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Myocardial injury in noncardiac surgery

Jungchan Park and Jong-Hwan Lee

1Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence to Jong-Hwan Lee, MD, PhD
Associate Professor, Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82 2 3410 2471; Fax: +82 2 3410 0361; E-mail: jonghwanlee75@gmail.com

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Abstract

Myocardial injury is defined as an elevation of cardiac troponin (cTn) without requiring an ischemic symptom. Robust evidences suggest that myocardial injury increases postoperative mortality of noncardiac surgery. The diagnostic criteria of myocardial injury after noncardiac surgery (MINS) include an elevation of cTn within 30 days after surgery without an evidence of non-ischemic etiology. The majority of MINS does not present ischemic symptom and is caused by oxygen supply-demand mismatch. Predictive models for general cardiac risk stratification can be considered for MINS. The risk factors include comorbidities, anemia, glucose level, and intraoperative blood pressure. Modifiable factors may be helpful in preventing MINS, but further investigation will be needed. Recent guidelines recommend a routine monitoring of cTn during postoperative 48 hours in high-risk patients because MINS occurs mostly during the first 3 days after surgery without symptom. The use of cardiovascular drugs such as aspirin, antihypertensive drugs, and statin has shown to be beneficial in MINS patients, and direct oral anticoagulant reduced MINS mortality in a randomized trial. Myocardial injury detected before noncardiac surgery also showed an association with postoperative mortality, and more studies are required.

Keywords: Troponin T; Troponin I; Mortality; Postoperative Complications; Postoperative Period; Patient Outcome Assessment
Introduction

The Fourth Universal Definition of myocardial infarction distinguished myocardial injury from myocardial infarction [1]. Myocardial injury is defined solely by at least one cardiac troponin value (cTn) above the 99th percentile upper reference limit (URL) of any assay without requiring an ischemic symptom [1]. In 2012, a large international observational cohort study prospectively collected postoperative cTn values of more than 40,000 patients from five continents and demonstrated a significant association with postoperative mortality without accounting for the presence of ischemic symptom [2]. The following study, limiting study population to those without ischemic feature, reproduced the association between myocardial injury and postoperative mortality [3,4]. The incidence of postoperative myocardial injury was found in about 18% of patients after noncardiac surgery, making it one of the most common complication related to postoperative mortality which is a main cause of death in developed countries [3,5]. In addition, more than 200 million patients undergo noncardiac surgeries worldwide every year [6,7]. So, this review aims to comprehensively cover myocardial injury in noncardiac surgery from characteristics of cTn, considerations in surgical patients, and pathophysiology, diagnostic criteria, clinical relevance, prevention, and treatment of postoperative myocardial injury in noncardiac surgery. We also briefly reviewed myocardial injury in the preoperative period, because it has also shown association with postoperative outcomes [8-10].

Characteristics of cTn

Numerous cardio-specific markers have been proposed to detect myocardial damage. CTn is a component of myofibrillar apparatus discovered in 1960s, but it was not until 1990s that the reliable
serum assay was introduced [11]. There are three types of cTn (C, I, and T), and each type plays different roles in a contractile regulatory complex as follows [12,13]: (1) cTn T binds to the actin filament, (2) cTn C acts as calcium ion binding site, and (3) cTn I inhibits interaction of actin with the myosin heads when the intracellular calcium concentration is insufficient to initiate muscle contraction. CTn exists also in skeletal muscle fibers, but a difference in version of cTn provides a tissue specificity for cardiac muscle [14]. Over the other cardiac markers, cTn has advantages with improved performance and superior sensitivity [12,13]. The both types of cTn I and T can be used for detecting myocardial damage, and the accuracies were similar in a direct comparison between the recently available assays [15].

There are following challenges in applying cTn assay. First is defining a normal cut-off limit. The 99th percentile URL is provided for each assay and is uniformly applied as a cut-off value. However, sex- and age-dependent difference in the 99th percentile URL has been reported [16]. Specifically, the rate of cTn elevation was enormously increased as the age limit of study patients were raised from over 50 years old to 70 years old [17,18]. In more recent studies, the prognostic relevance of cTn elevation above the 99th percentile URL maintained significance regardless of sex and age in surgical patients [19,20]. The current recommendation suggests the use of 99th percentile URL for any cTn assay that is available, but in future, different approach may be needed according to sex or age.

Another challenge is non-coronary cause for cTn elevation. Conditions that are not directly related to heart can raise cTn. These include chronic kidney disease, sepsis, stroke, cancer, and etc [21]. Therefore, cTn has been more commonly used to rapidly rule out myocardial infarction in patients presenting ischemic symptom [22]. So when interpreting cTn level in surgical patients without a definite ischemic symptom, the followings should be taken into account.

Considerations in surgical patients
The 99th URL is provided by immunoassay manufacturers based on blood samples derived from apparently healthy individuals [23]. Compared with the healthy individuals, surgical patients possess higher risk conditions that may elevate cTn in different degrees. Some studies argued that the change of pre- to postoperative cTn level needs to be considered in surgical patients [18,23]. A specific threshold was suggested for cTn T as an increase of peak level by at least 5 ng/L from the preoperative level of 20 ng/L [3]. The threshold of change has not been provided for the other assays, and the use of 99th URL is still recommended.

Diagnostic criteria need to be limited to a common shared pathophysiology to explore prevention and treatment modalities. However, cTn elevation shows a wide variety in noncardiac surgical patients and its etiology is not easy to distinguish. For instance, elevated cTn level in chronic kidney disease is related to decreased function of protein excretion and higher possibility of concurrent myocardial damage at the same time [24,25]. The current diagnostic criteria of myocardial injury after noncardiac surgery (MINS) was proposed by VISION (Vascular events In Noncardiac Surgery Patients Cohort Evaluation Study) investigators. They excluded cTn elevation with a definite non-ischemic etiology. The following part of our review will be based on the diagnostic criteria of MINS and its clinical relevance.

**Clinical relevance of MINS**

The series of VISION study have provided the most robust evidence for the clinical relevance for MINS [2,3,26]. The first insight came from the POISE (PeriOperative ISchemic Evaluation) trial, where most of postoperative myocardial infarction did not present ischemic symptom but was still associated with postoperative outcome [27]. The VISION investigators generated a cohort focusing
on the association between postoperative cTn level and mortality. The first report revealed that cTn level was associated with postoperative mortality regardless of ischemic symptom [2]. In the latter studies, this association was shown to be valid for high-sensitivity cTn T assay and for cTn elevations during 30 days after surgery [3-5]. The presence of ischemic symptom raised the mortality by 55% within the MINS patients. But this increase seems to be minor because the mortality is increased nearly up to 8.5 times according to the occurrence of MINS [3,26].

Based on VISION findings, the diagnostic criteria for MINS was proposed as at least one postoperative cTn measurement above the 99th percentile URL within 30 days after surgery which is deemed as the myocardial ischemic injury (i.e., supply-demand mismatch or thrombus) without an evidence of non-ischemic etiology [3,26,28]. It includes both myocardial infarction and ischemic myocardial injury [3,26,28]. The clinical relevance of postoperative cTn elevation has been validated in subtypes of noncardiac surgery such as vascular surgery, lung surgery, and transplantation [29-33]. MINS showed a prognostic relevance regardless of sex and age, although most of these studies including VISION cohort recruited high-risk patients aged over 45 years old [19,20].

**Pathophysiology and Incidence**

Non-ischemic etiology such as rapid atrial fibrillation, sepsis, stroke, and pulmonary embolism was reported with less than 15% of cTn elevation after noncardiac surgery [3,29]. The remaining majority is related to the ischemic etiology that meets MINS criteria. The distribution between oxygen supply-demand mismatch and thrombosis within the ischemic injury can be inferred from the studies on postoperative myocardial infarction [34,35]. In the OPTIMUS trial, 30 patients with operative non-ST elevation myocardial infarction were compared with another 30 patients with non-operative non-ST elevation myocardial infarction which are not related to the surgical procedures [34]. Cardiac
catheterization with optical coherence tomography revealed thrombus in 67% of the non-operative myocardial infarction, while 13% of the perioperative myocardial infarctions were found with thrombus. ST elevation myocardial infarction which was excluded from the OPTIMUS study is almost always related to thrombus [36]. Considering that ST elevation myocardial infarction accounts for 10 to 20% of perioperative myocardial infarction [27,37], 20 to 30% of patients with perioperative myocardial infarction can be assumed as thrombus formation. Similar results were reported by using the coronary computed tomographic angiographic images of postoperative myocardial infarction which revealed 24% of the patients with coronary plaque [35]. These studies did not include MINS patients without ischemic symptom, but thrombus formation is not likely to be more frequently found in patients without ischemic symptom. In a recent study, severe hypotension or anemia which induces oxygen supply-demand mismatch was associated with 72% of perioperative myocardial ischemia [38]. Taken together, about two-thirds to three-quarters of MINS are deemed to be originated from supply-demand mismatch while thrombus formation contributes to a quarter to a third at most.

Risk factors & Prevention

Risk factors of MINS are in line with perioperative myocardial infarction, because they share a common pathophysiology. Predictive models for general cardiac risk stratification can be considered for MINS. Those include old age and male sex as well as comorbidities such as heart disease, cerebrovascular disease, diabetes, peripheral artery disease, aortic disease, and renal insufficiency [28]. Operative variables including the duration, type, and extent of procedure also contribute to myocardial burden [39]. In addition, an exercise tolerance of the patients and measuring other cardiac makers such as brain natriuretic peptide could be helpful in predicting the risk [40-42].

Modifiable factors of MINS have been extensively evaluated for its prevention. In the preoperative
period, low hemoglobin level was shown to be associated with the development of MINS [43,44]. However, the benefit of treating anemia remains uncertain, because transfusion per se could increase the myocardial burden and mortality of surgical patients [45,46]. Other modalities to treat anemia may need to be investigated regarding the MINS occurrence. The sub-study of VISION cohort demonstrated that preoperatively high blood sugar test was associated with MINS [47]. Preoperative high glucose level was also associated with MINS while preoperative hemoglobin A1c did not show a significant association in a retrospective study [48]. This result suggests that immediate glucose control may still be crucial in preventing MINS, even in patients with poorly controlled long-term glucose level [48].

The primary concern during anesthesia is to maintain an adequate level of blood pressure. A brief drop of blood pressure during surgical procedure is known to increase renal and myocardial injuries and mortality [49-52]. Specifically, MINS was associated with the absolute level of mean arterial pressure below 65 mmHg and a relative decrease of more than 30% from the baseline [50]. The both of severity and duration of hypotension play as key determinants [50]. However, hypotension seems to have less effect than other pre-existing factors, while the clinical implication of this association is that intraoperative blood pressure could be controlled with large difference. Cardiac output-guided fluid therapy with low dose inotropic drug was evaluated, but MINS occurrence was not significantly decreased [53]. Tachycardia is also known to induce myocardial infarction by increasing oxygen demand with insufficient diastolic filling time [54]. By enhancing oxygen supply and demand mismatch, preoperative ambulatory heart rate showed association with the development of MINS [55]. An adequate pain control was reported with an association with MINS, but further investigation is needed [56,57].

Cardiovascular drugs prescription can be considered for MINS prevention. In the POISE trial, beta blocker decreased postoperative myocardial infarction but increased the incidence of stroke [58].
Thus, the use beta blocker immediately after surgery should be limited to “restart” in patients who were already on routine prescription [59]. The use of other cardiovascular drugs including aspirin, nitrous oxide, and clonidine in the preoperative period were investigated for MINS prevention, but the results were not significant [28].

**Monitoring postoperative cTn**

Ischemic symptoms in the perioperative period are likely to be masked under sedatives or confused with surgical pain [60]. The VISION cohort demonstrated that 40% of MINS occurs on the day of surgery, 40% on the first postoperative day, and 15% within two days after surgery [2,3,26]. But, those patients might be undetected without cTn monitoring, because more than 70% of MINS patients did not present any symptom [3,26,29]. So, a routine measurement of postoperative cTn may benefit patients with certain amount of risk. There are current recommendations to monitor cTn in the perioperative period. Initially, screening was recommended as an expert opinion for patients aged over 45 years old [61], and the following perioperative guidelines have also included cTn monitoring varying details [62-64]. In those guidelines from the American College of Cardiology/American Heart Association and the European Society of Cardiology/Anesthesiology, a routine cTn screening was recommended for those with ischemic symptoms or those at high risk for cardiovascular events [62,63]. The more recent Canadian Cardiovascular Society guideline made a stronger recommendation to obtain daily cTn for 2–3 days following the surgery in patients with a >5% cardiovascular risk, based on the finding that the vast majority of clinically important MINS may be undetected otherwise [4,64].

**Treatment**
The only treatment that has been established from a large randomized trial of MINS patients is the use of direct oral anticoagulant [65]. In the MANAGE trial, dabigatran 110 mg twice daily or placebo was prescribed for 877 patients in each group who were followed up for 16 months. According to the incidence of major vascular complications which was the primary endpoint, continuous use of dabigatran for long-term period was suggested for the patients with acceptable bleeding risk. Life-threatening organ bleeding which was the primary safety outcome was not increased by dabigatran. However, clinicians generally have a concern to use direct oral anticoagulant shortly after surgical procedure, so there seems to be a dilemma in daily clinical practice. Also, the benefit of using direct oral anticoagulant may seem odd, because the MINS related to oxygen supply-demand mismatch outnumbers ones that are related to thrombus formation [34,35]. This can be explained by the fact that the risk of thrombotic event is increased even in MINS caused by oxygen supply-demand mismatch [3,26]. Also, the MINS that actually resulted in mortality is more frequently related to thrombus formation [3,26].

There are other cardiovascular medical treatments that showed efficacy in observational studies. The early introduction or dose increase of cardiovascular drugs such as antiplatelet, statin, beta-blocker, and angiotensin-converting enzyme inhibitor demonstrated improved outcomes in MINS patients [66]. Aspirin was reported to be associated with lower risk of 30-day mortality in a sub-study of POISE trial [27]. Statin showed an improved long-term outcome for the patients who were discharged alive after experiencing MINS [67]. The benefit of statin use in MINS patients may not be limited to immediate lipid-lowering effect but may also be related to pleuritic effect, because the elevated C-reactive protein level at discharge after MINS was associated with mortality afterwards [68]. Based on these findings, the use of low dose aspirin and statin is recommended in the guideline [64]. Renin-angiotensin-aldosterone system inhibitor, a drug of choice for hypertensive patients with
comorbidities has also shown to be beneficial, and it was demonstrated for the both of two main types, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker [69,70].

A proper evaluation on coronary artery could be considered. Coronary angiographic or coronary computed tomographic angiographic images of perioperative myocardial infarction frequently reveal a remarkable portion of extensive or complex coronary artery in which coronary revascularization may be beneficial [71,72]. Conducting coronary angiographic evaluation was associated with lower mortality of postoperative myocardial infarction, and the most commonly performed modality for coronary revascularization was percutaneous coronary intervention [37]. However, only 21% of perioperative myocardial infarction and 8% of MINS were evaluated with coronary angiography [29,37]. In fact, the risk and benefit of coronary intervention should be taken into account more cautiously in patients who are at risk of bleeding shortly after surgery, because withdrawing antiplatelet therapy may lead to in-stent thrombosis [35]. Lastly, most of these practices are performed at the department of cardiologist, and an evaluation by cardiologist was demonstrated with improved outcome in MINS patients [73]. A management in a multidisciplinary manner may be helpful.

**Myocardial injury in the preoperative period**

As aforementioned, cTn level of surgical patient is frequently elevated even in the preoperative period. Chronic myocardial injury from the preoperative period demonstrated comparable effect on postoperative mortality with an acute injury [10]. The increase of risk was also observed for the minor elevation that did not exceed the 99th URL [74]. In other observational study, the mortality risk was related to both magnitude and timing of peak cTn [8]. Higher level of preoperative cTn was associated with higher postoperative mortality, but longer period from the peak level to surgery appeared to reduce this risk for mild elevations. Another interesting finding on preoperative myocardial injury
was that the mortality was improved when myocardial injury was attenuated postoperatively [9].
However, management of preoperative myocardial injury remains as clinical equipoise, so further
investigations are needed.

**Conclusion**

Myocardial injury, detected by cTn elevation in the perioperative period of noncardiac surgery is
associated with adverse outcome. A vast majority of MINS do not present ischemic symptom, so a
routine monitoring of cTn may be beneficial during 48 hours after surgery in which MINS is most
likely to occur. For the treatment, the use of dabigatran 110 mg twice a day has been reported to be
effective in randomized trial. Intensification of other cardiovascular drugs such as antiplatelet, anti-
hypertensive drugs, and statin was also shown to improve outcomes after MINS.
References


