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Perioperative myocardial infarction/injury after noncardiac surgery

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Summary

Cardiovascular complications, particularly perioperative myocardial infarction/injury, seem to be major contributors to mortality after noncardiac surgery. With surgical procedures being very frequent (900 000/year in Switzerland), perioperative myocardial injury is common in everyday clinical practice. Over 80% of patients experiencing perioperative myocardial injury do not report symptoms. Therefore perioperative myocardial injury remains undiagnosed and untreated. Moreover, its silent presentation results in limited awareness among both clinicians and the public. Despite being largely asymptomatic, perioperative myocardial injury increases 30-day mortality nearly 10-fold. This review aims to increase the awareness of perioperative myocardial injury/infarction and give an overview of the emerging evidence, including pathophysiology, clinical presentation, prevention, and potential future treatments.

Key words: *perioperative myocardial infarction; myocardial ischaemia; perioperative complications; diagnosis; prognosis*

Perioperative myocardial infarction/injury: a silent and neglected killer

Perioperative myocardial infarction/injury (PMI) is an episode of myocardial ischaemia occurring during or in the days after noncardiac surgery. As currently over 230 million major surgical procedures are performed annually worldwide, the perioperative setting is a common challenge for hospital physicians, and also for primary care physicians providing follow-up care. In resource-rich countries like Switzerland, the incidence of major surgery is about 1 procedure for every 10 citizens per year [1]. Despite advances in all fields of medicine, there is still a significant risk of death related to major noncardiac surgical procedures. The observed 30-day mortality depends on patient-related as well as procedural factors and ranges between 1% and 10% [2–9]. Cardiovascular complications, particularly PMI, seem to be major contributors to up to 40% of all deaths [2, 6]. Patients experiencing PMI had an odds ratio of 10 (95% confidence interval [CI] 7.8–12.9) for death and a composite of cardiovascular complications at 30 days [6]. Myocardial infarction (MI) is defined by consensus as dynamic elevations of cardiac troponin in combination with either ischaemic symptoms, electrocardiogram (ECG) changes, or imaging findings [10]. In contrast to patients with spontaneous acute MI (AMI), about 80% of PMI patients report no chest pain or any other typical ischaemic symptoms. The reasons for this are incompletely understood, but may include intense analgesia following surgery [2]. Therefore, PMI often occurs unnoticed, as highlighted by a recent large observational cohort including >15 000 patients undergoing major noncardiac surgery [6]. In spite of its silent manifestation, PMI is strongly associated with mortality. The 30-day mortality of patients with PMI was similar for asymptomatic patients and for those who had ischaemic symptoms (30-day mortality 12.6% in asymptomatic vs 9.8% in symptomatic patients, $p = 0.84$) [5]. ECG changes have low sensitivity for PMI as well, being present in only 35% of patients [6]. As a result of the masking of symptoms, which usually trigger further evaluation for MI, PMI is difficult to diagnose according to the current definition of MI [10]. As a first step, the concept of myocardial injury after noncardiac surgery (MINS) has been proposed for this setting [6]. In contrast to the diagnosis of spontaneous AMI, the diagnosis of MINS takes into account the silent presentation of PMI and is based on cardiac troponin only, i.e. it does not require the presence of symptoms. The combination of high associated mortality and major diagnostic challenges mandates increased focus on and awareness of PMI.

Mechanisms underlying perioperative myocardial infarction/injury

The predominant pathophysiology of PMI is incompletely understood. In patients presenting with spontaneous AMI to the emergency department, atherosclerotic plaque rupture with thrombus formation and distal embolisation is the dominant pathophysiological mechanism (type I MI, see table 1) [10]. For PMI, small angiographic studies have suggested that type I MI might be present in only about half of the patients [11–13].

However, these studies exclusively recruited the minority of symptomatic PMI patients (≈20%). Therefore, experts argue that even fewer cases of PMI might result from plaque rupture [14] and PMI might rather be caused by a supply-demand imbalance of oxygen without plaque rupture, so-called type II MI [10]. The perioperative phase is characterised by a situation of intense stress for the patient: the surgical trauma may lead to bleeding causing anaemia and hypotension; postoperative pain and a general inflammatory state lead to an increased sympathetic tone. Therefore, myocardial workload increases, potentially surpassing oxygen supply and causing PMI. This can be exacerbated by respiratory impairment limiting oxygen intake.

Finally, myocardial injury, resulting in troponin leak, can also occur from pathologies other than myocardial ischaemia, such as pulmonary embolism and severe sepsis [15–17]. In these cases myocardial injury might result from type II MI caused by haemodynamic changes (peripheral vasodilation, tachycardia), but could also stem from direct cytokine-mediated damage of cardiomyocytes. Irrespective of the exact underlying pathophysiology, myocardial damage in patients with severe sepsis predicts short- and long-term mortality [16–18]. With cardiovascular complications including PMI contributing strongly to postoperative mortality, efforts are needed in order to prevent, detect and/or treat PMI.

Prevention

Risk scores

Risk scores should identify high-risk patients who might profit from specific risk-reduction strategies [19]. The most commonly used, albeit imperfect, cardiovascular risk score is the Revised Cardiac Risk Score, the "Lee" risk score [20]. Current guidelines [21] now recommend the use of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) risk calculator [22]. Recent studies focused on improving the predictive value by adding cardiac biomarkers (e.g. cardiac troponin, B-type natriuretic peptide) [23]. Preoperative high-sensitivity cardiac troponin T measurements seem to be a valuable tool for risk stratification of patients, providing additional information to the currently used risk predictors based on clinical data, such as the Revised Cardiac Risk Score (AUC 0.68 vs 0.78, p = 0.07) [23].

Medication

In the following section, we will address some of the several cardiovascular medications that have been assessed for the prevention of PMI.

Beta-blockers

Multiple recent studies focused on the use of β-blockers, with trials showing conflicting results about the efficacy and safety of administration prior to surgery [21, 24, 25]. Beta-blockers should protect the heart by limiting the maximum heart rate in the high-stress setting during and shortly after surgery, but do this at an increased risk of perioperative hypotension. The largest randomised study, the POISE trial, found a significant decrease in the incidence of MI postoperatively, but accompanied by an increase in overall mortality caused by a sharp rise in stroke [25]. As β-blockers were administered without titration in this trial, this practise is currently discouraged [19]. Patients already receiving β-blockers should continue to take them. Whether earlier initiation and titration in the weeks before surgery improves outcome remains unclear [19, 26].

Acetylsalicylic acid

Aspirin (acetylsalicylic acid, ASA) represents a cornerstone of primary and secondary cardiovascular prevention in the nonsurgical setting; but the increased risk of bleeding made its perioperative use controversial [27]. In a recent large multicentre randomised trial, aspirin did not reduce the mortality or incidence of MI within 30 days after noncardiac surgery. In contrast, there was a significant increase of major bleeding. These results did not differ between patients who received ASA *de novo* and those already on chronic treatment [28]. Continuation of an already established ASA therapy may be considered and the risk of increased bleeding weighed against the cardiovascular benefit [19]. Notably, POISE 2 did not include patients with coronary stents, in whom ASA should be continued perioperatively [19, 29].

Statins

Statins play an important role in nonsurgical primary and secondary prevention of MI and have multiple effects ran-

Table 1: Different types of myocardial infarction (MI) according to the current definition of MI; adapted from Thygesen 2012, EHJ [10].

Universal classification of myocardial infarction		
Type I MI	Definition	Myocardial necrosis due to impaired blood flow to the myocardium
	Pathophysiology	Related to rupture of an atherosclerotic plaque, with resulting intracoronary thrombus leading to occlusion or distal embolisation in one or more coronary arteries
	Relation to CAD	Most patients have underlying severe CAD, but on occasion nonobstructive or no CAD
	Therapy	Revascularisation, dual antiplatelet therapy, statins, β-blockers
Type II MI	Definition	Myocardial injury with necrosis caused by an imbalance between myocardial oxygen supply and demand
	Pathophysiology	A condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anaemia, respiratory failure, hypotension and hypertension
	Relation to CAD	The patient may or may not have underlying CAD
	Therapy	Correction of underlying disease
Type III MI	Myocardial infarction resulting in death when biomarker values are unavailable	
Type IV MI	Myocardial infarction related to (a) percutaneous coronary intervention; (b) stent thrombosis	
Type V MI	Myocardial infarction related to coronary artery bypass grafting	
CAD = coronary artery disease		

ging from lowering cholesterol levels to plaque stabilisation and immunomodulation. An established therapy should be continued in the perioperative period [19, 27], as withdrawal can increase the risk of cardiovascular complications [30]. Two meta-analyses found a lower rate of cardiovascular complications after noncardiac surgery, but except for vascular surgery patients, no significant change in overall mortality was found [30, 31]. Therefore, evidence concerning the effect of newly established statin therapy is limited to vascular surgery, in which it is recommended that patients start statin therapy, preferably more than 2 weeks prior to surgery [19].

Dual antiplatelet therapy

Dual antiplatelet therapy is a requirement after a spontaneous MI or the implantation of a coronary stent [29], and early discontinuation for surgery is associated with high risk of potentially fatal stent thrombosis [32]. Therefore, it is recommended to postpone elective surgery until the end of the usual time course for dual antiplatelet therapy after percutaneous intervention [19]. For bare metal stents a minimum treatment duration of 1 to 3 months and for drug eluding stents 6 to 12 months (depending on stent generation) should be adhered to. In patients who received a coronary stent because of a MI, dual antiplatelet therapy should be continued for 12 months [19].

Prophylactic revascularisation

Although optimising the patient's coronary status by the use of preoperative revascularisation might seem an appealing option, preoperative prophylactic coronary revascularisation does not seem to improve outcome [33]. Current guidelines of the European Society of Cardiology recommend control of known myocardial ischaemia, if surgery can be safely delayed [19]. Hence it is important to consider scheduling accordingly, as a minimal time of dual antiplatelet therapy is required after a coronary intervention (see above). Overall indications for preoperative revascularisation are the same as with stable coronary artery disease, with no general recommendation for screening for myocardial ischaemia prior to surgery [19].

Anaesthesia and surgery

Anaesthesia and surgical techniques are major factors for all types of perioperative complications and are being constantly refined. Scientific evaluation of volatile versus intravenous anaesthesia showed similar efficacy of both [34, 35]. The use of neuroaxial analgesia instead of, or complementing, general anaesthesia and goal-directed volume management may potentially improve outcome [36].

Early detection and management

A recent publication has demonstrated that differences between hospitals, in terms of postoperative mortality, are mainly due not to the incidence of complications, but to the way in which they are managed [37]. These findings highlight the importance of preparing for the occurrence of complications. In the case of PMI, this means early detection of an often clinically silent disease. Patients are most vulnerable within the first 3 days after surgery [5, 38, 39], with 75% to 85% of PMIs occuring in this period, highlighting the need for screening to allow fast diagnosis and initiation of therapy.

Biomarker screening

Biomarkers can be measured easily as part of routine clinical blood draws. Cardiac troponin seems to be an especially promising screening tool. Multiple large observational cohorts have generated important insights concerning cardiac troponin in patients with PMI: the 30-day mortality of patients increases with increasing postoperative peak cardiac troponin, ranging from 1% at the lowest cardiac troponin T values (<10 ng/l) to 17% in the highest (>300 ng/l) group [2]. Prior work from the VISION trial showed an incidence of PMI of 8%, with an odds ratio (OR) of 10 (95% CI 7.8–12.9) for death after PMI. Nonetheless, the time between PMI and death of a patients seems to be a timeframe (median time to death 9–12 days) which would allow for potential interventions to improve prognosis [2, 4, 6]. It is important to mention again that the increased mortality risk seems to be independent of whether the patient experienced ischaemic symptoms or not [6].

A challenge in this setting (as well as in the emergency department) is posed by patients with chronic elevations, as patients at high cardiovascular risk often present with levels above the 99th percentile of healthy persons. In a recent study over 40% of patients had elevated baseline values of high-sensitivity cardiac troponin [40]. Therefore, it is important to repeat the cardiac troponin measurement after 3 hours if the diagnosis remains unclear.

Vital signs / blood pressure

Besides the biomarker screening, collection of further data is essential to evaluate fully the patient course during this critical period and also to help distinguish the different subtypes of PMI. Intraoperative monitoring of vital signs is standard of care worldwide. In contrast, the monitoring intensity in the postoperative period varies widely, and vital parameters are usually assessed only every few hours. Therefore, evidence is limited, especially concerning periods of hypotension. One large trial showed that hypotension on the surgical ward, identified because it required treatment, was associated with a relative risk of 5 for mortality at 30 days [25]. Perioperative hypoxaemia might also be a relevant factor. Severe hypoxaemia is known to be devastating, but even moderate hypoxaemia was linked to PMI [41, 42]. In a randomised controlled trial evaluating the use of pulse oximeters the event rate of PMI was significantly lower in the intervention group, with higher detection rates of hypoxaemic episodes [43]. This study helped to establish pulse oximetry in operating rooms and intensive care unit. Hypoxaemia also occurs frequently in the surgical ward and was shown to be associated with ST-deviations as a myocardial ischaemia-equivalent [44].

ECG monitoring / telemetry

Similarly to blood pressure and pulse oximetry, continuous ECG data in the postoperative period are also scarce. These data could, however, educate us regarding the true prevalence of important arrhythmias such as rapid atrial fibrillation, tachy- or bradycardia, conditions predisposing for

type II MIs. In a study including 185 patients after vascular surgery, all PMIs were preceded by an increase of heart rate [45]. Another study showed that a 10 bpm increase in heart rate was associated with a relative risk of 2.5 for PMI and 1.4 for long-term mortality [24]. ST-segment deviations, seen as ischaemia equivalents, seem to occur in up to 20% of vascular surgery patients [45, 46]. With ST-depression being much more frequent than ST-elevation, the underlying pathophysiology might be low flow and supply-demand imbalances rather than total occlusions after plaque rupture. Unfortunately ECG changes were only observed in 35% of all patients in the VISION study, indicating that ECG monitoring might not be sensitive enough to find PMIs. Furthermore, the personnel resources needed for continuous monitoring would be high.

Treatment

The basis for effective treatment is the differentiation of type I AMI from type II MI. This has enormous clinical consequences, as only type I AMI has been shown to benefit from aggressive anticoagulation, platelet inhibition and early coronary revascularisation [10], whereas these treatments may harm patients with type II MI, for example due to bleeding. The latter patients would benefit from rapid correction of the underlying condition, e.g. by volume replacement in the case of hypotension or blood transfusion in case of anaemia [12, 47, 48].

In clinical practice, the differentiation between type I MI, type II MI and nonischaemic myocardial injury is difficult. Although current guidelines [10] recommend a set of diagnostic hints (e.g. type I MI tends to present with spontaneous symptom onset, usually with ECG changes, higher cardiac troponin elevations, plaque rupture, intracoronary thrombus, or complex plaques on coronary angiography, and absence of conditions leading to elevated myocardial oxygen consumption or decreased myocardial blood flow), authors also state that these are difficult to apply in the perioperative setting [49]. The best criteria seem to be whether there are conditions present that suggest type II MI [50]: longer periods of tachycardia (>150 bpm), hypotension (systolic blood pressure <90 mm Hg), respiratory failure, or anaemia (haemoglobin <5.5 mmol/l).

Apart from these recommendations derived from the treatment of spontaneous AMI, guidelines for treatment of PMI are lacking. However, there is a window of opportunity following PMI: in recent trials the median time to death after PMI was 9–12 days [2, 4], a timeframe potentially allowing intervention. From large observational studies, preliminary evidence was obtained that statins and ASA might improve outcome after PMI [2, 31, 51]. More research needs to be done but currently only one large study evaluating treatment with dabigatran and omeprazole for patients with PMI is ongoing and might provide novel insights.

Summary: postoperative myocardial infarction/injury vs acute myocardial infarction

Currently, clinical awareness of PMI is often insufficient. To close this review, we want to compare PMI to a well-known and related disease, spontaneous AMI. First and most important, the vast majority of patients experiencing a PMI do not report acute chest pain or other symptoms typical of spontaneous AMI. Most likely, this is because these PMIs occur in a phase of intense postoperative analgesia [2, 3, 5, 7–9]. Accordingly, most patients with PMI are currently not detected in routine clinical practice. Missed diagnosis is invariably associated with a missed opportunity for the initiation of treatment. Second, the predominant pathophysiology of PMI is only incompletely characterised (plaque rupture versus supply/demand mismatch versus toxic) [14]. Third, because of our lack of knowledge regarding pathophysiology, it is unclear whether the benefit of treatment in PMI is similar to the huge benefit in spontaneous AMI. Fourth, in contrast to spontaneous MI, where cardiac troponin elevations must be accompanied by symptoms, electrocardiographic, or imaging criteria [10, 52], the limited applicability (chest pain in a period of intense postoperative analgesia) and sensitivity (ECG, imaging) of these criteria in the perioperative setting highlight the need for a different diagnostic approach for PMI, which needs to be defined.

Conclusion

Perioperative myocardial infarctions and injuries pose a problem more frequent than previously expected and are associated with a high mortality, thereby strongly contributing to postoperative mortality. As they often present asymptomatic due to factors specific to the perioperative setting such as analgesia, specific tools are needed to identify patients with PMI, e.g. biomarker screening. The identification of correct subtype (type I, type II, or nonischaemic) is essential for further therapy, but presents a challenge for physicians. Lastly, specific therapy needs to be defined.

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