High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: A prospective cohort study☆

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Objectives: To determine the proportion of noncardiac surgery patients exceeding the published 99th percentile or change criteria with the high sensitivity Troponin T (hs-TnT) assay.

Design and methods: We measured hs-TnT preoperatively and postoperatively on days 1, 2 and 3 in 325 adults.

Results: Postoperatively 45% (95% CI: 39–50%) of patients had hs-TnT ≥ 14 ng/L and 22% (95% CI: 17–26%) had an elevation (≥ 14 ng/L) and change (≥ 85%) in hs-TnT.

Conclusion: Further research is needed to inform the optimal hs-TnT threshold and change in this setting.

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Table 1
VISION Bio-bank substudy characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study population (n = 325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>Median (25th–75th percentile)</td>
<td>65 (57–75)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female n (%)</td>
<td>159 (49%)</td>
</tr>
<tr>
<td>Surgery n (%)</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>26 (8%)</td>
</tr>
<tr>
<td>General</td>
<td>53 (16%)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>33 (10%)</td>
</tr>
<tr>
<td>Major urology or gynecology</td>
<td>43 (13%)</td>
</tr>
<tr>
<td>Major orthopedic</td>
<td>94 (29%)</td>
</tr>
<tr>
<td>Major neurosurgery</td>
<td>25 (8%)</td>
</tr>
<tr>
<td>Low risk surgeries</td>
<td>64 (20%)</td>
</tr>
<tr>
<td>Revised cardiac risk index n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>177 (54%)</td>
</tr>
<tr>
<td>1</td>
<td>91 (28%)</td>
</tr>
<tr>
<td>2</td>
<td>37 (11%)</td>
</tr>
<tr>
<td>≥3</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Duration of surgery in minutes</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>143 ± 88</td>
</tr>
<tr>
<td>Median (25th–75th percentile)</td>
<td>124 (83–173)</td>
</tr>
</tbody>
</table>

hs-TnT (ng/L)*: Pre-operative median (25th–75th) 5 (3–12), Pre-operative prevalence (%): ≥ 14 ng/L Day 1 median (25th–75th percentile) 9 (3–17), Day 1 prevalence (%): ≥ 14 ng/L Day 2 median (25th–75th percentile) 10 (4–21), Day 2 prevalence (%): ≥ 14 ng/L Day 3 median (25th–75th percentile) 8 (3–16), Day 3 prevalence (%): ≥ 14 ng/L 30% (95% CI: 25–35%).

* hs-TnT preoperative concentration lower than postoperative days (p<0.001; Kruskal–Wallis all pairwise comparisons).

Methods

Study population

The VISION Bio-bank Study is a substudy of VISION, and includes a prospective sample of VISION patients who are ≥ 45 years of age, undergoing elective or emergent noncardiac surgery requiring overnight hospital admission, and receiving a general or regional anesthetic. Recruitment into the VISION Bio-bank Study has occurred at the following three Canadian hospitals: the Hamilton Health Sciences, Hamilton, Ontario, Saint Joseph’s Healthcare, Hamilton, Ontario, and Winnipeg Health Sciences Centre, Winnipeg, Manitoba. All VISION Bio-bank patients have blood drawn preoperatively and on the 1st, 2nd, and 3rd days after surgery. As evaluating change was one of the aims of this study, we included only those subjects with specimens in storage at all four time points (i.e., preoperative and days 1, 2, and 3 after surgery). For this study we planned to include the first 325 eligible subjects from the VISION Bio-bank.

Risk for these subjects was assessed using the Revised Cardiac Risk Index, which is the most commonly used perioperative risk index [7]. This index consists of 6 equally weighted risk factors: high-risk surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, use of insulin therapy for diabetes, and a preoperative serum creatinine > 175 μmol/L.

The non-parametric upper 95th (with 95% CIs) and 99th (with 90% CIs) percentiles were calculated for the preoperative specimens from the included patients [8]. Secondary analyses were also performed removing the 4 individuals who required emergent surgery (for a study population n = 321) and we determined the 95th percentile in those below and above 65 years of age and based on sex.

Laboratory measurements

As part of the VISION Study the TnT 4th generation assay was measured postoperatively on day 1 (n = 306 patients), day 2 (n = 297), and day 3 (n = 300) after surgery. The hs-TnT assay was measured from the bio-bank samples at all 4 time points and physicians were unaware of these results (n = 1300 specimens from 325 subjects). The reported limit of blank for the hs-TnT assay is 3 ng/L [2] with concentrations below this level also listed as 3 ng/L for this
analysis. The coefficient of variation (CV) for the hs-TnT assay over 1 month was 15% at 12 ng/L (serum control pool, n = 32); 5% at 26 ng/L (Roche PreciControl Level 1, n = 24) and 2% at 2200 ng/L (Roche PreciControl Level 2, n = 24).

Statistical analyses

Percentages for those subjects exceeding the various cutoffs (with 95% CIs) with or without change were calculated (Graphpad Prism). Descriptive statistics and differences between groups were determined by non-parametric methods with analyses being performed by Statsdirect and Analyze-it software (p < 0.05 was considered significant). This study has received research ethics board approval.

Results

The mean (SD) patient age was 65 (11) years, approximately half were female, and there was representation of all major surgical interventions, Table 1. The Revised Cardiac Risk Index suggested that the majority of participants were considered low-risk (i.e., scores of 0 or 1) for a major perioperative vascular complication.

The hs-TnT concentrations were higher postoperatively (days 1, 2, 3) as compared to the preoperative concentrations (Table 1). Preoperatively, 21% (95% CI: 17–25%) of the subjects exceeded the published 99th percentile, with the derived 99th percentile in the 325 individuals calculated as 71 ng/L (95% CI: 61–84) and the 95th percentile calculated as 33 ng/L (95% CI: 26–49) (Fig. 1A). Removal of the 4 emergent surgeries did not change these estimates. For subjects ≥65 years of age the calculated 95th percentile was 36 ng/L (95% CI: 32–40) as compared to 25 ng/L (95% CI: 18–31) for those <65 years. The female derived 95th percentile was 18 ng/L (95% CI: 14–22) and the male 95th percentile was 48 ng/L (95% CI: 32–62). Postoperatively the cumulative percent of subjects with hs-TnT ≥14 ng/L was 45% (95% CI: 39–50%) and those that had hs-TnT concentration change postoperatively exceeding 85% as compared to preoperative concentrations was 38% (95% CI: 33–43%). These percentages were significantly higher than those exceeding the other hs-TnT cutoffs (33 ng/L [16%; 95% CI: 12–20], 71 ng/L [5%; 95 CI: 3–8%]) or change criteria (242% criteria [15%; 95% CI: 12–19%]) (Fig. 1B).

The percentage of subjects (22%; 95% CI: 17–26%) that had both an elevation (≥14 ng/L) and change (>85%) in hs-TnT concentration

Fig. 1. Preoperative distribution of hs-TnT concentrations in the VISION cohort with cutoffs indicated (n = 325) (A), and the cumulative frequency of those exceeding different cutoffs or change criteria postoperatively (B).
postoperatively was significantly higher than any other combination of change and cutoff (e.g., prevalence of subjects ≥ 14 ng/L and >242% change = 12% [95% CI: 9–16%]; subjects >33 ng/L and >85% change = 10% [95% CI: 7–14%]; subjects >33 ng/L and >242% change = 7% [95% CI: 5–11%]). For comparison, the cumulative prevalence of subjects with the 4th generation TnT assay >0.03 μg/L on any postoperative day 1, 2, or 3 was 9% (95% CI: 6–12%) (Fig. 1B).

Postoperatively the cumulative percent of subjects with hs-TnT ≥ 14 ng/L was 27.7% (95% CI: 21.6–34.7%), 52.7% (95% CI: 42.6–62.7%), 56.8% (95% CI: 40.9–71.3%), and 80.0% (95% CI: 58.4–91.9%) for patients with a Revised Cardiac Risk Index score of 0, 1, 2, and ≥ 3, respectively. A total of 4 patients (all >65 years) died during the first 30 days after surgery (1% of study population). The concentration of TnT in these 4 patients using the 4th generation assay was <0.03 μg/L on all specimens (n = 12). Using the hs-TnT assay 3 patients (2 females, 1 male) had a peak concentration ≥ 14 ng/L and the other patient’s peak was 9 ng/L (male). Only 2 of these 4 patients met the >85% change criterion. The median peak hs-TnT concentration among the patients who died and survived was 23 ng/L and 12 ng/L, respectively.

Discussion

Our study demonstrates that patients undergoing noncardiac surgery represent a population with significant hs-TnT elevations. Using the published 99th percentile of ≥ 14 ng/L one in five adults exceeded this threshold prior to surgery. This positive rate increased postoperatively with over 40% of subjects having a postoperative hs-TnT concentration ≥ 14 ng/L. Some authors advocate the need for a change in concentration beyond surpassing a hs-TnT threshold. When both of these criteria are employed using published estimates (i.e. ≥ 14 ng/L [2] with >85% change [4]) in the postoperative samples, again one fifth of the subjects were identified as having evolving injury. Both of these estimates of myocardial injury were significantly higher than was observed using the 4th generation TnT assay (i.e., 9%).

There are several limitations to our study. Due to the small sample sizes of our subgroups (i.e., based on age and sex) we are unable to determine the 99th percentiles with reasonable confidence. Although prior studies have shown that an elevated postoperative TnT measurement is an independent predictor of a major cardiovascular complication and mortality [9,10], this has not been established for the hs-TnT assay. The descriptive nature of our analyses should be considered as a starting point for subsequent work assessing health outcomes with respect to different cutoffs and change criteria. These data presented are, however, of importance for those measuring hs-TnT in the perioperative setting, as they offer insights into the frequency of positive tests to expect based on various thresholds and indicate that incorporating change will decrease the prevalence of those with evolving myocardial injury as compared to only using the published 99th percentile from a healthy population. Using the preoperative VISION 99th percentile of 71 ng/L may yield similar diagnostic information as the current 4th generation TnT cutoff of >0.03 μg/L.

The ideal way to determine the optimal threshold is by relating it to an important outcome (e.g., death at 30 days). Until this research is completed physicians measuring the hs-TnT assay in patients undergoing noncardiac surgery can expect a high percentage of patients to exceed the reference standard based on a healthy population (≥ 14 ng/L).

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References