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Myocardial injury in noncardiac surgery

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Review Article

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Myocardial injury is defined as an elevation of cardiac troponin (cTn) levels with or without associated ischemic symptoms. Robust evidence suggests that myocardial injury increases postoperative mortality after noncardiac surgery. The diagnostic criteria for myocardial injury after noncardiac surgery (MINS) include an elevation of cTn levels within 30 d of surgery without evidence of non-ischemic etiology. The majority of cases of MINS do not present with ischemic symptoms and are caused by a mismatch in oxygen supply and demand. Predictive models for general cardiac risk stratification can be considered for MINS. Risk factors include comorbidities, anemia, glucose levels, and intraoperative blood pressure. Modifiable factors may help prevent MINS; however, further studies are needed. Recent guidelines recommend routine monitoring of cTn levels during the first 48 h post-operation in high-risk patients since MINS most often occurs in the first 3 days after surgery without symptoms. The use of cardiovascular drugs, such as aspirin, antihypertensives, and statins, has had beneficial effects in patients with MINS, and direct oral anticoagulants have been shown to reduce the mortality associated with MINS in a randomized controlled trial. Myocardial injury detected before noncardiac surgery was also found to be associated with postoperative mortality, though further studies are needed.

Keywords: Mortality; Patient outcome assessment; Postoperative complications; Postoperative period; Troponin I; Troponin T.

Introduction

The fourth universal definition of myocardial infarction distinguishes myocardial injury from myocardial infarction [1]. Myocardial injury is defined solely as the presence of at least one cardiac troponin (cTn) value above the 99th percentile upper reference limit (URL) of any assay and may or may not be associated with ischemic symptoms [1]. In 2012, a large international observational cohort study prospectively collected the postoperative cTn values of more than 40,000 patients from five continents and demonstrated a significant association between cTn values and postoperative mortality, without accounting for the presence of ischemic symptoms [2]. In a subsequent study, the study population was limited to those without ischemic features, and the significant association between myocardial injury and postoperative mortality was reproduced [3,4]. The incidence of postoperative myocardial injury in patients after noncardiac surgery is approximately 18%, making it one of the most common complications related to postoperative mortality, which is the main cause of death in developed countries [3,5]. In addition, more than 200 million patients undergo noncardiac surgeries annually worldwide [6,7]. Therefore, this review aims to provide a comprehensive examination of findings regarding myocardial injury in noncardiac surgery based on the characteristics of cTn levels, considerations of surgical patients, and the 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 since this has also been associated with postoperative outcomes [8–10].

Characteristics of cTn

Numerous cardio-specific markers have been proposed for the detection of myocardial damage. cTn is a component of the myofibrillar apparatus that was discovered in the 1960s, but it was not until the 1990s that a reliable serum assay was introduced [11]. There are three types of cTn (C, I, and T), each of which plays a different role in the contractile regulatory complex [12,13]. Specifically, cTn T binds to the actin filament, cTn C acts as a calcium ion binding site, and cTn I inhibits the interaction between actin and the myosin heads when the intracellular calcium concentration is insufficient to initiate muscle contraction. Additionally, cTn is present in skeletal muscle fibers; however, differences in the versions of cTn provide tissue specificity for cardiac muscle [14]. Compared to other cardiac markers, the advantage of cTn is that it performs better and has superior sensitivity [12,13]. Both cTn I and cTn T can be used to detect myocardial damage, with similar accuracy, as shown in a direct comparison between the recently available assays [15].

There are several challenges regarding the application of the cTn assay. The 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 differences in the 99th percentile URL have been reported [16]. Specifically, the rate of elevation in cTn levels increased considerably as the age limit of study patients was increased from those aged > 50 years to > 70 years [17,18]. In more recent studies, the prognostic relevance of cTn level elevation above the 99th percentile URL continued to be significant regardless of the sex and age of surgical patients [19,20]. The current recommendations suggest that the 99th percentile URL be used for any cTn assay that is available, but in the future, a different approach may be needed based on sex or age.

Another challenge is non-coronary causes of elevated cTn levels. Conditions that are not directly related to the heart can increase cTn levels. These include chronic kidney disease, sepsis, stroke, and cancer, among others [21]. Therefore, cTn levels have been more commonly used to rule out myocardial infarction in patients presenting with ischemic symptoms [22]. The following section describes what should be taken into account when interpreting cTn levels in surgical patients who do not have definite ischemic symptoms.

Considerations for surgical patients

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

Diagnostic criteria need to be limited to a common shared pathophysiology to explore prevention and treatment modalities. However, there are wide variations in the elevation of cTn levels in non-cardiac surgical patients, and the etiologies are not easily distinguishable. For instance, elevated cTn levels in chronic kidney disease are related to both a decrease in protein excretion and a higher possibility of concurrent myocardial damage [24,25]. The current diagnostic criteria for myocardial injury after noncardiac surgery (MINS) were proposed by the VISION (Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study) investigators. They excluded all cTn level elevations with a definite non-ischemic etiology. The following section of our review will be based on the diagnostic criteria of MINS and its clinical relevance.

Clinical relevance of MINS

The series of studies conducted by the VISION investigators have provided the most robust evidence for the clinical relevance of MINS [2,3,26]. The first insight came from the PeriOperative ISchemic Evaluation (POISE) trial. Most of the patients with postoperative myocardial infarctions in this trial did not have ischemic symptoms but still had postoperative outcomes [27]. The VISION investigators generated a cohort focusing on the association between postoperative cTn levels and mortality. The first report found that cTn levels were associated with postoperative mortality regardless of ischemic symptoms [2]. In the following studies, this association was maintained for high-sensitivity cTn T assays and for elevations in cTn levels during the first 30 days after surgery [3–5]. The presence of ischemic symptoms increased mortality by 55% in MINS patients. However, this increase was minor considering that the mortality rate in those who experienced MINS was nearly 8.5 times that of those who did not experience MINS [3,26].

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

Pathophysiology and incidence

Non-ischemic etiologies, such as rapid atrial fibrillation, sepsis, stroke, and pulmonary embolism, were reported in less than 15% of patients with cTn level elevations after noncardiac surgery [3,29]. The majority of the remaining cases that met the MINS criteria were found to be related to ischemic etiology. Of those with an ischemic etiology, the distribution of cases with oxygen supply-demand mismatch compared to those with thrombosis can be inferred from studies on postoperative myocardial infarction [34,35]. In the OPTIMUS trial, 30 patients with operative non-ST elevation myocardial infarction were compared with 30 patients with non-operative non-ST elevation myocardial infarction that were not related to the surgical procedure [34]. Cardiac catheterization with optical coherence tomography revealed that 67% of the non-operative myocardial infarctions had a thrombus, while only 13% of the perioperative myocardial infarctions were found to be associated with a thrombus. ST elevation myocardial infarctions, which were excluded from the OPTIMUS study, are almost always associated with thrombi [36]. Considering that ST elevation myocardial infarctions account for 10–20% of perioperative myocardial infarctions [27,37], 20–30% of patients with perioperative myocardial infarctions can be assumed to have a thrombus. Similar results were reported using coronary computed tomographic angiographic images of postoperative myocardial infarction, which revealed that 24% of the patients had coronary plaque [35]. While these studies only included patients with MINS who had ischemic symptoms, thrombus formation is not likely to be more common in patients who do not have ischemic symptoms. In a recent study, severe hypotension or anemia, which is known to induce an oxygen supply-demand mismatch, was associated with 72% of perioperative myocardial ischemic symptoms [38]. Taken together, about two-thirds to three-quarters of MINS are deemed to originate from an oxygen supply-demand mismatch, while thrombus formation contributes to a quarter or to a third at most.

Risk factors and prevention

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

Modifiable factors of MINS have been extensively evaluated. In the preoperative period, a low hemoglobin level was shown to be associated with the development of MINS [43,44]. However, the benefit of treating anemia remains controversial because transfusions could increase the myocardial burden and mortality of surgical patients [45,46]. Other treatment modalities for anemia may need to be investigated in relation to the occurrence of MINS. A sub-study of the VISION cohort demonstrated that a high preoperative blood glucose test was associated with MINS [47]. Similarly, a retrospective study also found that high preoperative glucose levels were associated with MINS; however, this study also found that preoperative hemoglobin A1c levels were not significantly associated [48]. This result suggests that immediate glucose control may still be crucial for preventing MINS, even in patients with poorly controlled glucose levels long-term [48].

The primary concern during anesthesia is maintaining an adequate blood pressure. A brief drop in blood pressure during surgical procedures is known to increase renal and myocardial injuries and mortality [49–52]. Specifically, MINS has been associated with an absolute mean arterial pressure < 65 mmHg and a relative decrease in the absolute mean arterial pressure > 30% from baseline [50]. Both the severity and duration of hypotension are key determinants [50]. However, hypotension seems to have less effect on MINS than other pre-existing factors, while the clinical implication of this association is that intraoperative blood pressure could be controlled with a large difference. Cardiac output-guided fluid therapy with low-dose inotropic drugs was evaluated in one study, but MINS occurrence was not significantly decreased [53]. Tachycardia is also known to induce myocardial infarction by increasing oxygen demand and causing insufficient diastolic filling time [54]. By enhancing the oxygen supply-de-

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mand mismatch, the preoperative ambulatory heart rate has been associated with the development of MINS [55]. Adequate pain control has been reported to be associated with MINS; however, further investigation is needed [56,57].

Cardiovascular drug prescriptions can also be considered as a preventive for MINS. In the POISE trial, beta-blockers were associated with a decrease in postoperative myocardial infarctions but an increase in the incidence of stroke [58]. Thus, the use of beta-blockers immediately after surgery should be limited to those patients who already have routine prescriptions [59]. The use of other cardiovascular drugs, including aspirin, nitrous oxide, and clonidine, in the preoperative period was also investigated as a preventative for MINS, but the results were not significant [28].

Monitoring postoperative cTn

Ischemic symptoms in the perioperative period are likely to be masked by sedatives or confused with surgical pain [60]. The VISION cohort demonstrated that 40% of MINS occurred on the day of surgery, 40% on the first postoperative day, and 15% within 2 days after surgery [2,3,26]. However, without cTn monitoring, most of these myocardial injuries would likely go undetected, because more than 70% of patients with MINS do not present with any symptoms [3,26,29]. Therefore, routine postoperative cTn measurements may benefit patients with a certain amount of risk. Currently, recommendations suggest that cTn should be monitored in the perioperative period. Initially, the expert opinion was that screening should be conducted for patients aged > 45 years [61], and the following perioperative guidelines have also included various recommendations regarding cTn monitoring [62–64]. According to the guidelines of the American College of Cardiology/American Heart Association and the European Society of Cardiology/Anesthesiology, routine cTn screening is recommended for those with ischemic symptoms or those at high risk for cardiovascular events [62,63]. The most recent Canadian Cardiovascular Society guidelines made a stronger recommendation for cTn levels to be obtained daily for 2–3 days following surgery in patients with a cardiovascular risk > 5% based on the finding that the vast majority of clinically important MINS would otherwise go undetected [4,64].

Treatment

The only treatment that has been established by a large randomized trial of patients with MINS is the use of direct oral anticoagulants [65]. In the MANAGE trial, dabigatran 110 mg twice daily or placebo was prescribed to 877 patients in each group who were followed up for 16 months. Based on the incidence of major vascular complications, which was the primary outcome, the long-term continuous use of dabigatran was suggested for patients with acceptable bleeding risk. Life-threatening organ bleeding, which was the primary safety outcome, was not found to be increased by dabigatran. However, clinicians are generally concerned about the use of direct oral anticoagulants shortly after a surgical procedure, so there seems to be a dilemma in daily clinical practice. In addition, the benefit of using direct oral anticoagulants may appear contradictory since MINS is much more associated with oxygen supply-demand mismatch than with thrombus formation [34,35]. However, the direct oral anticoagulants are beneficial because the risk of thrombotic events is increased even in MINS caused by oxygen supply-demand mismatch [3,26]. In addition, the mortality associated with MINS is more frequently related to thrombus formation [3,26].

Observational studies have found other cardiovascular medical treatments to also be effective. An increase in the dose or early introduction of cardiovascular drugs, such as antiplatelets, statins, beta-blockers, and angiotensin-converting enzyme inhibitors have demonstrated improved outcomes in patients with MINS [66]. Aspirin was reported to be associated with a lower risk of 30-day mortality in a sub-study of the POISE trial [27]. Statins were associated with an improvement in long-term outcomes for patients who were discharged alive after experiencing MINS [67]. The benefit of statins for patients with MINS may not be limited to immediate lipid-lowering effects but may also be related to the pleuritic effect, because elevated C-reactive protein levels at discharge have been associated with mortality in this patient population [68]. Based on these findings, the use of low-dose aspirin and statins is recommended [64]. The two main types of renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), which are the drugs of choice for hypertensive patients with comorbidities, have also been found to be beneficial [69,70].

A proper evaluation of the coronary artery should be considered. Coronary angiographic or coronary computed tomographic angiographic images of perioperative myocardial infarctions frequently reveal a remarkable portion of extensive or complex coronary arteries that could benefit from coronary revascularization [71,72]. Conducting coronary angiographic evaluations has been associated with lower mortality from postoperative myocardial infarctions, with percutaneous coronary intervention being the most common modality for coronary revascularization [37]. However, only 21% of patients with perioperative myocardial infarctions and 8% of patients with MINS are evaluated using coronary angiography [29,37]. In fact, the risk and benefit of coronary interventions 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 procedures are performed in the cardiology department, and an evaluation by a cardiologist has been associated with improved outcomes in patients with MINS [73], though multidisciplinary management may also be helpful.

Myocardial injury in the preoperative period

As mentioned previously, cTn levels in surgical patients are frequently elevated even in the preoperative period. Chronic myocardial injury in the preoperative period was found to have a comparable effect on postoperative mortality with acute injury [10]. An increase in risk was also observed for minor elevations that did not exceed the 99th percentile URL [74]. In another observational study, the mortality risk was related to both the magnitude and timing of the peak cTn level [8]. While a higher preoperative cTn level was associated with higher postoperative mortality, a longer period of time between the peak level and surgery appeared to reduce this risk for mild elevations. Additionally, mortality was improved when myocardial injury was attenuated postoperatively [9]. However, since managing preoperative myocardial injury remains a clinical necessity, further investigations are needed to clarify these findings.

Conclusion

Myocardial injury, detected by cTn level elevations in the perioperative period of noncardiac surgery, is associated with adverse outcomes. A vast majority of patients with MINS do not have ischemic symptoms; therefore, routine monitoring of cTn may be beneficial during the first 48 h after surgery when MINS is most likely to occur. The use of dabigatran 110 mg twice daily has been reported to be effective in randomized controlled trials. Intensification of other cardiovascular drugs such as antiplatelets, antihypertensives, and statins has also been shown to improve outcomes after MINS.

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Conflicts of Interest

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

Author Contributions

Jungchan Park (Conceptualization; Project administration; Writing – original draft)
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