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Prognostic Value of Cardiac Troponin I Elevation After Percutaneous Coronary Intervention in Patients With Chronic Renal Insufficiency: A 12-Month Outcome Analysis

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Serum cardiac troponin I (cTnI) is a highly specific marker for myocardial damage in patients with chronic renal insufficiency (CRI), unlike creatine kinase myocardial band fraction (CK-MB), which may be elevated in the absence of myocardial injury in patients with CRI. We studied 116 consecutive CRI patients (serum creatinine ≥ 1.8 mg/dL, not on dialysis) with normal baseline cTnI levels who underwent successful percutaneous coronary intervention (PCI). Patients were divided into two groups: group 1, elevated post-procedural cTnI (n = 50), and group 2, normal cTnI (n = 66). Patients with elevated cTnI were older and had a higher incidence of postinfarction angina and lower creatinine clearance compared to patients who did not have cTnI elevation. Atheroablative devices (rotational and directional atherectomy and excimer laser coronary angioplasty) were more frequently used in group 1 patients (27.1% vs. 18.5%; *P* = 0.04). In-hospital mortality, cardiac mortality, and Q-wave myocardial infarction rates did not differ between the two groups. At 12-month follow-up, total mortality rates were significantly higher in group 1 (28.0% vs. 9.9%; *P* = 0.002). Multivariate analysis showed that cTnI was an independent predictor of late mortality (OR = 2.26; CI = 1.07–4.77; *P* = 0.03). Thus, in patients with CRI, elevated cTnI levels after successful PCI is an important predictor of poor long-term outcome. Our data suggest that patients with cTnI elevation > 3 times above normal values are particularly at higher risk. *Cathet Cardiovasc Intervent 2002;55: 174–179.*

Key words: angioplasty; coronary; dialysis; stent

INTRODUCTION

Serum cardiac troponin T and cardiac troponin I (cTnI) have become important laboratory markers of myocardial injury with high sensitivity and specificity for the detection and diagnosis of minor myocardial injury [1–3]. However, in patients with chronic renal insufficiency (CRI), especially those on dialysis replacement therapy, levels of cardiac troponin T and creatine kinase myocardial band fraction (CK-MB) may be increased even in the absence of diagnosed heart disease [1–4]. By contrast, cTnI levels are generally not increased in patients with CRI [5,6]. In recent years, considerable investigative interest has focused on troponin elevation after percutaneous coronary intervention (PCI). Although several recent studies have shown a correlation between elevated cTnI levels following coronary intervention and in-hospital adverse outcome, the significance of cTnI elevation after successful PCI in patients with CRI has not been determined [7–9]. We sought to analyze the short- and long-term outcomes of patients with known CRI who had cTnI elevation following successful PCI and to determine whether this increase is an independent predictor of adverse outcome in this patient population.

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MATERIALS AND METHODS

Patient Population

The patient population consisted of 116 consecutive patients with CRI who underwent PCI between January 1994 and August 1999. Patients were divided into two groups. Group 1 (n = 50) comprised of patients with elevated postprocedural cTnI levels (≥ 0.15 ng/ml) and group 2 (n = 66) included patients with normal cTnI levels. Patients on dialysis, patients with increased cTnI baseline values (≥ 0.15 ng/ml), and patients with acute myocardial infarction within the previous 72 hr were excluded from the study.

All patients had cTnI, CK-MB, and serum creatinine levels measured upon admission to the hospital or arrival to the medical ward. cTnI values were measured by paramagnetic-particle chemiluscent immunoenzymatic assay (Beckman, Coulter, CA) at baseline and at 6 and 18–24 hr after intervention. If any values were elevated, repeated measurements were performed every 8 hr until peak levels were reached and decreased to normal.

Dedicated personnel performed all data management and analysis at data-coordinating center. Clinical follow-up was performed by either telephone contact or office visit at 6 and 12 months. The occurrence of major late clinical events was recorded, including death, Q-wave myocardial infarction, and target lesion revascularization (whether surgical or percutaneous). These events were adjudicated by supporting documents.

Clinical Definitions

CRI was defined as the presence of previously documented renal insufficiency and/or a baseline serum creatinine of at least 1.8 mg/dL (159.1 μmol/L) [10]. Patients on dialysis were excluded from the study. Creatinine clearance (CrCl) was calculated applying the Cockcroft-Gault formula [11] using the baseline serum creatinine: $CrCl = [(140 - age) \times weight/serum\ creatinine \times 72]$ with female gender adjustment ($CrCl_{female} = CrCl \times 0.85$). Q-wave myocardial infarction was defined by the presence of new pathological Q-waves in the electrocardiogram associated with an elevation of CK-MB enzyme levels at least three times the upper normal value. Non–Q-wave myocardial infarction was defined as CK-MB > 3 times normal values in the absence of new Q-waves in the electrocardiogram [12]. Angiographic success was defined as a revascularization procedure with a final residual diameter stenosis < 50% and TIMI 3 flow. Clinical success was defined as a successful revascularization in the absence of death, myocardial infarction, or emergency coronary artery bypass graft surgery.

Revascularization Procedure

Patients underwent routine intravenous hydration with 0.5 normal saline 75–100 ml/hr for 12 hr prior and for 6 hr after the procedure. An ionic low-osmolar-contrast agent (ioxaglate meglumine, Hexabrix, Mallinkrodt Medical) was used during conventional PCI [13,14]. Weight-adjusted heparin dosage was administered during the procedure in order to maintain an activated clotting time of 250–300 sec. Heparin was routinely discontinued at the end of the procedure. Patients received aspirin 325 mg at least 24 hr before the procedure and continued indefinitely afterward. Patients who underwent stenting were treated concomitantly with either ticlopidine 250 mg b.i.d. for 4 weeks or clopidogrel 75 mg q.d. for 2 weeks per the routine protocol. Glycoprotein IIb/IIIa inhibitors were used in less than 3% of all patients in both groups.

Statistical Analysis

Statistical analyses were performed using SAS 6.10 (SAS Institute, Cary, NC). Continuous variables are presented as mean ± 1 standard deviation and are compared using student's *t*-test or regression analysis. Categorical variables are presented as percentages and are compared using the chi-square test or the Fisher exact test. Kaplan-Meier survival curves were used to compare freedom from death. Multivariate logistic analysis with backward regression was used to model independent predictors of in-hospital and late mortality. Variables included in the multivariate model were age, cTnI elevation, diabetes mellitus, saphenous vein graft intervention, left ventricular ejection fraction, debulking (rotational and directional atherectomy and excimer laser coronary angioplasty), CK-MB > 3 times normal values, and stent deployment. A P value < 0.05 was considered significant.

RESULTS

Baseline clinical characteristics are shown in Table I. Group 1 patients were older and had a higher incidence of postinfarction angina and lower creatinine clearance compared to patients with normal cTnI, who did not have cTnI elevation. Diabetes was also more common in the former group, although it was not statistically significant ($P = 0.06$). Contrast volume used during the procedure (210 ± 115 ml and 194 ± 101 ml; $P = 0.31$) and peak serum creatinine levels (2.95 ± 1.6 ml/dL and 3.00 ± 2.4 ml/dL; $P = 0.88$) were similar between the two groups.

Lesion characteristics were similar between the two groups and are summarized in Table II. The percentage of restenotic lesions (28.3% vs. 27.3%; $P = 0.82$) and in-stent restenosis lesions (22.9% vs. 19.4%; $P = 0.40$) that were treated was also similar between the two groups. Device use (rotational and directional atherectomy and excimer laser coronary angioplasty) was more frequent in group 1 (42.4% vs. 23.3%; $P = 0.003$).

Quantitative coronary analysis did not reveal significant differences in percent diameter stenosis (62.3% vs.

TABLE I. Baseline Clinical Characteristics

	Group 1, elevated cTnI (n = 50)	Group 2, normal cTnI (n = 66)	*P*
Age (years)	73 ± 9	69 ± 10	0.004
Male (%)	76.0	68.2	0.36
Unstable angina (%)	69.7	58.6	0.10
Postinfarction angina (%)	18.0	8.6	0.04
Prior infarction (%)	60.5	51.2	0.19
Prior bypass surgery (%)	71.7	64.3	0.25
Prior intervention (%)	57.8	56.3	0.82
Baseline creatinine (mg/dL)	2.3 ± 0.8	2.5 ± 1.9	0.19
Baseline creatinine clearance (ml/min)	32.7 ± 12	40.1 ± 19	0.001
Baseline CK-MB (ng/dL)	3.08 ± 3.8	3.68 ± 8.3	0.50
Baseline cTnI (ng/mL)	0.09 ± 0.45	0.09 ± 0.45	0.99
Hypertension (%)	43.5	51.9	0.22
Diabetes mellitus (%)	55.4	42.4	0.06
Insulin dependent (%)	31.5	27.1	0.48
Hyperlipidemia (%)	72.8	69.5	0.60
Ejection fraction	0.39 ± 0.17	0.41 ± 0.16	0.55

TABLE II. Baseline Lesion Characteristics

	Group 1, elevated cTnI (n = 188)	Group 2, normal cTnI (n = 216)	*P*
Lesion location			
Left main (%)	5.6	4.9	0.74
Left anterior descending (%)	22.0	20.5	0.73
Left circumflex (%)	30.5	27.0	0.46
Right coronary artery (%)	19.8	20.0	0.96
Saphenous vein graft (%)	22.0	27.6	0.22
Lesion characteristics			
Ostial location (%)	13.1	12.8	0.93
Thrombus (%)	5.9	2.9	0.89
Calcification (%)	29.4	34.4	0.46
Total occlusion (%)	6.3	14.3	0.64
Device use			
Balloon angioplasty (%)	90.4	93.7	0.24
Stent (%)	53.7	51.9	0.71
Total device use (%)	27.1	18.5	0.04
Rotational atherectomy (%)	15.2	9.8	0.11
Directional atherectomy (%)	1.7	2.4	0.73
Excimer laser angioplasty (%)	11.2	8.3	0.33

61.3%; $P = 0.89$), reference vessel diameter (3.4 ± 1.4 mm vs. 3.6 ± 1.4 mm; $P = 0.58$), or minimal lumen diameter (1.27 ± 0.81 mm vs. 1.36 ± 1.02 mm; $P = 0.75$) before the procedure between group 1 and group 2, respectively.

In-Hospital Outcome

In-hospital outcome is detailed in Table III. Angiographic and clinical success was equally high in both groups. Length of stay, in-hospital mortality, Q-wave myocardial infarction, and emergency bypass surgery rates did not differ between the two groups. Abnormal baseline CK-MB levels were detected in 12.7% of group 1 patients and in 15.1% of group 2 ($P = 0.63$). Postprocedural CK-MB levels were higher in group 1 patients, with 42.2% of these patients having an increase > 3 times normal values compared to 10.8% in group 2 ($P < 0.0001$) and 28.9% vs. 6.7% in group 2 ($P < 0.0001$) had an increase > 5 times normal values.

Late Outcome

Cumulative 12-month follow-up results are detailed in Table IV and Figure 1. Total cumulative mortality was significantly higher in patients with elevated cTnI ($P = 0.002$). Analysis of the data for death-free survival according to normal (< 0.15 ng/ml), intermediate (0.15–0.45 ng/ml, 1–3 times normal levels), and high (> 0.45 ng/ml, > 3 times normal levels) cTnI levels is shown in Figure 2. Patients with intermediate elevation of cTnI (43% of the patients with cTnI elevation) had similar

TABLE III. In-Hospital Outcome

	Group 1, elevated cTnI (n = 50)	Group 2, normal cTnI-I (n = 66)	*P*
Clinical success (%)	90.2	93.0	0.45
Abrupt closure (%)	1.6	0.5	0.34
Death (%)	4.3	1.6	0.24
Cardiac death (%)	2.2	1.6	1
Q-wave infarction (%)	0.0	0.0	
Non–Q-wave infarction (%)	42.2	10.8	< 0.0001
Emergency/urgent bypass surgery (%)	0.0	0.8	1
Repeat angioplasty (%)	3.3	3.1	1
Length of stay (days)	7 ± 4	5 ± 5	0.22

TABLE IV. Long-Term Outcome

	Group 1, elevated cTnI (n = 50)	Group 2, normal cTnI (n = 66)	*P*
Death (%)	28.0	9.9	0.002
Myocardial infarction (%)	25.0	13.8	0.06
Death/myocardial infarction (%)	33.3	13.9	0.002
Target lesion revascularization (%)	19.0	20.0	0.88
Balloon angioplasty (%)	19.0	18.9	0.99
Bypass surgery (%)	0.0	1.1	1
Major adverse cardiac events[a] (%)	40.3	30.1	0.16

[a]Death, myocardial infarction, and target lesion revascularization.

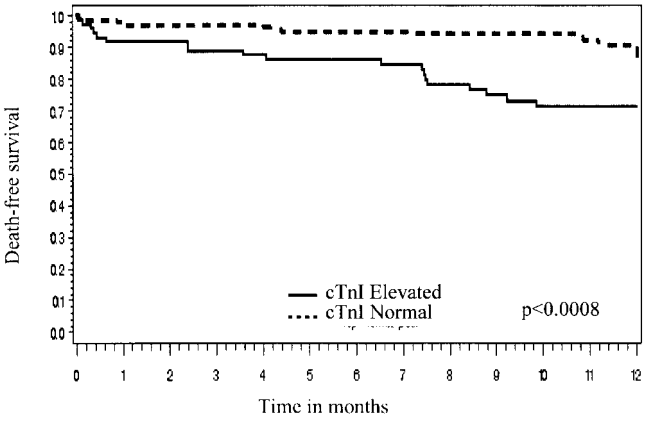

Fig. 1. Kaplan-Meier curves illustrating death-free survival curves at 12-month follow-up.

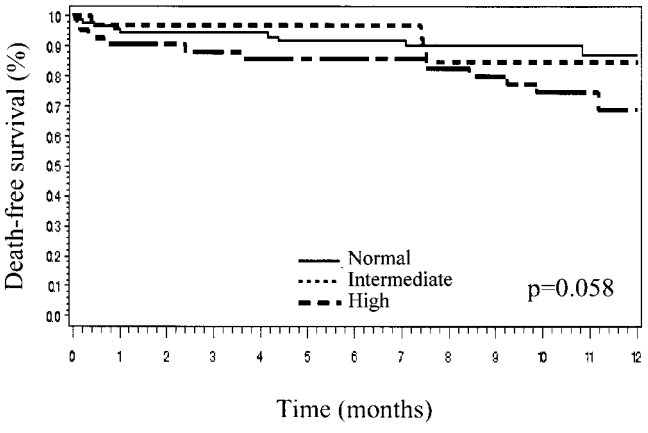

Fig. 2. Kaplan-Meier curves illustrating death-free survival according to normal (< 0.15 ng/ml; solid line), intermediate (0.15–0.45 ng/ml; short dashes), and high (> 0.45 ng/ml; long dashes) cTnI levels.

long-term outcome as patients with normal cTnI levels, whereas a more than threefold increase in cTnI levels was associated with a worse outcome at 1-year follow-up ($P = 0.058$; Fig. 2). Myocardial infarction (Q-wave and non–Q-wave) rates were higher in group 1 (25.0% vs. 13.8%), although this difference was of borderline statistical significance ($P = 0.06$). Target vessel revascularization rates by either balloon angioplasty or bypass surgery were similar between the two groups. On multivariate analysis, cTnI (OR = 2.26; CI = 1.07–4.77; $P = 0.03$), age (OR = 1.05; CI = 1.006–1.09; $P = 0.03$), and CK-MB > 3 times upper normal (OR = 2.43; 95% CI = 1.16–5.08; $P = 0.02$) were the only independent predictors of late mortality.

DISCUSSION

The present study demonstrates that cTnI elevation following PCI occurs frequently in patients with CRI and is associated with increased long-term mortality. Although we demonstrated that overall elevated cTnI levels were associated with late death, elevations of cTnI less

than three times normal values (0.15–0.45 ng/ml) were not associated with increased late mortality. After controlling for other clinical factors in a multivariate regression analysis, cTnI remained an important predictor of late mortality.

The interpretation of periprocedural enzyme elevation is particularly complicated and can be misleading, especially in patients with preexisting CRI due to presence of false positive CK-MB in these patients. In our experience, more than 13% of patients in both groups had elevated baseline CK-MB levels despite normal cTnI levels. The finding of these enzymes in the sera of patients with CRI and particularly in those with end-stage renal disease on chronic hemodialysis has been attributed to noncardiac causes, such as skeletal myopathy and immunoassay cross-reactivity [15], but recent data suggest that cardiac troponin T elevations truly reflect minor myocardial damage, regardless of whether heart disease has been diagnosed [2]. Therefore, in the clinical setting of renal disease, elevated levels of these enzymes must be interpreted with caution unless normal baseline levels are available for comparison [15–17].

The use of newer, nonballoon interventional devices, such as directional or rotational atherectomy, have been associated in previous studies with more frequent and greater increases in CK-MB release, probably related to an increased rate of distal embolization, although its correlation with event-free survival is still unclear [18–22]. Similarly, in the present study, atheroablative devices were associated with a higher percentage of patients with cTnI elevation (27.1%) compared to only 18.5% of patients without elevation ($P = 0.04$), probably reflecting a more aggressive interventional approach by the operator driven by a perceived more extensive disease and/or heavy calcification in the former group. The use of more interventional devices in these patients, however, was not associated with a higher incidence of periprocedural complications, albeit higher rates of non–Q-wave MI. However, by multivariate analysis, device use did not correlate with late mortality.

Previous Studies

Previous studies in a relatively small number of patients with normal renal function have shown that, although cTnI is more sensitive in detecting minor myocardial injury after PCI than CK-MB, it is associated with increased in-hospital but not with intermediate or long-term adverse clinical outcome [23]. Two separate studies have shown that the long-term event-free survival was similar in patients with and without cTnI elevation [7,24]. A more recent report by Garbarz et al. [8] of 109 patients who underwent stented angioplasty showed that cTnI elevation is common after stenting (27%), usually related with in-laboratory complications, and was not a marker for intermediate (8-month follow-up) major adverse cardiac events. We have recently reported the outcomes of 345 consecutive patients who underwent PCI and had $>$ 3 times the upper normal limit of cTnI [9]. Although these patients were at a higher risk for major in-hospital complications, at 8-month follow-up, they did not have an increased risk in cardiac events or death [9]. Therefore, contrary to these observations in patients with normal renal function, elevated cTnI in patients with CRI is associated with adverse long-term outcome.

Study Limitations

The interpretation of these results may be complicated by several limitations. Because of the small sample size, this study may be subject to beta error. The retrospective nature of the analysis limits the results and the conclusions inherent in this type of reports despite independent chart review, data entry, follow-up, and adjudication by independent personnel according to prespecified criteria. The more frequent use of nonballoon devices in patients with elevated cTnI may be related to more severe and extensive disease in these patients, i.e., diffuse and/or calcified lesions that cannot be adequately assessed by coronary angiography and would require more sensitive methods, such as intravascular ultrasound.

The present study shows that in patients with CRI, elevated cTnI levels after successful PCI is an important predictor of poor long-term outcome. Patients with cTnI elevation $>$ 3 times above normal levels are at a particularly high risk. Newer therapeutic alternatives with preintervention treatment with beta-blockers and periprocedural glycoprotein IIb/IIIa inhibitors in this high-risk population deserve further study.

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