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The Significance of Elevated Troponin T in Patients with Nondialysis-Dependent Renal Insufficiency: A Validation with Coronary Angiography

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Summary

Background: Patients with elevated troponin are at high risk of adverse outcomes, future cardiac events, and are more likely to have hemodynamically significant coronary artery stenoses. Elevated troponin T (cTnT) in patients with poor renal function portends a poor prognosis; however, findings of significant coronary artery disease (CAD) by coronary angiography have not been demonstrated in patients with poor renal function and elevated cTnT.

Hypothesis: The purpose of this study was to correlate the angiographic findings of patients with elevated cTnT with respect to renal function in patients with nondialysis-dependent renal insufficiency.

Methods: We retrospectively identified 342 patients with elevated cTnT who underwent coronary angiography in the setting of acute coronary syndrome. Patients were divided into poor (< 40 ml/min) and normal (> 40 ml/min) renal function by measuring their glomerular filtration rate. Our primary outcome was CAD stenosis, defined as epicardial stenosis ≥ 70%. Secondary outcomes were rates of contrast nephropathy, initiation of hemodialysis, revascularization, length of stay (LOS), and in-hospital mortality.

Results: There was no significant difference in the prevalence of CAD between patients who had positive cTnT with poor renal function versus patients with positive cTnT and normal renal function (87.1 vs. 89.7%, p = 0.54). This finding persisted after stratifying by age. Patients with impaired renal function had a higher mortality, longer LOS, and a higher rate contrast nephropathy requiring hemodialysis.

Conclusion: The association between elevated cTnT and significant CAD stenosis does not vary with renal function.

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Introduction

Troponins have emerged as a valuable marker for diagnosing and risk stratifying patients with acute coronary syndrome (ACS).[1–4] Troponins have also been shown to be better predictors of mortality and cardiac events than the previous standard of reference, creatine kinase (CK)-MB.[5,6] Elevated troponin T (cTnT) has been associated with significant coronary artery disease (CAD) on angiography.[3,7–9]

The diagnostic and prognostic utility of troponins is frequently questioned in patients with renal insufficiency (RI). In the absence of myocardial ischemic symptoms, the elevation of cTnT levels in patients with chronic kidney disease has been considered a false-positive.[10] Multiple studies have found elevations of cTnT in asymptomatic patients with renal failure.[11,12] Other studies have found no association between cardiac events and elevated cTnT in patients with poor renal function.[13,14]

Roppolo *et al.* concluded that in patients with no suspicion of myocardial ischemia on hemodialysis, elevated cTnT was an important prognosticator of adverse cardiac outcomes and suggested a strong association between elevated cTnT and risk of death.[15,16] Another study evaluated 100 asymptomatic patients on hemodialysis and found that cTnT and congestive heart failure (CHF) were the only significant predictors of death.[17]

There appear to be ample data regarding the significance of troponins in patients on chronic dialysis. However, the number of patients with nondialysis-dependent renal failure is considerably larger and less well studied, even though RI is associated with an increased risk of cardiovascular mortality.[18]

To consider the diagnostic utility of cTnT in patients with nondialysis-dependent RI, we examined the presence of CAD in 342 consecutive cTnT-positive patients with and without RI who underwent coronary angiography (CA).

Methods

Study Setting and Intervention

We retrospectively identified cTnT-positive (> 0.1 ng/ml) patients who underwent CA within 2 weeks. The level of cTnT

$$\text{Estimated GFR} = \frac{(140 - \text{age}) \times \text{ideal body weight}}{72 \times \text{serum Cr}}$$

(multiply by 0.85 for females)

FIG. 1 Cockcroft-Gault equation. GFR = glomerular filtration rate, Cr = creatinine.

was measured by second generation commercial enzyme-linked immunosorbent assay (ELISA) on an Elecsys 2010 Immunoassay Analyzer (Enzymun Troponin T, Boehringer Mannheim, Indianapolis, Ind., USA). The lower limit of detection of this assay is 0.01 ng/ml. The level of glomerular filtration rate (GFR) was calculated for each patient based on the Cockroft-Gault formula for estimated creatinine clearance (Fig. 1). Information regarding CA, demographics, illness severity, and mortality were obtained from the Duke Cardiovascular Disease Database. Patients on hemodialysis and those who underwent CA for reasons other than evaluation of CAD were excluded from this study.

Outcome Measures

The primary outcome was to determine the degree of CAD stenosis (≥ 70% lesions), as interpreted by the cardiologist who performed the catheterization with respect to renal function. Secondary outcomes included ejection fraction (EF), incidence of contrast nephropathy (defined as an increase in serum creatinine > 1.0 mg/dl within 72 h of catheterization), hemodialysis within 1 week of catheterization, revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass surgery [CABG]), length of stay (LOS), and in-hospital mortality.

Statistical Analysis

Patients were grouped as having low (≤ 40 ml/min) or normal (> 40 ml/min) GFR. The GFR value of 40 ml/min was selected to include patients with moderate to severe RI.[19] Descriptive statistics for categorical variables were reported as the number and percent in each group with the characteristic. Age, weight, and EF were described in terms of means and standard deviations. Medians with 25th and 75th percentiles were reported in describing LOS and cTnT level. To compare low with normal GFR levels in the patients, Fisher's exact tests were used for categorical outcome variables. Age, weight, and EF were compared using two sample *t*-tests. Wilcoxon rank sums test was used to compare the groups with respect to cTnT level. Relationships were considered significant when the two-sided p value was ≤ 0.05. Kaplan Meier analysis was used to compare hospital LOS between the two groups. Patients who died before being discharged were censored at the time of death. A log-rank p value of ≤ 0.05 was considered significant. To control for the possible confounding effect of age, each analysis was repeated after stratifying by age. Patients were grouped into those ≤ 70 years and those > 70 years of age.

Results

Demographic and patient characteristics are shown in Table I. Baseline characteristics differed significantly between the normal and RI groups. Patients in the RI group were older (72.4 vs. 59 years), weighed less (72.4 kg vs. 84.2 kg), and were less likely to be male (37.1 vs. 73.9%). They had a higher prevalence of diabetes (42.9 vs. 27.9%) and hypertension (80.0 vs. 51.8%), but were less likely to have a history of tobacco use (44.3 vs. 68.4%). There were no significant differences in the use of stress tests between the two groups (5.75 vs. 6.6%), hyperlipidemia (22.9 vs. 17.3%), or the likelihood of having a family history of CAD (37.1 vs. 44.1%). The median cTnT level was significantly lower in the low GFR group (0.35 vs. 1.15).

TABLE I Baseline characteristics and results

	Glomerular filtration rate		
	≤ 40 (n = 70)	> 40 (n = 272)	p Value
Age	72.4 (9.9) [b]	59.6 (12.1)	< 0.001
Male	26 (37.1) [c]	201 (73.9)	< 0.001
Weight	72.4 (16.6)	84.2 (20.3)	< 0.001
Diabetes	30 (42.9)	76 (27.9)	0.02
Hypertension	56 (80.0)	141 (51.8)	< 0.001
Tobacco use	31 (44.3)	186 (68.4)	< 0.001
Hyperlipidemia	16 (22.9)	47 (17.3)	0.30
Family history of coronary disease	26 (37.1)	120 (44.1)	0.34
Exercise stress testing	4 (5.7)	18 (6.6)	1.00
Troponin T	0.4 (0.2–1.1) [a]	1.2 (0.4–3)	< 0.001
Coronary artery disease			
1 or more vessels	61 (87.1)	244 (89.7)	0.52
3 vessels	31 (44.3)	88 (32.4)	0.07
Ejection fraction	48.3 (15.3)	47.2 (14.5)	0.62
Contrast nephropathy	12 (17.1)	7 (2.6)	< 0.001
Hemodialysis	4 (5.7)	0 (0.0)	< 0.001
Revascularization	34 (48.6)	189 (69.5)	< 0.001
PCI	18 (25.7)	131 (48.2)	< 0.001
CABG	16 (22.9)	58 (21.3)	0.38
Death at discharge	9 (12.9)	12 (4.4)	0.02
Hospital length of stay	9 (5–14)	5 (4–9)	< 0.001

[a] Descriptive statistics for troponin T and length of stay are reported as the median and 25th to 75th% (in parentheses). P value for troponin T is from Wilcoxon rank sums test. P value for length of stay is from Kaplan Meier log rank statistic.

[b] Descriptive statistics for age, weight, and ejection fraction are reported as means and standard deviations (in parentheses). P values are from two sample *t*-tests.

[c] Descriptive statistics for categorical variables are reported as the number and percent with the characteristic (in parentheses). P values are from Fisher's exact tests.

Abbreviations: CABG = coronary artery bypass graft surgery, PCI = percutaneous coronary intervention, n = number of patients.

Despite substantial differences in underlying risk factors, the proportion of patients with significant CAD (stenosis ≥ 70%) was not significantly different between the two groups (87.1 vs. 89.7%). There was a trend toward a higher prevalence of triple-vessel disease in patients with renal insufficiency (44.3 vs. 32.4%). Ejection fraction did not differ between the groups (48.3 vs. 47.2%). Patients with low GFR were more likely to experience contrast nephropathy (17.1 vs. 2.6%), require subsequent hemodialysis (5.7 vs. 0.0%), and were less likely to undergo PCI (48.6 vs. 69.5%). The group with RI had a higher mortality (12.9 vs. 4.4%) and LOS (9 days vs. 5 days).

After stratifying by age, there remained no significant difference in the identification of significant CAD between the patients with low versus normal renal function (Table II). In the younger age group with RI, the statistically significant increase in contrast nephropathy (28.0 vs. 2.4%), hemodialysis (8.0 vs. 0.0%), mortality (20 vs. 3.8%), and LOS (11.5 days vs. 5 days) persisted.

Discussion

To our knowledge, this is the first study to examine the interaction of RI with cTnT and CAD defined by CA. The overall rate of significant CAD in our population was 89.1%, which is similar to that seen in previous studies of cTnT-positive patients. Our study found that among patients with elevated cTnT, the prevalence of CAD did not vary with declining renal function (87.1 vs. 89.7%). These results stand in contrast to previous studies suggesting that the diagnostic and prognostic value of cTnT is diminished in patients with RI. The median troponin level of patients with RI was significantly lower than that of the patients with normal renal function. Thus, they had an equivalent severity of disease despite a lower absolute cTnT. Patients with decreased renal function were more likely to experience complications (i.e., contrast nephropathy) from catheterization. At the same time, patients with decreased GFR were less likely to undergo PCI.

Early studies identified patients with renal failure who had elevated cTnT with no evidence of CAD. This may have been due to the first generation cTnT assay's 1–2% cross reactivity with skeletal muscle.[11, 14] Muller-Bardorff *et al.* developed a second-generation cTnT assay that involves the addition of a second cardiac-specific antibody to the old biotinylated antibody. The new assay has been shown to have higher sensitivity and specificity for ACS.[20]

Despite the increased cardiac specificity, cTnT can still be elevated in asymptomatic patients with RI.[12, 13] Different theories may explain this phenomenon: (1) cross reactivity with skeletal muscle, (2) coronary leak (i.e., clinically silent my-

TABLE II Characteristics and results stratified by age

	Age ≤ 70			Age > 70		
	≤ 40 (n = 25)	> 40 (n = 212)	p Value	≤ 40 (n = 45)	> 40 (n = 60)	p Value
Males	11 (44.0) [b]	160 (75.5)	< 0.001	15 (33.3)	41 (68.3)	< 0.001
Weight	78 (18.8) [c]	86.4 (20.8)	0.06	69.3 (14.6)	76.7 (16.3)	0.02
Diabetes	12 (48.0)	60 (28.3)	0.06	18 (40.0)	16 (26.7)	0.21
Hypertension	19 (76.0)	112 (52.8)	0.03	37 (82.2)	29 (48.3)	< 0.001
Tobacco use	11 (44.0)	151 (71.2)	0.01	20 (44.4)	35 (58.3)	0.17
Hyperlipidemia	7 (28.0)	38 (17.9)	0.28	9 (20.0)	9 (15.0)	0.60
Family history	8 (32.0)	96 (45.3)	0.29	18 (40.0)	24 (40.0)	1.00
Exercise stress testing	2 (8.0)	13 (6.2)	0.66	2 (4.4)	5 (8.3)	0.70
Coronary artery disease						
1 or more vessels	21 (84.0)	189 (89.2)	0.50	40 (88.9)	55 (91.7)	0.74
3 vessels	7 (28.0)	59 (27.8)	1.00	24 (53.3)	29 (48.3)	0.70
Ejection fraction	47 (34–56)	49 (37–58)	0.53	49 (38–60)	47 (35–57)	0.28
Troponin T	0.4 (0.2–1.1) [a]	1.2 (0.5–2.9)	0.01	0.3 (0.2–0.8)	1.0 (0.2–3.2)	0.04
Contrast nephropathy	7 (28.0)	5 (2.4)	< 0.001	5 (11.1)	2 (3.3)	0.14
Hemodialysis	2 (8.0)	0 (0.0)	0.01	2 (4.4)	0 (0.0)	0.18
Revascularization	12 (48.0)	150 (70.8)	0.04	22 (48.9)	39 (65.0)	0.11
In-hospital death	5 (20)	8 (3.8)	0.01	4 (8.9)	4 (6.7)	0.72
Hospital length of stay	13 (7–16)	5 (4–8)	< 0.001	8 (5–13)	9 (5–12)	0.69

[a] Descriptive statistics for troponin T and length of stay are reported as the median and 25th to 75th% (in parentheses). P value for troponin T is from Wilcoxon rank sums test. P value for length of stay is from Kaplan Meier log rank statistic.

[b] Descriptive statistics for categorical variables are reported as the number and percent with the characteristic (in parentheses). P values are from Fisher's exact tests.

[c] Descriptive statistics for age, weight, and ejection fraction are reported as means and standard deviations (in parentheses). P values are from two sample *t*-tests.

ocardial ischemia, and (3) re-expression of cTnT in skeletal muscle in patients with renal failure.[13, 14, 18] In the largest study to date, Van Lente *et al.* performed a prospective case-matched study with 153 patients and found that positive troponin did not predict adverse outcomes in patients with elevated creatinine as well as it did in those with normal creatinine. However, they noted that patients with elevated creatinine and positive troponin had a greater chance of developing CHF and a trend toward higher mortality.[13] Aviles *et al.* evaluated the GUSTO IV patients and found that patients with RI and positive cTnT had similar short-term prognosis.[21]

Patients suspected of having ACS who have elevated cTnT are more likely to have significant CAD than those with normal cTnT. Previous studies have reported rates of significant CAD ranging from 87–95% in patients with elevated cTnT, and this association appears to hold across a broad spectrum of disease. DeFillipi *et al.* followed 414 patients with no ischemic electrocardiographic (ECG) changes who were admitted to a chest pain unit (CPU). Of the 37 patients with elevated cTnT, 30 underwent CA and 90% were found to have significant CAD versus 23% of the 144 patients with normal cTnT.[3] They found that cTnT-positive patients were more likely to have multivessel CAD. Newby *et al.* identified 88 low-risk patients admitted to a CPU who subsequently underwent CA.[6] Patients with elevated cTnT had an 89% prevalence of significant stenoses compared with 49% in patients who were cTnT negative.

Limitations

Our study has the following limitations. First, it is a retrospective analysis utilizing information prospectively entered into a large database. Second, the relatively small number of patients precludes a multivariable analysis; such an analysis would determine whether the differences in outcomes would be attributable to the significant differences in baseline characteristics between our two groups. Finally, our population included only those patients with positive cTnT who underwent CA. We have no information on those patients who had positive troponin and who did not undergo CA. This is a major limitation of the study due to selection bias. Patients who may have had severe renal insufficiency diagnosed by the primary physician may not have been sent for CA. However, the fact that there was no difference in the utilization of stress testing between the two groups suggests that the precatheterization suspicion may have been similar. Thus, precatherization kidney disease may not have been a limiting factor in referral.

Conclusion

The strong association between elevated cTnT and CAD does not change with renal function. Therefore, patients with nondialysis-dependent renal insufficiency and elevated levels of cTnT should be considered to have a similar risk of significant CAD as do patients with normal renal function.

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