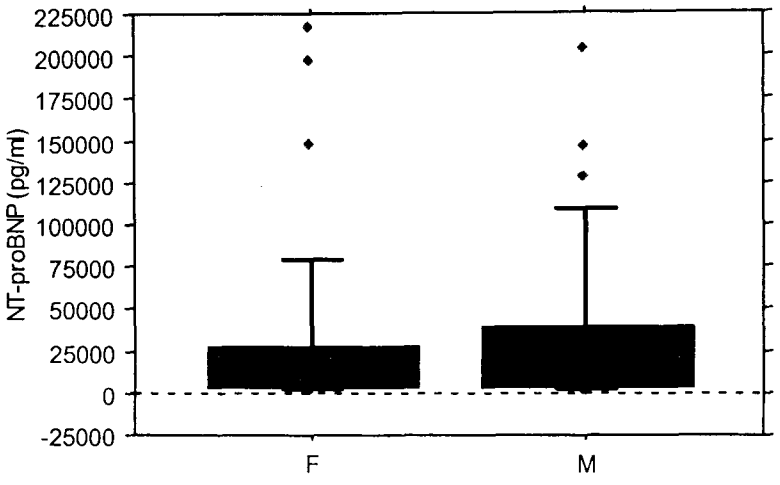

Fig. 1. **Plasma NT-proBNP in male (M) and female (F) chronic renal failure patients with chronic dialysis. Each modified box-plot represents the mean and the 10^{th} and 90^{th} percentiles. The error bars represent the lowest and highest values. There was no statistically significant difference between males and females ($p > 0.05$).**

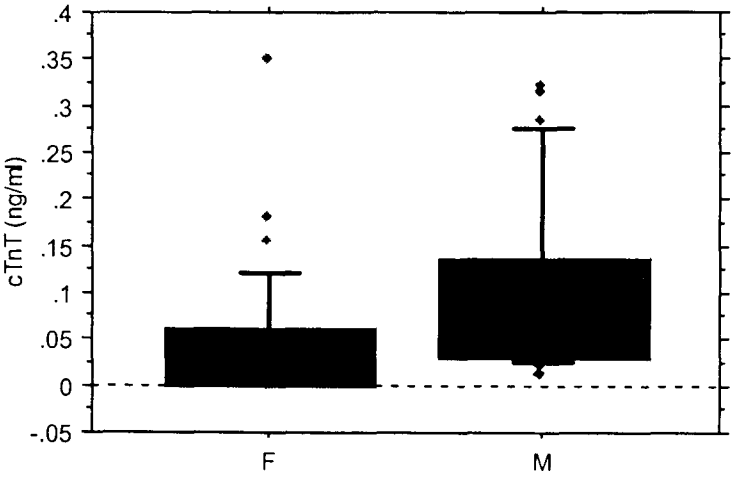

Fig. 2. **Plasma cTnT in male (M) and female (F) chronic renal failure patients with chronic dialysis. Each modified box-plot represents the mean and the 10^{th} and 90^{th} percentiles. The error bars represent the lowest and highest values. There was a statistically significant difference between males and females ($p < 0.05$).**

of patients ($p < 0.05$). Fig. 3 shows the positive correlation between NT-proBNP and cTnT. The equation of the fitted model is NT-proBNP = 16,774.382 + 232,383.754xcTnT ($p < 0.01$, $r = 0.401$). Since the p-value in the ANOVA table is less than 0.01, there is a statistically significant relationship between NT-proBNP and cTnT at the 99 per cent confidence level. The correlation coefficient equals 0.401, indicating a relatively weak relationship between NT-proBNP and cTnT.

DISCUSSION

CRF with chronic dialysis patients are at a very high cardiovascular risk comprise of myocardial

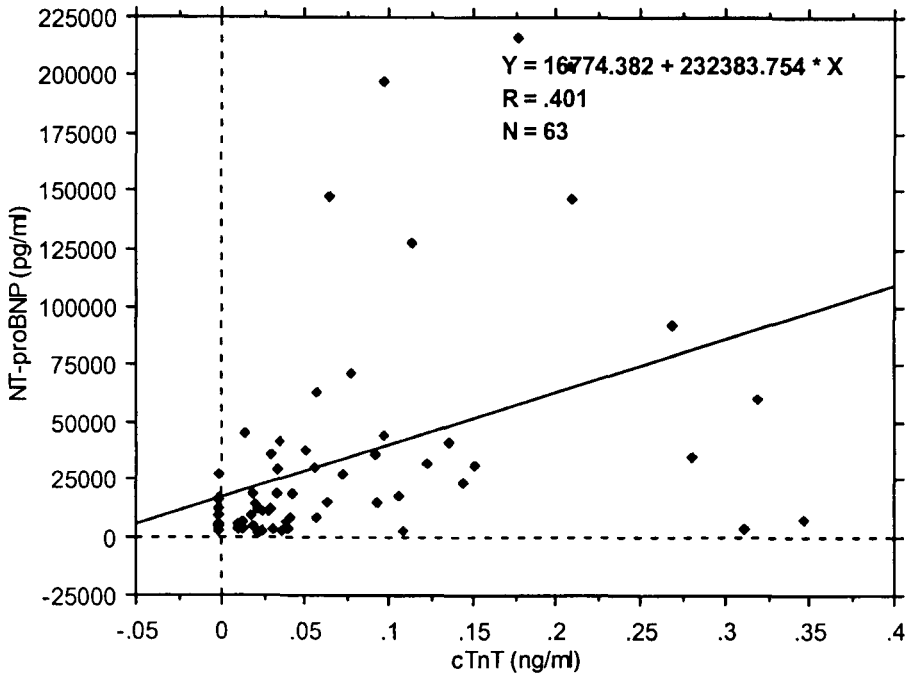

Fig. 3. Regression plot between NT-proBNP and cTnT in 63 CRF patients with chronic dialysis.

infarction and congestive heart failure[6,12,15,16]. In the past, elevated cTnT in chronic dialysis patients has been ascribed to a false-positive biomarker for the assessment of acute coronary syndrome (ACS) [13,17,18]. Several studies have now demonstrated that significant angiographic findings are linked to cTnT elevations, identifying patients with ACS who will benefit from antithrombotic therapy[19-22]. The finding of the present study, using a cut-off value ≥ 0.1 ng/ml, 23.8 per cent of the cTnT concentration was increased. This result was compatible with the study of Haller et al who reported that 29 per cent of hemodialysis patients had increased cTnT concentrations[17]. They also showed that, although the reasons for the increased cTnT concentrations in the blood of chronic dialysis patients without clinical evidence of myocardial cell injury are not clear, but the cTnT measured in these patients was cardiac in origin. From the study of Apple et al, who evaluated the long-term survival in a large number of end stage renal disease (ESRD) patients (n = 733), they found that 20.2 per cent of these patients had increased cTnT[19]. Moreover, they concluded that increased cTnT concentrations in ESRD patients might trigger a more aggressive approach to diagnosis and therapy of coronary artery disease (CAD) in this population.

CRF patients also suffer from cardiomyopathy. A proper biochemical marker for heart failure to detect the condition of cardiac complications in these patients may improve the therapeutic strategy and survival. In the present study, 100 per cent of the chronic dialysis patients had circulating NT-proBNP over the cut-off (> 334 pg/ml). Ishii et al reported that 95 per cent of ESRD patients had an increase in BNP concentrations[23]. When the authors correlated the circulating cTnT with NT-proBNP, a weak correlation between the two markers was found. A significant association of NT-proBNP with clinical heart failure was not found. This condition contrasts with the elevated NT-proBNP concentrations seen in nonuremic patients with heart failure or acute myocardial infarction[24-26]. Theoretically, the mechanism for the elevation of NT-proBNP concentrations in the plasma of patients with chronic dialysis could also include the disappearance of hormone clearance (decreased excretion or metabolism) by the kidney. The authors suggested that the cut-off value for NT-proBNP in chronic dialysis patients should be different from nonuremic patients.

In conclusion, the present study demonstrated that increased cTnT concentrations in chronic dialy-

sis patients was common and could be used as the prognostic indicator. All patients with elevation of cTnT should urgently be worked up with a functional cardiac study or coronary angiography especially if an elective procedure is being planned. On the other hand, all patients with elevation of NT-proBNP over the normal cut-off did not show a significant correlation with clinical heart failure. There might be an urgent need for another cut-off value for NT-proBNP with specific use for chronic dialysis patients to detect the heart failure stage. Further studies in this area are suggested.

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REFERENCES

1. Tonolo G, McMillan M, Polonia J, et al. Plasma clearance and effects of alpha-hANP infused in patients with end-stage renal failure. Am J Physiol 1988; 254: F895-9.
2. Buckley MG, Sethi D, Markandu ND, Sagnella GA, Singer DR, MacGregor GA. Plasma concentrations and comparisons of brain natriuretic peptide and atrial natriuretic peptide in normal subjects, cardiac transplant recipients and patients with dialysis-independent or dialysis-dependent chronic renal failure. Clin Sci (Lond) 1992; 83: 437-44.
3. Corboy JC, Walker RJ, Simmonds MB, Wilkins GT, Richards AM, Espiner EA. Plasma natriuretic peptides and cardiac volume during acute changes in intravascular volume in haemodialysis patients. Clin Sci (Lond) 1994; 87: 679-84.
4. Chen HH, Burnett JC Jr. The natriuretic peptides in heart failure: Diagnostic and therapeutic potentials. Proc Assoc Am Physicians 1999; 111: 406-16.
5. Parfrey PS. Cardiac and cerebrovascular disease in chronic uremia. Am J Kidney Dis 1993; 21: 77-80.
6. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995; 47: 186-92.
7. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: Identifying opportunities for intervention. Am J Kidney Dis 1996; 27: 347-54.
8. Zoccali C, Mallamaci F, Benedetto FA, et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. J Am Soc Nephrol 2001; 12: 1508-15.
9. Mallamaci F, Zoccali C, Tripepi G, et al. Diagnostic potential of cardiac natriuretic peptides in dialysis patients. Kidney Int 2001; 59: 1559-66.
10. Akiba T, Tachibana K, Togashi K, Hiroe M, Marumo F. Plasma human brain natriuretic peptide in chronic renal failure. Clin Nephrol 1995; 44 (Suppl 1): S61-4.
11. Nishikimi T, Futoo Y, Tamano K, et al. Plasma brain natriuretic peptide levels in chronic hemodialysis patients: Influence of coronary artery disease. Am J Kidney Dis 2001; 37: 1201-8.
12. Dierkes J, Domrose U, Westphal S, et al. Cardiac troponin T predicts mortality in patients with end-stage renal disease. Circulation 2000; 102: 1964-9.
13. Frankel WL, Herold DA, Ziegler TW, Fitzgerald RL. Cardiac troponin T is elevated in asymptomatic patients with chronic renal failure. Am J Clin Pathol 1996; 106: 118-23.
14. Roppolo LP, 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 a Veteran's Hospital: A pilot study. J Am Coll Cardiol 1999; 34: 448-54.
15. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. Kidney Int 1999; 55: 1553-9.
16. Ooi DS, Zimmerman D, Graham J, Wells GA. Cardiac troponin T predicts long-term outcomes in hemodialysis patients. Clin Chem 2001; 47: 412-7.
17. Haller C, Zehelein J, Remppis A, Muller-Bardorff M, Katus HA. Cardiac troponin T in patients with end-stage renal disease: Absence of expression in truncal skeletal muscle. Clin Chem 1998; 44: 930-8.
18. Li D, Keffer J, Corry K, Vazquez M, Jialal I. Nonspecific elevation of troponin T levels in patients with chronic renal failure. Clin Biochem 1995; 28: 474-7.
19. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation 2002; 106: 2941-5.
20. deFilippi CR, Tocchi M, Parmar RJ, et al. Cardiac troponin T in chest pain unit patients without ischemic electrocardiographic changes: Angiographic correlates and long-term clinical outcomes. J Am Coll Cardiol 2000; 35: 1827-34.
21. Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 2002; 346: 2047-52.
22. Panteghini M, Cuccia C, Pagani F, Turla C, Bonetti G, Bonini E. Coronary angiographic findings in patients with clinical unstable angina according to cardiac troponin I and T concentrations in serum. Arch Pathol Lab Med 2002; 126: 448-51.
23. Ishii J, Nomura M, Okuma T, et al. Risk stratification using serum concentrations of cardiac troponin T in patients with end-stage renal disease on chronic maintenance dialysis. Clin Chim Acta 2001; 312: 69-79.
24. Masson S, Vago T, Baldi G, et al. Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. Clin Chem Lab Med 2002; 40: 761-3.
25. Luchner A, Hengstenberg C, Lowel H, et al. N-terminal pro-brain natriuretic peptide after myocardial infarction: A marker of cardio-renal function. Hypertension 2002; 39: 99-104.
26. Latini R, Masson S, de Angelis N, Anand I. Role of brain natriuretic peptide in the diagnosis and management of heart failure: Current concepts. J Card Fail 2002; 8: 288-99.

ระดับของเอ็นที-โปรบีเอ็นพีและคาร์ดิแอกโทรโปนินทีในกระแสเลือดในผู้ป่วยไตวายที่ต้องทำการล้างไตสม่ำเสมอ

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ในกลุ่มประชากรทั่วไประดับความเข้มข้นของคาร์ดิแอกโทรโปนินทีและเอ็นที-โปรบีเอ็นพีมีประโยชน์อย่างมากในการบ่งชี้ถึงภาวะหัวใจขาดเลือดและหัวใจวาย แต่ในผู้ป่วยไตวายที่ต้องทำการล้างไตอย่างสม่ำเสมอนั้นยังไม่สามารถบอกได้ว่าทั้งคาร์ดิแอกโทรโปนินทีและเอ็นที-โปรบีเอ็นพีจะมีประโยชน์เช่นเดียวกันหรือไม่ในกรณีของผู้ป่วยไตวาย ทางคณะผู้วิจัยจึงได้ทำการศึกษาเพื่อตรวจวัดระดับความเข้มข้นของคาร์ดิแอกโทรโปนินทีและเอ็นที-โปรบีเอ็นพีในผู้ป่วยไตวายที่ต้องทำการล้างไตอย่างสม่ำเสมอจำนวน 63 ราย เป็นเพศชาย 30 รายและเพศหญิง 33 ราย โดยมีช่วงอายุระหว่าง 26 ปี ถึง 77 ปี (ค่าเฉลี่ย $\pm$ ค่าเบี่ยงเบนมาตรฐาน, 55.9 $\pm$ 12.6 ปี) การตรวจวัดระดับความเข้มข้นของคาร์ดิแอกโทรโปนินทีและเอ็นที-โปรบีเอ็นพีในกระแสเลือดทำโดยใช้เครื่องมือตรวจอัตโนมัติ อิเล็คซีส 2010 (โรช, ประเทศสวิสเซอร์แลนด์) ผลการวิจัยพบว่า 23.8 เปอร์เซ็นต์ของผู้ป่วยไตวายมีระดับความเข้มข้นของคาร์ดิแอกโทรโปนินทีเพิ่มสูงขึ้นกว่าปกติ ($\geq$ 0.1 ng/ml) และ 100 เปอร์เซ็นต์ของผู้ป่วยไตวายมีระดับความเข้มข้นของเอ็นที-โปรบีเอ็นพีในกระแสเลือดเพิ่มสูงขึ้นกว่าค่าปกติ (> 334 pg/ml) สำหรับคาร์ดิแอก-โทรโปนินทีในเพศหญิงมีค่าต่ำกว่าในเพศชายอย่างมีนัยสำคัญทางสถิติในขณะที่ค่าเอ็นที-โปรบีเอ็นพีระหว่างเพศหญิงและเพศชายไม่มีความแตกต่างกันอย่างมีนัยสำคัญดังเช่นที่พบในประชากรปกติ นอกจากนั้นยังพบความสัมพันธ์แบบอ่อน ๆ ระหว่างการเพิ่มสูงขึ้นของคาร์ดิแอกโทรโปนินทีและเอ็นที-โปรบีเอ็นพีในผู้ป่วยกลุ่มนี้ ($r = 0.401$, $p < 0.05$) จะเห็นได้ว่า คาร์ดิแอก-โทรโปนินที ที่เพิ่มสูงขึ้นน่าจะมีประโยชน์ในเรื่องการบ่งชี้ถึงภาวะหัวใจขาดเลือดได้ดีโดยไม่ต้องปรับค่าปกติที่ใช้อยู่เดิมแต่ในกรณีของเอ็นที-โปรบีเอ็นพีคงไม่สามารถนำมาใช้บอกภาวะหัวใจวายในผู้ป่วยกลุ่มนี้ได้หากใช้ค่าปกติเดียวกับประชากรทั่วไปจำเป็นจะต้องหาค่าปกติใหม่ที่เหมาะสมกับผู้ป่วยไตวาย นอกจากนั้นยังพบว่าหากใช้ทั้งคาร์ดิแอกโทรโปนินทีและเอ็นที-โปรบีเอ็นพีเป็นดัชนีชี้บ่งถึงภาวะหัวใจขาดเลือดและภาวะหัวใจวายร่วมกันไปน่าจะมีผลช่วยให้ผู้ป่วยไตวายได้รับการดูแลรักษาได้รวดเร็วขึ้นและอาจลดอัตราการเสียชีวิตจากภาวะหัวใจในผู้ป่วยกลุ่มนี้ลงได้

คำสำคัญ : การล้างไต, ไตวายเรื้อรัง, เอ็นที-โปรบีเอ็นพี, คาร์ดิแอกโทรโปนินที,

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