Troponin I Levels and Postoperative Myocardial Infarction following Renal Transplantation

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Key Words
Troponin  Transplant  Myocardial infarction  Postoperative

Abstract
Background: The relationship of routine postoperative troponin I (TnI) monitoring in kidney transplant recipients and in-hospital myocardial infarction (MI) is not known. Methods: This observational study evaluated the prevalence of abnormal postoperative TnI (Ortho Clinical Diagnostics assay) in 376 consecutive kidney or kidney/pancreas transplant recipients. In-hospital MI was adjudicated using the universal definition. Rates of death and coronary revascularizations at 1 year were studied. Logistic regression analysis was performed to identify independent predictors of abnormal TnI. Results: Ninety-five (25%) recipients had abnormal TnI (>0.04 ng/ml) following transplantation. Abnormal TnI levels were more common in older (mean age: 52.2 ± 13.4 vs. 48.3 ± 13.2 years, p = 0.01), diabetic (57.9 vs. 45.6%, p = 0.04), and prior coronary artery disease (31.6 vs. 20.3%, p = 0.02) patients. In-hospital MI occurred in 6 patients (1.6%). All subsequent in-hospital cardiovascular events occurred in the abnormal postoperative TnI group; most in those with TnI levels >1 ng/ml. Previous coronary artery disease was the only independent predictor of a postoperative TnI level >1 ng/ml in multivariate analysis (odds ratio 4.61, 95% confidence interval 1.49–14.32). At 1 year there was no significant difference in death (3.2 vs. 1.8%, p = 0.42) and borderline significant difference in coronary revascularization (5.3 vs. 1.4%, p = 0.049) in abnormal versus normal TnI groups. Conclusions: In-hospital MI was infrequent, but abnormal TnI highly prevalent following renal transplantation. Normal TnI levels following renal transplantation had a high negative predictive value in excluding patients likely to develop subsequent postoperative MI. The role of a higher TnI cut-off for screening for postoperative MI in high-risk subgroups deserves future prospective evaluation.

Introduction

Cardiovascular (CV) disease accounts for 43% of all deaths in patients with end-stage renal disease [1]. In particular, the mortality rate of patients on maintenance dialysis following myocardial infarction (MI) is extremely high [2]. CV disease continues to remain the leading cause of mortality and morbidity following renal transplantation [3]. Renal transplant recipients have signifi-
cantly higher mortality rates compared to patients on dialysis in the first 3 months following transplantation; this risk is highest (about three-fold) in the first 2 weeks [4]. Perioperative MI following non-cardiac surgery is associated with an increased risk of in-hospital mortality, future cardiac death and recurrent MI [5]. Furthermore, CV complications following renal transplantation surgery are associated with long-term allograft dysfunction [6]. Since renal transplantation confers a significant survival advantage relative to patients on dialysis or wait-listed for transplantation in the long-term, early detection and appropriate management of early CV events is a clinical priority in renal transplant recipients.

It is well established that cardiac troponin levels are independent predictors of adverse long-term CV events and mortality in patients with chronic kidney disease and end-stage renal disease [7, 8]. Apple et al. [9] showed in patients with end-stage renal disease that the adjusted relative risk of mortality associated with elevated troponin T (TnT) and troponin I (TnI) isoforms was 3.9 and 2.1, respectively. Connolly et al. [10] found that TnT levels are independently predictive of mortality in asymptomatic renal transplant recipients. Hickson et al. [11, 12] have demonstrated that TnT levels obtained in patients wait-listed for renal transplantation as well as obtained immediately pre-transplantation are independently predictive of long-term survival. Additionally, Claes et al. [13] have shown that TnI levels obtained immediately pre-transplant are predictive of adverse CV events in the postoperative period.

However, pre-transplant troponin levels are rarely available to guide management in routine clinical practice. Moreover, the baseline prevalence of abnormal troponin levels in patients with renal failure is high, making it challenging to interpret elevated levels in the context of detecting early postoperative CV events [7, 14, 15]. In this observational study, we sought to investigate the prevalence of abnormal postoperative TnI levels in renal transplant recipients and their relation to subsequent postoperative MI and future CV events at 1 year.

Methods

The institutional review board at the University of Minnesota approved this study. All patients undergoing kidney and kidney/pancreas transplantation at the University of Minnesota underwent routine measurement of TnI levels between November 1, 2005 and September 1, 2007 according to a surgical post-transplant management order set (3 TnI level measurements 8 h apart after arriving from the operating room). A TnI level was considered abnormal if ≥0.04 ng/ml (Vitros®, Ortho Clinical Diagnostics; reported imprecision 10% CV at 0.04 ng/ml). The first TnI level after arrival from the operating room and the highest among the three TnI values measured in the immediate postoperative period were recorded. The results of the post-transplant TnI levels were available in the routine care of the renal transplant recipients but clinical testing or management was not mandated by the order set. Postoperative transplant recipients were initially observed in the post-anesthesia care unit and then admitted to a telemetry floor for post-transplant management, with transfer to the intensive care unit reserved only for patients who demonstrated clinical instability.

We retrospectively studied the transplantation database to identify the incidence of in-hospital CV events (defined as death, MI, arrhythmia or heart failure). The diagnosis of in-hospital MI was retrospectively adjudicated by a single cardiologist (G.R.S.) based on the universal consensus criteria for MI defined by the combination of elevated TnI levels (above the 99% percentile and associated with rise and fall in TnI levels) plus any one of the following 3 criteria: symptoms of ischemia, changes on electrocardiogram of new ischemia/infarction, or imaging evidence of new ischemia/infarction [16]. In addition, the timing of the diagnosis of the in-hospital CV event was also recorded by retrospective chart review. Coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft surgery) were not recorded as in-hospital CV events due to the inability to determine if the revascularization was ‘driven’ by (i.e. if revascularization occurred as a result of) the abnormal postoperative TnI alone due to the retrospective nature of the study design. We evaluated the rates of death and coronary revascularization at 1 year following the transplantation procedure (including the immediate postoperative period). Chi-square analysis and Fisher’s exact test were used to study the difference between categorical variables and the Student’s t test was used for continuous variables. Logistic regression analysis of multiple clinical covariates was performed to identify independent predictors of abnormal TnI. These covariates included recipient age, gender, race, and cardiac risk factors including hypertension, diabetes, smoking and previous diagnosis of obstructive coronary artery disease or congestive heart failure. A forward selection process was used with a p < 0.05 entry criteria. Odds ratios (OR) and 95% confidence intervals (CI) are presented for each significant measure. Due to low event rates, multivariate analysis for independent predictors of postoperative CV events was not feasible. All analyses were done using SAS 9.2 (Cary, N.C., USA).

Results

376 consecutive renal and renal/pancreas transplant recipients had postoperative TnI levels measured following transplantation in the study period. Ninety-five (25%) recipients had at least one abnormal TnI value (≥0.04 ng/ml) following transplantation; 37 (9.8%) between 0.04–0.10 ng/ml, 38 (10.1%) between 0.11–0.99 ng/ml, and 20 (5.3%) ≥1.0 ng/ml. The baseline characteristics of the population studied are summarized in table 1. Compared to patients with normal post-transplant TnI levels, patients with abnormal TnI levels were older (mean age: 54.70.40.11 - 11/7/2017 2:13:48 AM
52.2 ± 13.4 vs. 48.3 ± 13.2 years, p = 0.01), more likely to have diabetes (58.5 vs. 45.6%, p = 0.04) and a history of previous coronary artery disease (31.6 vs. 20.3%, p = 0.02), especially coronary artery bypass graft surgery (16.8 vs. 6.1%, p = 0.001). Among patients with abnormal post-transplant TnI levels 78/95 patients (82%) underwent preoperative CV risk testing (42 patients underwent preoperative stress testing and 47 patients underwent preoperative coronary angiography) whereas 17/95 (18%) had no preoperative testing for CV risk stratification prior to renal transplantation.

Table 2 summarizes the cardiac events that occurred during the hospital stay and within 1 year after renal transplantation. Among patients with abnormal post-transplant TnI levels, 6 MI, 1 cardiac arrest, and 1 heart failure occurred. Notably, all in-hospital CV events occurred in patients with abnormal routine postoperative TnI values, and most in-hospital cardiac events occurred in patients with a routine postoperative TnI value >1 ng/ml. 7/20 patients with routine postoperative TnI >1 ng/ml had an in-hospital cardiac event versus 1/75 patients with TnI <1 ng/ml (p < 0.0001 using χ² analysis). When followed at 1 year, patients with abnormal TnI were more likely to undergo coronary revascularization (coronary artery bypass graft surgery or percutaneous coronary intervention) compared to patients with normal postoperative TnI values (5.3 vs. 1.4%, p = 0.049). However, mortality rates were not significantly different at 1 year (3.2 vs. 1.8%, p = 0.42).

Table 3 provides details of the in-hospital cardiac events occurring in patients following renal transplantation. Five patients were diagnosed to have non-ST elevation MI (NSTEMI) and 1 patient was diagnosed to have ST elevation MI (STEMI) during their hospital stay. Among these patients, 3 underwent emergent coronary revascularization during the hospital stay and 3 were medically managed. No in-hospital cardiac events occurred in patients with normal postoperative TnI levels. Most postoperative cardiac events occurred on postoperative days 0 or 1. It was notable that the STEMI event occurred on postoperative day 4. Although preoperative TnI levels were not available in this study, the first routine post-transplant TnI level was within normal limits for most patients who sustained a postoperative cardiac event, suggesting that these were not likely to be patients with chronically elevated TnI levels. Patients 1, 2 and 3 described in Table 3 needed to be transferred to the intensive care unit.
sive care unit from the post-transplant unit for clinical concerns (hypotension, arrhythmia, and shock, respectively).

Details of the multivariate analysis are presented in table 4. Pre-transplant diabetes was a predictor of postoperative TnI ≥0.04 ng/ml (OR 1.68, 95% CI 1.03–2.74) in univariate analysis but this relationship was not maintained after logistic regression analysis using multiple clinical correlates (OR 1.56, CI 0.92–2.67). Previous coronary artery disease was the only independent predictor of a postoperative TnI level >1 ng/ml in univariate analysis (OR 5.46, 95% CI 2.04–14.6) and in multivariate analysis (OR 4.61, 95% CI 1.49–14.32). A cut-off value >1 ng/ml for a routine post-transplant TnI had a diagnostic sensitivity of 88% and specificity of 96% for the detection of subsequent postoperative in-hospital cardiac events.

Discussion

This retrospective study examined the value of routine post-transplant TnI measurements in relation to perioperative MI and early cardiac events. Despite the high baseline prevalence (25%) of abnormal post-transplant TnI levels, the incidence of perioperative MI was only 1.6%. Notably, all in-hospital cardiac events occurred only in the abnormal post-transplant TnI group, and most cardiac events occurred in patients with a routine post-transplant TnI level >1 ng/ml. The occurrence of at least one abnormal postoperative TnI level immediately following renal transplantation was associated with increased rates of coronary revascularization but not mortality at 1 year.

Patients with renal failure have been shown to have a high baseline prevalence of abnormal TnI levels, albeit lower than the prevalence of abnormal TnT levels [11, 12, 15]. Claes et al. [13] obtained TnI levels in 331 kidney transplant recipients at the time of engraftment, and found that 11.5% patients had a TnI level >0.07 g/l (99th percentile). The difference in prevalence compared to our study likely reflects variations in the assay and the diagnostic cut-off value. The high baseline prevalence of abnormal TnI levels in renal transplant recipients can pose a management conundrum to the clinician attempting to balance the immediate postoperative risks and long-term risk of adverse CV outcomes portended by abnormal TnI levels. Elevated troponin values in patients with renal insufficiency have been shown to occur secondary to multiple clinical mechanisms other than ischemic heart disease, including left ventricular dilatation and systolic/diastolic dysfunction [17]. Indeed, a majority of abnormal postoperative TnI levels in renal transplant recipients in

### Table 3. In-hospital cardiac events occurring in patients following renal transplantation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>DM</th>
<th>First study TnI</th>
<th>Peak study TnI</th>
<th>In-hospital cardiac event</th>
<th>Timing of event</th>
<th>Revascularization*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>M</td>
<td>yes</td>
<td>&lt;0.04</td>
<td>10.8</td>
<td>NSTEMI</td>
<td>POD 0</td>
<td>PCI and CABG</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>yes</td>
<td>0.34</td>
<td>7.53</td>
<td>Torsades de pointes/ventricular fibrillation (hyperkalemia)</td>
<td>POD 1</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>F</td>
<td>yes</td>
<td>&lt;0.04</td>
<td>4.75</td>
<td>STEMI, cardiogenic shock, complete heart block</td>
<td>POD 4</td>
<td>PCI</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>yes</td>
<td>0.07</td>
<td>4.57</td>
<td>NSTEMI</td>
<td>POD 0</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>M</td>
<td>no</td>
<td>&lt;0.04</td>
<td>4.3</td>
<td>NSTEMI</td>
<td>POD 1</td>
<td>PCI</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>M</td>
<td>yes</td>
<td>&lt;0.04</td>
<td>3.52</td>
<td>NSTEMI and atrial fibrillation</td>
<td>POD 1</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>M</td>
<td>no</td>
<td>&lt;0.04</td>
<td>1.13</td>
<td>NSTEMI</td>
<td>POD 0</td>
<td>CABG</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>M</td>
<td>yes</td>
<td>&lt;0.04</td>
<td>0.29</td>
<td>Heart failure</td>
<td>POD 2</td>
<td>None</td>
</tr>
</tbody>
</table>

TnI levels are presented in ng/ml. PCI = Percutaneous coronary intervention; DM = diabetes mellitus; POD = postoperative day.

* Revascularization rates at 12 months from index transplantation surgery.

### Table 4. Clinical predictors of abnormal TnI using multivariate analysis (data presented as OR with 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>TnI ≥0.04 ng/ml (n = 95)</th>
<th>TnI &gt;1 ng/ml (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40–60 years</td>
<td>1.06 (0.55–2.05)</td>
<td>0.54 (0.14–2.16)</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>1.66 (0.78–3.55)</td>
<td>0.85 (0.19–3.84)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.80 (0.48–1.35)</td>
<td>1.96 (0.60–6.39)</td>
</tr>
<tr>
<td>Deceased donor</td>
<td>0.85 (0.51–1.43)</td>
<td>0.80 (0.29–2.23)</td>
</tr>
<tr>
<td>Black</td>
<td>0.91 (0.28–2.95)</td>
<td>1.67 (0.31–9.04)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.60 (0.93–2.74)</td>
<td>1.59 (0.53–4.79)</td>
</tr>
<tr>
<td>Pre-CAD</td>
<td>1.42 (0.78–2.57)</td>
<td>4.59 (1.48–14.26)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.91 (0.55–1.50)</td>
<td>0.76 (0.28–2.08)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.98 (0.48–2.01)</td>
<td>–</td>
</tr>
</tbody>
</table>

Pre-CAD = Prior diagnosis of coronary artery disease.
our study were not associated with in-hospital MI. Additionally, abnormal postoperative TnI levels were predicted by demographics and clinical variables (age, coronary artery disease and diabetes). These clinical variables identify a population that needs to be targeted to prevent perioperative CV complications, irrespective of troponin levels [18].

Interestingly, in this study all patients with a cardiac event during their subsequent hospital stay had abnormal TnI in the immediate postoperative period. Thus, negative TnI immediately following renal transplantation had a high negative predictive value in excluding patients likely to develop in-hospital postoperative MI. Conversely, the 25% patients with an abnormal TnI level might deserve more focused clinical attention to identify those at risk of a future in-hospital cardiac event. In fact, patients with higher postoperative TnI levels (>1 ng/ml; 5.3% of the study population) were more likely to develop an in-hospital cardiac event. Use of a higher TnI threshold (e.g. >1 ng/ml) attention to a rise/fall in TnI levels and simultaneous electrocardiogram changes may help further refine a prospective screening strategy for early detection of postoperative cardiac events. The clinical and cost-effectiveness of such an approach should be comprehensively evaluated in a prospectively designed study.

TnI levels in this study also provide information pertaining to the timing of postoperative MI in renal transplant recipients. In most patients, the first postoperative TnI level was normal but 1 of the 3 postoperative study TnI levels was elevated (table 3). NSTEMI occurred in 5 patients and was diagnosed on postoperative day 0 or 1. One patient sustained an STEMI that was detected on postoperative day 4; but notably this patient had a markedly abnormal routine postoperative TnI level prior to the diagnosis of the actual clinical event. This observation suggests the possibility of a ruptured plaque that occurred in the immediate postoperative period that later evolved into an ST segment elevation MI during the hospital stay. Postoperative MI most likely occurs either intraoperatively or immediately following surgery, corresponding to periods associated with significant hemodynamic stress in a pro-inflammatory milieu [5]. This period is associated with a confluence of factors contributing to a combination of increased coronary artery shear stress (precipitating plaque fissuring and thrombosis) and increased myocardial oxygen demand [5]. Routine post-transplant TnI elevation could signal more subtle myonecrosis caused by a ruptured or vulnerable plaque in the postoperative period that evolves later into a postoperative MI (as observed in patient No. 3 in our study).

The incidence of MI following renal transplantation in this study is identical to that reported by Humar et al. [19], who described a 6% risk of perioperative cardiac events including 1.6% risk of MI among 2,694 renal transplants at the University of Minnesota over a span of 14 years. Claes et al. [13] reported a 3.3% incidence of short-term cardiac events in a study of 331 renal transplant patients at the University Hospitals, Leuven. Coronary revascularization was incorporated in the primary endpoint in addition to death and MI in this study, explaining the higher incidence of cardiac events reported. Lentine et al. [20] evaluated 35,847 patients using the United States Renal Data System (USRDS) and determined that the incidence of postoperative MI (from administrative records) was 4.3%. The lower incidence of MI in single-center studies compared to USRDS data likely reflects a combination of factors including patient selection, preoperative CV risk stratification, and possibly more aggressive medical management.

This study has limitations inherent to retrospective studies including selection and ascertainment bias. Because of the retrospective nature of the study it was not possible to determine precisely in what percentage of patients with cardiac events the routine TnI levels may have contributed to the diagnosis or altered the clinical course. It is possible that the routine postoperative TnI levels could have altered the clinician’s approach and influenced patient management and outcomes in ways that cannot be detected by the retrospective study design. Similarly, it was not possible to accurately determine if patients had symptoms attributable to cardiac ischemia in the postoperative period. The absence of preoperative TnI levels is a limitation, but does reflect routine clinical practice where in preoperative TnI levels are not usually available to the clinician. Moreover, the first postoperative TnI level was not elevated in most patients in this study, making it unlikely that these patients had significant baseline TnI elevation. The influence of preoperative cardiac risk stratification on postoperative cardiac events and TnI elevation is not known in this study. A randomized, controlled trial would be the best way of determining whether obtaining routine TnI levels after renal transplantation in the background of optimal medical therapy improves long-term outcomes. However, the results of the current retrospective study suggest that such a trial would need to be extremely large to achieve adequate statistical power because of the low incidence of postoperative cardiac events.

In conclusion, the low incidence of postoperative MI coupled with a high baseline prevalence of abnormal TnI levels in this population does not support a routine strategy of post-transplant TnI monitoring for the detection of...
early cardiac events in renal transplant recipients. This conclusion supports the recommendations of societal guidelines (‘routine measurement of cardiac-specific troponin after non-cardiac surgery is more likely to identify patients without acute MI than with MI’), and justifies the applicability of these guideline recommendations to the renal transplant population [21]. However, the observation that every postoperative cardiac event was heralded by an abnormal TnI measurement in the immediate post-transplant period needs future prospective evaluation. The role of screening TnI in high-risk subgroups (e.g. those with coronary artery disease, or diabetics) and use of a higher cut-off TnI level (e.g. >1 ng/ml) for screening for postoperative MI deserves future prospective evaluation.

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References


