

Post-operative high sensitivity troponin T (hsTnT): toward an extending use for diagnosis and management of myocardial injury after noncardiac surgery?

Xavier Chapalain, Olivier Huet

Department of Anesthesiology and Intensive Care Medicine, Brest University Hospital, Brest cedex, France

Correspondence to: Olivier Huet, PhD. Department of Anesthesiology and Intensive Care Medicine, Boulevard Tanguy Prigent, Brest University Hospital, Brest cedex, France. Email: olivier.huet@chu-brest.fr.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Ming Zhong (Department of Critical Care Medicine, Zhongshan Hospital Fudan University, Shanghai, China).

Comment on: Devereaux PJ, Biccari BM, Sigamani A, *et al.* Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA* 2017;317:1642-51.

Submitted Jun 20, 2017. Accepted for publication Jun 22, 2017.

doi: 10.21037/jtd.2017.06.146

View this article at: <http://dx.doi.org/10.21037/jtd.2017.06.146>

Vascular death is a major cause of perioperative fatality which were responsible for approximately 50% of death (1). Myocardial injury after noncardiac surgery (MINS) is defined as an ischemic injury occurring within 30 days after surgery. After a noncardiac surgery, about 5% of patients have a myocardial infarction (1) but the incidence of MINS may vary and depend on the definition used. In this context, experts have divided in five categories the definition of myocardial infarction (2). According to these guidelines, patients who have an elevation of troponin T (TnT) level and more than one clinical sign (an ischemic symptom or a new ST-T abnormality on the electrocardiogram) fulfill MINS diagnosis criteria. After noncardiac surgery, two types of myocardial injury (MI) may occur. The type I myocardial infarction is an event related to atherosclerotic plaque rupture or ulceration and it represent nearly half of MINS events (2). Type II correspond to an imbalance between oxygen myocardial supply and/or demand (2). Several clinical and biological risk factors have been individualized like age, history of coronary artery disease or cerebrovascular accident and scores have been developed to categorize individual peri-operative cardiac risk (3). Among them, cardiac risk index (CRI) is the most commonly used (4). However, despite a good preoperative risk stratification, some patients still present a MI or a myocardial infarction (1,5). As nearly 60% of myocardial infarction are asymptomatic the diagnosis of these events is

often difficult (1). Thus, physicians need specific biomarkers to identify a MI such as cardiac troponin (cTn) or Mb fraction of creatinine kinase (CK-Mb). cTn C and T are a part of contractile system of myocardial cells and are expressed exclusively in heart which make them accurate bio-markers of myocardial cells damage. The incidence of the postoperative elevation of cTn vary from 6% to 31%, and may differ depending on the type of measurements and the laboratory assay used (6-8). About the measurement of TnT, several manufacturers develop kit to measure TnT.

The VISION cohort (The Vascular events In noncardiac Surgery patients cOhort evaluationN) is an international, observational, multicenter, prospective cohort designed to assess peri operative complications (clinicaltrial.gov, NCT00512109). Twenty-nine centers in 15 countries included approximately 40,000 patients aged from 45 years and older were between 2007 and 2013. Using the VISION cohort, several reports have been published during last years which studied diagnostic criteria, risk scoring systems and prognosis of MINS (1,5,9-12). A particular interest of the VISION investigators was to determine a prognostic value of TnT level (5,11). The first results of this work concerning prognostic value of the fourth-generation measurement of non-high sensitivity troponin T (non-hsTnT) level were published in 2012 in a previous issue of the *JAMA* (3). Because of an extensive use of hsTnT in the management of MI/infarction, studies on fifth-generation

measurements of hsTnT were urgently needed. In the April issue of the *JAMA* journal, we read with great interest the last report of the VISION investigators. This study was designed to determine the association between elevation of hsTnT level, MI and 30-day post-operative mortality after non-cardiac surgery (5). More than 20,000 patients were included in the analyses, which 17.9% of them fulfilled the diagnosis of MINS. In this cohort of patients, hsTnT was measured during the first 3 days of surgery. Different statistical methods can be used to determine prognostic values of biological parameters. Devereaux and colleagues used a modified Mazumdar approach (13) to categorized peri-operative prognostic value of hsTnT. Generally, this approach consists in separating risk group according to minimum P value and/or maximum chi-square testing. This allow defining an optimal cutpoint to stratify low-risk and high-risk patients (13,14). An adjustment of inflated P value is necessary with modified Bonferroni correction or other correction formula (14). In the VISION cohort study, hsTnT threshold was identified according to adjusted hazard ratio (aHR) and P value from likelihood ratio corresponding to each hsTnT values. To choose the best troponin threshold, investigators considered an aHR ≥ 3 associated with a peak of hsTnT as significant to assess patient prognostic. The main finding of this study is that a peak of postoperative hsTnT was associated with 30-day mortality. To be associated to an increased postoperative mortality the threshold of the hsTnT peak must be above 5 ng/L [with an aHR of 3.73 (1.58–8.82), P value of 0.003]. In addition, more the peak of hsTnT is high more the adjusted HR of 30-day mortality increases [with a threshold < 5 ng/L as a reference group: aHR =3.73 (1.5–8.82) for a threshold between 5 and 14 ng/L, an aHR =9.11 (3.76–22.09) for a threshold between 14 and 21 ng/L, an aHR =23.63 (10.32–54.09) for a threshold between 21 and 65 ng/L]. Eventually, this significant association persisted with or without the presence of clinical ischemic manifestation. Furthermore, absolute changes between preoperative value and postoperative peak were associated with an increasing risk of 30-day mortality [with an absolute change of at least 5 ng/L aHR =2.81 (1.63–4.82) and aHR =15.68 (8.94–27.51) with an absolute change of 40 ng/L]. After excluding non-ischemic etiologies, patients with an elevation of hsTnT superior to 20 ng/L were considered by adjudicators to have a MINS even if they had not reported ischemic symptoms. Considering this threshold, MINS was statistically associated with 30-day mortality. Among the 3,904 patients who fulfilled MINS diagnostic criteria, only

3.6% had chest pain and 93.1% of them did not experienced ischemic symptoms. In the absence of postoperative systematic screening using hsTnT, these patients presenting a MINS would not have been detected. Therefore, this make the VISION cohort the first cohort reporting an association of hsTnT levels and its perioperative evolution with 30-day postoperative mortality.

International guidelines recommend a rapid measurement of troponin level in case of suspicion of MI or ischemia (3), whereas a routine screening is not recommended in unselected patients. The VISION study reinforces the interest of biomarkers in the diagnosis and the management of MINS. An association between a peak of post-operative troponin, presence of MINS and 30-day mortality in an unselected population of patients suggest that the screening of a larger population of patients with fifth-generation hsTnT assay after noncardiac surgery would be of interest. Several consideration and perioperative management can be recommended to minimize post MI after non-cardiac surgery: choice of anesthetic techniques or agent, pain management or choice in intra-operative monitoring devices. However, there are no guidelines available to manage patients presenting an acute ischemic heart event after surgery. Therefore, screening hsTnT levels would probably help investigators to select and include patients in large multicenter, randomized, controlled trials to evaluate and find effective intervention to diminish mortality and complications after surgery. There is definitely a need for such studies to evaluate the importance of hsTnT sampling in the diagnosis of asymptomatic MINS is hard to predict.

Development of highly sensitive assay for cTn has already been evaluated during management of coronary artery disease. Studies performed in ischemic heart disease patient's population provide interesting findings, which inspire further studies in the perioperative context. During unstable angina, troponin level has been individualized as an independent risk predictor (15). In case of myocardial ischemia without ST-elevation, troponin level is a good point of care testing in deciding to treat patients with an early invasive procedure (15,16) including events with low-level elevation of troponin. An early invasive management with coronarography contributed to diminish composite outcome of myocardial infarction, death or rehospitalization for acute coronary syndrome especially in patients with minor elevation of cardiac biomarkers (patients with Troponin C level of 0.1 ng/mL or more) (15). Contribution of troponin during stable coronary artery disease has also been evaluated. The PEACE trial evaluated high

sensitivity assay in detecting minor elevation of TnT from a population of nearly 3,600 patients with stable coronary artery disease and preserved left ventricular function (17). During more than 5 years of follow up, cumulative incidence of cardiovascular death was associated with an increase of cardiac TnT level (17). Interestingly, among the 3,630 patients of the PEACE cohort hsTnT level (fifth-generation assay) provided a relevant prognosis information that wouldn't have been detected with a conventional assay (fourth-generation assay). In this subgroup of patients, hsTnT elevation was also statistically associated with cardiovascular death (17). After myocardial infarction, peak TnT elevation is strongly correlated with infarct size and left ventricular function at day 5 (R-value are respectively 0.702 and -0.394 , P value <0.001) and day 30 (R-value are respectively 0.655 and -0.496 , P value <0.001) (18). More recently, Hall and colleagues showed a strong and significant association between an elevation of troponin I (TnI) and cardiac events (cardiogenic shock, cardiac heart failure, arrhythmia) after ST-elevation myocardial infarction (19). There are no data on functional outcome (cardiac status, quality of life) of patients which presented an elevation after noncardiac surgery. Therefore, more studies are needed to evaluate hsTnT prognosis value.

There are interesting implications of the VISION cohort findings suggesting a larger use of hsTnT in postoperative context. Many strengths of VISION cohort (large, international, representative, prospective cohort) provide interesting information about hsTnT. The use of a fifth-generation assay provides a new tool for detecting minor elevation and/or absolute changes of peri-operative TnT levels and predict postoperative mortality. Several limitations were mentioned by authors (5). Thus, several areas must be explored in the future. First of all, implementation of recent guidelines need to be evaluated with registries (3). Secondly, gaps in care concerning all aspects of perioperative care (preoperative risk stratification, perioperative therapeutic adaptation, intraoperative monitoring) must be identified within each center. Thirdly, specific intervention during MINS management has to be evaluated. Therapeutic decisions making process (use of anti-platelet agents, coronarography) based on hsTnT might be harmful during the peri-operative period, especially because of the increase risk of bleeding induced by surgery. Several clinical trials are urgently needed to determine real impact of a large use of hsTnT and the cost-effectiveness of these practices. Elevation of hsTnT can help trialists to design clinical trials in challenging

new therapeutics in the peri-operative context. Taking into considerations recent advances in cardiology (15-19), these future investigations must try to document pathophysiological mechanism involved in MINS and also patients reported outcomes after MINS. The MANAGE trial (Management of myocardial injury After NonArAic surGERy trial, clinicaltrial.gov, NCT01661101) will may be clarify the role of hsTnT during the postoperative period. This randomized, controlled, factorial study is designed to evaluate dabigatran and omeprazole *vs.* double placebo to diminish major vascular complications in a population of patients suffering from MINS. If case of clinical benefit, large medico economic evaluation is probably needed to evaluate impact of this monitoring. Finally, these findings need to be translate into clinical practice therefore more clinical data are needed in the near future to help the peri-operative team to use correctly hsTnT monitoring in order to diagnose and manage MINS.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011;154:523-8.
2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.
3. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014;64:e77-137.
4. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043-9.
5. Devereaux PJ, Biccari BM, Sigamani A, et al. Association

- of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *JAMA* 2017;317:1642-51.
6. Jules-Elysee K, Urban MK, Urquhart B, et al. Troponin I as a diagnostic marker of a perioperative myocardial infarction in the orthopedic population. *J Clin Anesth* 2001;13:556-60.
 7. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation* 2002;106:2366-71.
 8. Martinez EA, Nass CM, Jermyn RM, et al. Intermittent cardiac troponin-I screening is an effective means of surveillance for a perioperative myocardial infarction. *J Cardiothorac Vasc Anesth* 2005;19:577-82.
 9. Abbott TEF, Ackland GL, Archbold RA, et al. Preoperative heart rate and myocardial injury after non-cardiac surgery: results of a predefined secondary analysis of the VISION study. *Br J Anaesth* 2016;117:172-81.
 10. VISION Pilot Study Investigators, Devereaux PJ, Bradley D, et al. An international prospective cohort study evaluating major vascular complications among patients undergoing noncardiac surgery: the VISION Pilot Study. *Open Med* 2011;5:e193-200.
 11. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Devereaux PJ, Chan MT, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012;307:2295-304.
 12. Roshanov PS, Walsh M, Devereaux PJ, et al. External validation of the Revised Cardiac Risk Index and update of its renal variable to predict 30-day risk of major cardiac complications after non-cardiac surgery: rationale and plan for analyses of the VISION study. *BMJ Open* 2017;7:e013510.
 13. Mazumdar M, Smith A, Bacik J. Methods for categorizing a prognostic variable in a multivariable setting. *Stat Med* 2003;22:559-71.
 14. Mazumdar M, Glassman JR. Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. *Stat Med* 2000;19:113-32.
 15. Morrow DA, Cannon CP, Rifai N, et al. Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial. *JAMA*. 2001;286:2405-12.
 16. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
 17. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;361:2538-47.
 18. Chia S, Senatore F, Raffel OC, et al. Utility of Cardiac Biomarkers in Predicting Infarct Size, Left Ventricular Function, and Clinical Outcome After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv* 2008;1:415-23.
 19. Hall TS, Hallén J, Krucoff MW, et al. Cardiac troponin I for prediction of clinical outcomes and cardiac function through 3-month follow-up after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am Heart J* 2015;169:257-65.e1.

Cite this article as: Chapalain X, Huet O. Post-operative high sensitivity troponin T (hsTnT): toward an extending use for diagnosis and management of myocardial injury after noncardiac surgery? *J Thorac Dis* 2017;9(8):2231-2234. doi: 10.21037/jtd.2017.06.146