The Relationship between Serum Concentration of Cardiac Troponin I in Chronic Renal Failure Patients and Cardiovascular Events

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Objective: *The purpose of this study was to evaluate the relationship between serum cardiac troponin I in asymptomatic chronic renal failure patients and cardiovascular events.*
Background: *Short-term follow-up studies on this subject produced conflicting results.*
Material and Method: *A total of 63 asymptomatic patients with chronic renal failure (CRF) with regular hemodialysis were followed for 18 months for cardiac mortality, myocardial infarction events and interventional procedures such as percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG). Serum cTnI and other blood chemistries were measured at the time of the study.*
Results: *Forty seven chronic dialysis patients (75%) had an elevated level of cTnI concentration more than the 0.08 ng/ml cutoff but only fourteen patients (22%) had and elevated cTnI concentration of more than the AMI cutoff (0.4ng/ml). When using the 0.08 ng/ml cutoff, the NT-proBNP concentrations of the elevated groups were significantly higher than the normal groups. The authors also found that the elevated groups above the AMI cutoff had significantly higher cardiovascular events.*
Conclusion: *Elevated cTnI concentrations are commonly found in chronic renal failure patients. The AMI cutoff level of cTnI (0.4 ng/ml) seem to have a benefit for predicting the cardiovascular events in asymptomatic chronic renal failure patients while the 0.08 ng/ml cutoff doesn't have usefulness for this purpose. Further studies are needed to clarify this hypothesis.*

Keywords: *Chronic renal failure, Cardiovascular events, cTnI, NT-proBNP*

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The diagnostic and prognostic utilities of cardiac troponins are now well established. They have emerged as sensitive and specific markers to detect myocardial injury and infarction. In addition to detecting acute myocardial infarction, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) can identify high-risk patients with cardiac diseases who tend to have subsequent cardiovascular events[1-3].

Cardiovascular events are highly prevalent in patients with end-staged renal disease and cause approximately 50% of the annual mortality in hemodialysis patients[4-6]. The prevalence of coronary artery disease may be as high as 73% in this population[7]. Diagnosing ischemic heart disease in this patient population remains challenging because these patients frequently have silent or atypical symptoms and a reduced reliability on creatinine kinase -MB isoenzyme (CK-MB). Several studies questioned the usefulness of the cardiac troponins, particularly cTnT, in the presence of renal disease. Troponins T elevations have been reported in noncardiac conditions[8-10] but some reports do not agree with this belief[11-13].

Because cardiac Troponin I is exclusively of cardiac origin. Unlike CK-MB and cTnT, cTnI does not express in the skeletal muscle at any development stage.

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It has been shown to be more specific for the detection of myocardial injury in patients with chronic renal failure[14-16]. The present study was conducted to evaluate the relationship between serum concentration of cardiac troponin I in asymptomatic chronic renal failure patients with stable hemodialysis and cardiovascular events.

Material and Method

Patient population

The study was approved by the Institutional Review Board for Human Subjects Research of Siriraj Hospital, Mahidol University. Written, informed consent was received from all of the participants. A total of 63 patients with chronic renal failure treated with hemodialysis in the Hemodialysis Unit of Siriraj Hospital were included in the present study. The minimal duration of hemodialysis was one year.

Exclusion criteria were: 1) acute coronary syndrome within three months; 2) chronic stable angina pectoris; 3) chest pain in the peridialysis period or during the four weeks before enrollment; 4) recent major cardiovascular surgery; 5) significant electrocardiogram (ECG) changes suggestive of myocardial injury or ischemia and 6) patients who did not agree to participate.

The patients were evaluated by a complete medical history and physical examination. Blood samples were drawn before dialysis on the patient's routinely scheduled hemodialysis day. Cardiac troponin I, cardiac troponin T, cholesterol, triglyceride, HDL, blood urea nitrogen, creatinine, uric acid, calcium, phosphate, magnesium, sodium, potassium, chloride, bicarbonate, homocysteine, NT-pro BNP levels were measured from all blood samples.

Biochemical markers

All of the serum samples were centrifuged for 5 min at 2,300 revolutions per minute to remove any particular matter. Each tube was labeled with the patient number and accession number. The technicians who performed the assays had no knowledge of the clinical data. Specimens were re-analyzed at random or to verify an abnormal result to eliminate technical errors.

The Vitros ECi immunodiagnostic system (Ortho-Clinical, Johnson & Johnson company, USA.) was used to analyze the serum cTnI level. In a normal healthy population, it is less than 0.08 ng/ml while the AMI cutoff is at 0.4 ng/ml. The Elecsys 2010 (3rd generation cardiac troponin T assay, Roche Diagnostics, Switzerland) was used to analyze the cTnT and NT-proBNP. In a normal healthy population, the serum cTnT level is less than 0.03 ng/ml while the AMI cutoff is 0.1 ng/ml. Plasma Homocysteine was analyzed by using IMx immuno-diagnostic (Abbott Laboratories, USA). The other blood chemistries were measured with Hitachi 917 Analyzer (Roche Diagnostics, Switzerland) and using routine methods according to the manufacture's protocols.

Follow-up

The study group was classified in groups according to the serum cTnI level on initial enrollment. All patients were followed up for 18 months from the time of their initial enrollment in the present study. The end points studied were 1) cardiac mortality; 2) acute myocardial infarction events and 3) the intervention such as PTCA or CABG. Hospital records, out patient clinical records and interviews with the patient or primary physician were used for confirmation of the events.

Statistical analysis

Continuous variables were expressed as the mean value $\pm$ SD and were analyzed by Student t test unpaired or Mann-Whitney U test. Categorical variables were expressed as percentages and were analyzed by Chi-square test or Fisher's exact test. A two-tailed p value < 0.05 was considered significant. All of the statistical analyses were performed using SPSS, version 12.0 (SPSS Inc., Chicago, USA).

Results

Forty seven chronic dialysis patients (75%) had elevated levels of cTnI concentrations, more than the 0.08 ng/ml cutoff, but only fourteen patients (22%) had cTnI concentrations of more than the AMI cut-off (0.4 ng/ml).

At first the authors used the 0.08 ng/ml cut-off, the baseline characteristics of patients with normal troponin I levels were similar to those with elevated levels ($\geq$ 0.08 ng/ml) (Table 1). Similarly, there was no significant difference in the baseline biochemical profiles between the two groups, except for higher potassium (mean $\pm$ SD, 5.23 $\pm$ 0.78 vs 4.69 $\pm$ 0.73; [p = 0.020]) and NT-pro BNP concentration (median, 17405 vs 7404.50; [p = 0.016]) in the group with elevated cTnI (Table 2). None of the patients in the normal cTnI group died. However, two (4%) of the elevated group died during the 18- months follow-up period. One (2%) from the elevated cTnI group had myocardial infarction and three (6%) were intervened by PTCA. None

Table 1. Baseline clinical characteristics: Comparison between patients with normal cTnI levels and those with elevated levels, when using the 0.08 ng/ml cutoff (n = 63)

Characteristics	Normal cTnI (cTnI < 0.08 ng/ml) (n = 16)	Elevated cTnI (cTnI ≥ 0.08 ng/ml) (n = 47)	p value
Male	8 (50%)	22 (47%)	1.000
Age (yrs)*	59.6 ± 10.7	54.6 ± 13.0	0.175
Duration of dialysis (yrs)*	5.0 ± 3.14	6.2 ± 3.43	0.240
Hypertension	13 (81%)	36 (77%)	0.337
Diabetes	8 (50%)	14 (30%)	0.246
Hyperlipidemia	3 (19%)	13 (28%)	0.928
Smoking history	1 (6%)	5 (11%)	1.000
Family history of cardiovascular disease	0 (0%)	2 (4%)	1.000

Data are presented as number (%) of patients. The data were analyzed by Chi-square test
* These data were analyzed by Student t test unpaired and data are presented as the mean ± SD

Table 2. Baseline serum biochemical profiles: Comparison between patients with normal cTnI levels and those with elevated levels, using the 0.08 ng/ml cutoff (n = 63)

Blood chemistries	Normal cTnI (cTnI < 0.08 ng/ml) (n = 16)	Elevated cTnI (cTnI ≥ 0.08 ng/ml) (n = 47)	p value
Cholesterol (mg/dl)	188.81 ± 48.71	180.15 ± 36.49	0.455
Triglyceride (mg/dl)	120.56 ± 46.51	114.49 ± 60.12	0.714
HDL-C (mg/dl)	48.81 ± 14.36	44.85 ± 14.00	0.335
BUN (mg/dl)	82.73 ± 17.02	84.57 ± 19.51	0.744
Creatinine (mg/dl)	12.37 ± 2.89	12.73 ± 3.48	0.722
Uric acid (mg/dl)	8.79 ± 1.49	9.14 ± 1.71	0.465
Calcium (mg/dl)	9.60 ± 0.81	9.49 ± 0.89	0.688
Phosphate (mg/dl)	6.14 ± 2.25	6.19 ± 1.98	0.945
Magnesium (mg/dl)	2.87 ± 0.47	2.99 ± 0.51	0.419
Sodium (mmol/L)	138.13 ± 2.31	137.38 ± 2.82	0.347
Potassium (mmol/L)	4.69 ± 0.73	5.23 ± 0.78	0.020
Chloride (mmol/L)	101.19 ± 2.90	101.38 ± 4.18	0.863
Bicarbonate (mmol/L)	21.00 ± 3.27	20.34 ± 2.94	0.454
Homocysteine (μmol/L)	30.76 ± 6.27	27.33 ± 8.75	0.155
cTnT (ng/ml)	0.06 ± 0.08	0.08 ± 0.09	0.525
NT-pro BNP (pg/ml)*	7404.50	17405	0.016

Data are presented as the mean value ± SD. The data were analyzed by unpaired student t test
* This data was analyzed by Mann-Whitney U test and presented as the median value

of both groups had CABG done. Three (6%) of the elevated group had unstable angina during the follow-up period while one (2%) of this group had stable angina. None of the normal group had angina. There was no significant difference (p = 0.053) in cardiovascular events between the two groups (Table 3).

In the second time we used the AMI cutoff (0.4 ng/ml), the elevated group (cTnI ≥ 0.4 ng/ml) had a significantly older age (Table 4). The other baseline clinical characteristics and baseline serum biochemical profiles showed no significant differences between the two groups (Table 5). Two (4%) of forty-nine normal cTnI patients had cardiac death during the follow-up period. However, none of the elevated cTnI group died during this period. One (7%) of the elevated group had myocardial infarction. While two (4%) of the normal

Table 3. Cardiovascular deaths and cardiovascular events: Comparison between patients with normal cardiac troponin I levels and those with elevated levels, using the 0.08 ng/ml cutoff (N = 63)

End Point	Normal cTnI (cTnI < 0.08 ng/ml) (n = 16)	Elevated cTnI (cTnI ≥ 0.08 ng/ml) (n = 47)	p value
Cardiac death	0 (0%)	2 (4%)	0.513
Myocardial infarction	0 (0%)	1 (2%)	1.000
PTCA	0 (0%)	3 (6%)	0.564
CABG	0 (0%)	0 (0%)	-
Unstable angina	0 (0%)	3 (6%)	0.564
Stable angina	0 (0%)	1 (2%)	1.000
Total	0 (0%)	10 (20%)	0.053

Data are presented as the number (%) of the patients and were analyzed by Fisher's exact test

Table 4. Baseline clinical characteristics: Comparison between patients with normal cTnI levels and those with elevated levels, when using the AMI cutoff

Characteristics	Normal cTnI (cTnI < 0.4 ng/ml) (n = 49)	Elevated cTnI (cTnI ≥ 0.4 ng/ml) (n = 14)	p value
Male	25 (5%)	5 (36%)	0.479
Age (yrs)*	53.84 ± 12.82	63.21 ± 8.71	0.003
Duration of dialysis (yrs)*	5.76 ± 3.689	6.50 ± 2.03	0.478
Hypertension	37 (76%)	12 (86%)	0.846
Diabetes	16 (33%)	6 (43%)	0.698
Hyperlipidemia	10 (20%)	6 (43%)	0.622
Smoking history	3 (6%)	3 (21%)	0.530
Family history of cardiovascular disease	1 (2%)	1 (7%)	1.000

Data are presented as number (%) of patients. The data were analyzed by Chi-square test or Fisher'exact test
* These data were analyzed by unpaired student t test and data are presented as the mean value ± SD

group and one (7%) of the elevated group had PTCA done. None had CABG done. One (2%) of the normal group had unstable angina, while two (14%) and one (7%) of the elevated group had unstable and stable angina respectively. There was significantly higher incidences of cardiovascular events (35% vs 10%; p = 0.035) in the elevated group when using the AMI cut off (Table 6).

Discussion

Cardiovascular complications are the most important cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The diagnostic and prognostic utilities of the cardiac troponins are now well established in normal populations. Several studies have questioned the usefulness of the cardiac troponin in the presence of renal disease. Short-term follow-up studies on this subject produced conflicting results[8-13].

Because Troponin I is a highly sensitive and specific marker for myocardial ischemia. Unlike creatine kinase, creatine kinase-MB and even troponin T, cTnI is not expressed by tissues other than the myocardium[14-16]. This specificity has engendered a great deal of interest in its value as a marker of subclinical ischemia and as a predictor of adverse cardiac outcomes. The object of the present study was to evaluate the relationship between serum concentration of cardiac troponin I in asymptomatic chronic renal failure patients and cardiovascular events.

In the present study, the authors found that the elevated group when using the 0.4 ng/ml cutoff was associated with cardiovascular events. But there was no significant correlation when using the 0.08 ng/

Table 5. Baseline serum biochemical profiles: Comparison between patients with normal cTnI levels and those with elevated levels, using the AMI cutoff

Blood chemistries	Normal cTnI (cTnI < 0.4 ng/ml) (n = 49)	Elevated cTnI (cTnI ≥ 0.4 ng/ml) (n = 14)	p value
Cholesterol (mg/dl)	180.12 ± 35.83	190.14 ± 51.92	0.409
Triglyceride (mg/dl)	109.18 ± 46.17	140.00 ± 81.55	0.195
HDL-C (mg/dl)	46.86 ± 13.68	42.36 ± 15.45	0.296
BUN (mg/dl)	84.90 ± 18.95	81.50 ± 18.81	0.557
Creatinine (mg/dl)	12.58 ± 3.30	12.84 ± 3.51	0.799
Uric acid (mg/dl)	9.05 ± 1.67	9.06 ± 1.66	0.987
Calcium (mg/dl)	9.47 ± 0.89	9.69 ± 0.79	0.423
Phosphate (mg/dl)	6.19 ± 2.14	6.14 ± 1.67	0.936
Magnesium (mg/dl)	2.93 ± 0.49	3.04 ± 0.52	0.473
Sodium (mmol/L)	137.69 ± 2.82	137.14 ± 2.28	0.506
Potassium (mmol/L)	5.07 ± 0.82	5.16 ± 0.76	0.726
Chloride (mmol/L)	101.78 ± 3.99	99.79 ± 3.12	0.090
Bicarbonate (mmol/L)	20.18 ± 3.01	21.64 ± 2.87	0.111
Homocysteine (μmol/L)	27.60 ± 7.56	30.29 ± 10.47	0.287
cTnT (ng/ml)	0.07 ± 0.08	0.09 ± 0.09	0.593
NT-pro BNP(pg/ml)*	13483	26287	0.498

Data are presented as the mean value ± SD. The data were analyzed by unpaired student t test
* This data was analyzed by Mann-Whitney U test and presented as the median value

Table 6. Cardiovascular deaths and cardiovascular events, comparison between patients with normal cardiac troponin I levels and those with elevated levels, using the AMI cutoff

End Point	Normal cTnI (cTnI < 0.4 ng/ml) (n = 49)	Elevated cTnI (cTnI ≥ 0.4 ng/ml) (n = 14)	p value
Cardiac death	2 (4%)	0 (0%)	1.000
Myocardial infarction	0 (0%)	1 (7%)	0.222
PTCA	2 (4%)	1 (7%)	0.536
CABG	0 (0%)	0 (0%)	-
Unstable angina	1 (2%)	2 (14%)	0.121
Stable angina	0 (0%)	1 (7%)	0.222
Total	5 (10%)	5 (35%)	0.035

Data are presented as the number (%) of the patients and were analyzed by Fishers'exact test

ml cutoff. The AMI cutoff level of cTnI (0.4 ng/ml) seem to have more benefit to predict the cardiovascular events in chronic renal failure patients while the 0.08 ng/ml cutoff doesn't seem to have usefulness for this purpose. Further studies are needed to clarify this hypothesis.

The authors found no correlation between cTnI and NT-proBNP concentration. By contrast with the authors' previous study in chronic asymptomatic hemodialysis renal failure patients, it was found that the elevated cTnT groups (both using the 0.03 ng/ml and the AMI cutoff) had a significantly higher NT-proBNP concentration.

The authors considered the possibility that the hemodialysis treatment itself could induce myocardial ischemia and release a small degree of troponin I. Thus, a rise in troponin I levels after a hemodialysis might be associated with cardiovascular events and the 0.4 ng/ml cutoff may has a benefit for this purpose.

The AMI cutoff (0.4 ng/ml) seems to have more benefit for predicting the risk of cardiovascular events, So an aggressive approach for cardiovascular assessment in hemodialysis patients is beneficial.

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ความสัมพันธ์ระหว่างระดับคาร์ดิแอกโทรโปนินอัยย์ในกระแสเลือดของผู้ป่วยไตวายเรื้อรัง กับการเกิดภาวะหัวใจขาดเลือด

กิติกร วิชัยเรืองธรรม, วัฒนา เลี้ยววัฒนา, ลีนา องอาจยุทธ, ศศิกานต์ โพธิ์คำ

วัตถุประสงค์: *เปรียบเทียบระดับคาร์ดิแอกโทรโปนินอัยย์ในกระแสเลือดของผู้ป่วยไตวายเรื้อรัง เพื่อหาความสัมพันธ์ระหว่างสารนี้ กับการเกิดภาวะหัวใจขาดเลือด*

ที่มาของการศึกษา: *การศึกษาก่อนหน้านี้ มีการผลการศึกษาขัดแย้ง ยังไม่สามารถหาข้อสรุปได้ชัดเจน*

วัสดุและวิธีการ: *ได้ทำการศึกษาผู้ป่วยไตวายเรื้อรัง 63 รายโดยวัดระดับคาร์ดิแอกโทรโปนิน อัยย์ และสารเคมีอื่นในเลือด หลังจากนั้นทำการเฝ้าติดตาม อุบัติการณ์โรคหลอดเลือดหัวใจ ของผู้ป่วยเป็นระยะเวลา 18 เดือนนับจากวันที่ได้ทำการเจาะเลือด*

ผลการศึกษา: *ผู้ป่วย 47 ราย (75%) มีระดับคาร์ดิแอกโทรโปนินอัยย์ สูงกว่าจุดตัด 0.08 นาโนกรัม/มล. ในขณะที่พบเพียง 14 ราย (22%) ที่มีระดับที่สูงกว่าจุดตัดที่ใช้บอกว่าผู้ป่วยมีกล้ามเนื้อหัวใจขาดเลือด (0.4 นาโนกรัม/มล.) ผู้ป่วยกลุ่มที่มีระดับคาร์ดิแอกโทรโปนินอัยย์สูงกว่าจุดตัด 0.4นาโนกรัม/มล. พบว่ามีระดับเอ็นที-โปรบีเอ็นพีสูงกว่าอย่างมีนัยทางสถิติ การศึกษานี้พบความสัมพันธ์ระหว่างระดับคาร์ดิแอกโทรโปนินอัยย์ที่สูงกว่าจุดตัด 0.4 นาโนกรัม/มล. กับการเกิดภาวะหัวใจขาดเลือดที่มากขึ้น*

สรุป: *พบความสัมพันธ์ระหว่างระดับสารคาร์ดิแอกโทรโปนินอัยย์ในผู้ป่วยไตวายเรื้อรังที่สูงกว่าจุดตัด 0.4 นาโนกรัม/มล. กับการเกิดเพิ่มขึ้นของภาวะหัวใจขาดเลือด ดังนั้นจุดตัดที่ 0.4 นาโนกรัม/มล. มีประโยชน์ในการทำนายโอกาสการเกิดภาวะหัวใจขาดเลือดที่จะตามมาของผู้ป่วยไตวายเรื้อรังที่ยังไม่เกิดอาการ*