Moderate Renal Dysfunction is not Associated with Elevated Troponin T in Acute Coronary Syndromes

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Abstract
Background: Interpretation of troponin results in patients with acute coronary syndromes (ACS) and renal disease is confused by the fact that renal dysfunction increases troponin levels, regardless of myocardial necrosis. Although it has been demonstrated that end-stage renal disease is associated with elevated cardiac troponin T (cTnT) levels, it is not known whether this biomarker is altered by less than severe degrees of renal impairment.

Objective: To evaluate whether moderate renal dysfunction is associated with cTnT elevation in patients with ACS.

Methods: One hundred, forty-five individuals with ACS and creatinine clearance ≥ 30 ml/min were studied. Creatinine clearance was estimated by the Cockcroft-Gault formula and cTnT was measured at hospital admission. Moderate renal dysfunction was defined as a creatinine clearance of 30-59 ml/min and positive cTnT as levels ≥ 0.01 ug/l.

Results: No correlation was observed between creatinine clearance and cTnT (r = - 0.06, P=0.45). The levels of cTnT were similar among individuals in the first (median=0.05 ug/l), second (median=0 ug/l), third (median=0.07 ug/l) and fourth quartiles (median=0 ug/l) of creatinine clearance - P=0.63. Similarly, there was no difference in troponin values between individuals with moderate renal dysfunction (median=0.02 ug/l) and individuals with normal/near normal function (median=0.03 ug/l) - P=0.63. The prevalence of positive cTnT was similar between individuals with moderate renal dysfunction and normal/near normal renal function (55% vs 52%, P=0.65).

Conclusion: Moderate renal dysfunction is not associated with cTnT elevation in patients with ACS. (Arq Bras Cardiol. 2010; [online]. ahead print, PP 0-0)

Key words: Troponin T/analysis; kidney disease; coronary disease.

Introduction
It has been established that elevated cardiac troponin T (cTnT) is commonly elevated in patients with end-stage renal dysfunction, regardless of myocardial necrosis1-7. This phenomenon represents a confounding factor for the interpretation of cTnT in the setting of acute coronary syndromes (ACS) in individuals with renal dysfunction. Moderate renal impairment is present in 40% of individuals with ACS8. Contrary to end-stage renal dysfunction, data are limited and conflicting on whether cTnT is elevated at this level of renal dysfunction. Abbas et al9 reported positive cTnT in 11% of 56 stable individuals with moderate renal dysfunction9, but Chew et al9 did not find any correlation between renal function and cTnT in patients with ACS and renal insufficiency.

If less-than-severe renal impairment influences cTnT levels, some type of correlation or categorical association is expected between renal function and cTnT in the range of normal to moderate dysfunction. In order to test this hypothesis, we studied 145 patients admitted with ACS and non-severe renal dysfunction. Correlation analysis between creatinine clearance and cTnT was performed and the rates of positive cTnT compared among groups defined by the level of renal function.

Methods
Sample selection
Consecutive patients admitted with ACS in the coronary care unit of our Hospital and who were at least 18 years of age were considered candidates for participating in a local prospective registry. Inclusion criteria for the registry were defined as chest pain or equivalent within 24 hours of admission and at least one of the following characteristics: 1) electrocardiographic ischemic changes, defined as dynamic T-wave inversion, ST-segment depression or ST-segment elevation; 2) serum markers of myocardial necrosis above the upper limit of normality; 3) previous documentation of coronary artery disease. All participants provided written informed consent and the protocol was approved by the

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Overall, five hundred patients were included in the registry during the period between 1999 and 2007. In this database, 151 individuals had available results of both troponin and serum creatinine levels. From this group, 145 individuals with creatinine clearance ≥ 30 ml/min (normal renal function, mild or moderate renal dysfunction) were included in the present study. Thus, as defined by the target population of this study, individuals with severe renal dysfunction did not participate in the analysis.

Study protocol and definitions
Blood samples for measurement of cTnT and creatinine levels were obtained at the initial presentation to the emergency room. Cardiac troponin T was measured by chemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, Indiana, USA) and positive troponin T was defined as values ≥ 0.01 ug/l, which is the method’s lowest detection limit and represents values above the 99th percentile of the general population10. Creatinine was measured by the colorimetric Jaffe method (Dade-Behring, Newark, Delaware, USA)11. Creatinine clearance was calculated by the Cockcroft-Gault formula, defined as [(140 - age) x weight kg] / (72 x serum creatinine mg/dl) x (0.85 if females), in which lean body weight was utilized instead of total body weight12. Lean body weight was calculated using the formula [0.9 x (height cm - 152)] + (50 if male, 45.5 if female)13. Moderate renal dysfunction was defined as creatinine clearance between 30 and 59 ml/min11.

Data analysis
Because of the non-normal distribution of cTnT, this variable was described as medians and interquartile ranges, while non-parametric statistical tests were preferred. Creatinine clearance, normally distributed, was described as means ± standard deviations. As a means to evaluate the influence of renal function on cTnT levels, the linear association between creatinine clearance and cTnT was tested by Spearman’s correlation coefficient in the entire sample. In order to evaluate if exaggerated influence of extreme values was responsible for the results, a secondary analysis was performed after exclusion of outliers, defined as studentized residual higher than 3 standard deviations from its mean. In addition, cTnT values were compared among quartiles of creatinine clearance by Kruskal-Wallis test and between individuals dichotomized as moderate renal dysfunction (creatinine clearance = 30 - 59 ml/min) or normal/mildly impaired function (≥ 60 ml/min) by Mann-Whitney test. Finally, the frequency of cTnT patients was compared among quartiles of creatinine clearance and between individuals dichotomized by moderate renal dysfunction, utilizing chi-square test. SPSS version 10.0 was used for data analysis and a P value < 0.05 was considered statistically significant.

Statistical power calculation
As a convenience sample of 145 patients was studied, statistical power, instead of sample size, was calculated: considering the observed standard deviation of 2.69 ug/l for troponin and 25 ml/min for creatinine clearance, the actual number of patients provided 98% statistical power to detect a significant correlation coefficient of at least 0.3, under a 0.05 level of significance. The RegPower software program, release 4.0 (PM Gallagher & DS Sharp 1993-2001, PEPI) was used for this calculation.

Results
Population characteristics
One hundred, forty-five patients were studied, aged 67 ± 11 years old, 57% males, 17% defined during admission as ST-elevation AMI, and the remaining characterized as non-ST-elevation ACS. Time delay between symptom onset and laboratory determination had a median of 3.9 hours (interquartile range = 1.5 - 12), indicating a relatively early measurement of myocardial necrosis markers. Cardiac troponin T had a median of 0.02 ug/l (0.01 - 0.34 ug/l) and 53% of the individuals had positive cTnT (> 0.01 ug/l). Creatinine clearance averaged 68 ± 25 ml/min and 46% had moderate renal dysfunction (30 - 59 ml/min), 36% mild renal dysfunction (60 - 89 ml/min) and 18% normal renal function. Clinical characteristics are depicted on Table 1 and therapy during hospitalization on Table 2.

Relationship between renal function and cardiac troponin T
No correlation was observed between creatinine clearance and cTnT (r = - 0.06, P = 0.45), indicating no influence of renal function on cTnT variability - Figure 1.

Table 1 - Clinical and laboratory characteristics of the sample population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>67±11</td>
</tr>
<tr>
<td>Men</td>
<td>83 (57%)</td>
</tr>
<tr>
<td>Time symptoms to lab (hours)</td>
<td>3.9 (1.5 – 12)</td>
</tr>
<tr>
<td>Troponin T (ug/l)</td>
<td>0.02 (0.01 – 0.34)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>68±25</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.1±0.32</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73±16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27±4.9</td>
</tr>
<tr>
<td>ST-elevation AMI</td>
<td>24 (17%)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>26 (18%)</td>
</tr>
<tr>
<td>Killip &gt; 1</td>
<td>14 (10%)</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>35 (27%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (30%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>118 (31%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>56 (39%)</td>
</tr>
<tr>
<td>GRACE score</td>
<td>121 (98 – 143)</td>
</tr>
</tbody>
</table>

Troponin T, GRACE Score and time symptoms to lab are expressed in median and interquartile range. Remaining numeric variables are expressed in mean ± standard deviation. BMI - body mass index; AMI - acute myocardial infarction.
Table 2 - Treatment during hospitalization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>138 (95%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>138 (95%)</td>
</tr>
<tr>
<td>Heparin</td>
<td>134 (92%)</td>
</tr>
<tr>
<td>Ilb/Ilia blocker</td>
<td>24 (16%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>115 (81%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>115 (81%)</td>
</tr>
<tr>
<td>Statins</td>
<td>140 (97%)</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>70 (48%)</td>
</tr>
<tr>
<td>Surgical coronary revascularization</td>
<td>25 (17%)</td>
</tr>
</tbody>
</table>

Panel A. This finding remained after the exclusion of outliers (N = 138, r = -0.05, P = 0.55). The absence of correlation between creatinine clearance and cTnT was also seen (r = -0.06, P = 0.63) when only individuals with detectable cTnT (> 0 ug/l) were evaluated - Figure 1, Panel B. The first, second, third and fourth quartiles of creatinine clearance were distributed as < 51 ml/min, 51-64 ml/min, 65-83 ml/min, > 83 ml/min, respectively. The levels of troponin T were similar among individuals in the first (median = 0.05 ug/l; interquartile range = 0 - 0.37 ug/l), second (median = 0 ug/l; interquartile range = 0 - 0.22 ug/l), third (median = 0.07 ug/l; interquartile range = 0 - 0.32 ug/l) and fourth quartiles (median = 0 ug/l; interquartile range = 0 - 0.58 ug/l) of creatinine clearance - P = 0.63 - Figure 2, Panel A. Similarly, individuals with moderate renal dysfunction (creatinine clearance = 30 - 59 ml/min) and those with normal/near normal function (≥ 60 ml/min) had similar cTnT values (0.02 ug/l; 0 - 0.36 ug/l vs 0.03 ug/l; 0 - 0.33 ug/l) - P = 0.63 - Figure 2, Panel B. The prevalence of positive cTnT was similar among individuals in the first, second, third and fourth quartile of clearance (58% vs 47% vs 62% vs 44%, respectively, P = 0.36) and between individuals with moderate renal dysfunction and normal/near normal renal function (55% vs 52%, P = 0.65) - Figure 3.

Discussion

The present study indicates that renal function does not influence cTnT levels at hospital admission in individuals with ACS, ranging from normal to moderate renal impairment. This observation was consistently reproduced by different forms of data analysis: correlation between cTnT and creatinine clearance, comparison of cTnT among groups defined by clearance levels and comparison of the frequency of positive cTnT among those groups.

The absence of linear correlation with 98% statistical power provides evidence against the influence of mild to moderate renal dysfunction on cTnT in patients with ACS. However, it does not exclude a non-linear relationship. To solve this issue, cTnT was compared among quartiles of creatinine clearance and no difference was observed either. In addition, cTnT was analyzed as a dichotomous variable (positive or negative) and the frequency of positive cTnT was similar among groups of different levels of renal functions, from one extreme of normal function to the other extreme of moderate dysfunction. We did not evaluate serial troponin measurements, but this approach is unlikely to show different results, because troponin elevation due to renal dysfunction is a chronic phenomenon and a first sample measurement should be enough to assess this finding.

Fifty-three percent of the individuals in our sample had detectable levels of cTnT (≥ 0.01 ug/l), which corresponds to values above the 99th percentile. In this study, we did not intend to establish the exact cause of cTnT elevations and our conclusion is focused on renal function interference on cTnT. But we can speculate that, as the population studied consisted of individuals with ACS, the pretest probability of myocardial...
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Figure 2 - Comparison of Troponin T according to groups defined by creatinine clearance. Panel A represents troponin values according to quartiles of creatinine clearance. Panel B compares troponin T according to the two groups dichotomized into moderate renal dysfunction and normal/near normal renal function.

Figure 3 - Prevalence of positive troponin (≥ 0.01 ug/l) according to quartiles of creatinine clearance.

infarction was high. This pretest probability, coupled with our information that renal function does not influence cTnT levels, strongly suggests that ischemic myocardial injury was the cause of elevated cTnT.

The exact mechanism by which renal dysfunction increases cTnT levels is a matter of discussion. In healthy subjects, high sensitivity assays are able to detect very small amounts of serum cTnT, indicating that continuous microloss of cardiomyocytes is normal\(^{15}\). These cTnT molecules are fragmented to be cleared by the kidneys. Based on our findings, we can speculate that moderate renal dysfunction in not enough to promote accumulation of troponin fragments.

Limitations of the study should be pointed out. Firstly, since we did not include individuals with creatinine clearance < 30 ml/min, our findings cannot be extrapolated to nondialysis patients with severe renal dysfunction. Our original sample population included very few of these patients and no conclusion could be drawn regarding this level of renal function. Thus, we did not include these patients and chose to focus on the range of normal to moderately impaired renal function and secondly, our sample size is not large enough to totally rule-out association when creatinine clearance gets closer to 30 ml/min. For instance, only 15 patients had a clearance between 30 and 40 ml/min. Thirdly, we did not have data on follow-up measurements of cTnT. If that was
the case, late normalization of cTnT levels would suggest that the cases of positive cTnT represented myocardial infarction.

The usefulness of the present results regarding the interpretation of cTnT levels in patients with ACS should be emphasized. When renal disease is present, the level of dysfunction should be assessed. If dysfunction is not severe, a cTnT elevation should not be attributed to renal disease and interpretation of these values should be performed regardless of the presence of renal impairment. In conclusion, moderate renal dysfunction is not associated with cTnT elevation in patients with ACS.

Potential Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Study Association
This study is not associated with any post-graduation program.

References