Chapter 4

Perioperative myocardial perfusion:
An anesthesiologists’ concern?

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ABSTRACT

Purpose of review
Cardiac complications following noncardiac surgery are the leading cause of death in the perioperative period. Disturbances in myocardial perfusion are at the basis of these complications. The purpose of this review was to summarize the most recent findings on factors affecting myocardial perfusion in the perioperative period and possibilities for monitoring disturbances in myocardial perfusion.

Recent findings
Clinical studies in cardiovascular healthy patients show mild influences of general anesthetics on myocardial perfusion. No clear benefit could be detected for the use of volatile anesthetics over intravenous anesthetics in patients at-risk for disturbances in myocardial perfusion. Etomidate should be used with caution in ASA class 3 and 4 patients. Recent studies focused on effects of decreased perfusion pressure, lowering myocardial oxygen demand and impaired oxygen delivery on myocardial perfusion. Promising results are reported on monitoring perioperative myocardial perfusion using troponin and NT-proBNP.

Summary
General anesthesia only mildly influences myocardial perfusion in cardiovascular healthy patients. Further research is necessary to determine whether this is also the case for cardiovascular-compromised patients. Monitoring troponin levels in the perioperative setting may be useful for predicting cardiovascular events in at-risk patients.

Keywords
Myocardial perfusion, perioperative cardiac complications, general anesthetics, troponin, NT-proBNP
INTRODUCTION

Cardiac complications after noncardiac surgery remain a major cause of death in the perioperative period.\textsuperscript{1,2} Disturbances in myocardial perfusion due to an imbalance in oxygen demand and delivery or preexisting coronary artery disease are at the root of these complications.\textsuperscript{3} This review highlights the most recent evidence on the influence of general anesthesia on myocardial perfusion, on perioperative factors affecting myocardial perfusion and on the need for monitoring cardiac events using biomarkers.

**Importance of measuring myocardial perfusion**

During myocardial ischemia, abnormal perfusion occurs before a decline in function and an altered electrocardiogram.\textsuperscript{4} Consequently, assessing myocardial blood flow (MBF; in milliliters per minute per gram tissue) and the vasodilator capacity (coronary flow reserve) of the myocardial vascular bed instead of function yields a higher sensitivity for detection of abnormalities in perfusion and coronary anatomy.\textsuperscript{5} MBF typically increases 3.5- to 4-fold in response to vasodilating agents such as adenosine; this response is reduced in the presence of coronary artery disease or microvascular dysfunction.\textsuperscript{6}

**General anesthesia influences myocardial perfusion**

Already in the 70s it was shown that halothane produces a dose-dependent decrease in myocardial function and blood flow in healthy volunteers.\textsuperscript{7} Isoflurane anesthesia resulted in coronary vasodilation in patients with critical coronary artery stenosis.\textsuperscript{8} Some years later, experimental investigations showed that sevoflurane, isoflurane and halothane are potent coronary vasodilators.\textsuperscript{9-11} If perfusion pressure was kept constant in these experiments, coronary vasodilation led to an increase in basal coronary blood flow. Maximal coronary vasodilator capacity evaluated with adenosine was not affected by volatile anesthetics.\textsuperscript{12} After a relatively silent decade with respect to studies concerning anesthesia and myocardial perfusion, recently two studies were published further investigating this relation. First, the effects of xenon anesthesia on MBF and systemic hemodynamics were studied in six healthy volunteers.\textsuperscript{13} Blood flow was measured using positron-emission tomography at baseline (awake) and during xenon anesthesia. A decrease in MBF with xenon anesthesia was observed, although not statistically significant in this small population. The authors concluded that xenon anesthesia has only minimal effects on coronary hemodynamics and could therefore be an attractive alternative in patients at risk for perioperative myocardial ischemia. This conclusion may be supported by previous findings in patients with known coronary artery disease scheduled for noncardiac surgery. In these patients, xenon anesthesia preserved mean arterial pressure and left ventricular performance better compared to propofol anesthesia.\textsuperscript{14} A possible role for xenon anesthesia in patients at risk for perioperative cardiac events depends on future studies addressing postoperative outcome.
A more recent study investigated the effect of sevoflurane anesthesia on MBF in cardiovascular healthy patients.\textsuperscript{15} Compared to baseline values (awake), sevoflurane anesthesia preserved MBF despite a decrease in perfusion pressure. The blood volume within myocardial capillaries was lower during sevoflurane anesthesia. Adenosine-induced hyperemia during sevoflurane resulted in a decrease in mean arterial pressure so that the mechanistic connection between sevoflurane and decreased myocardial blood volume could not be made. Nevertheless, MBF increased in response to adenosine infusion suggesting preservation of myocardial vasodilator response. These results suggest that sevoflurane anesthesia only mildly influences MBF. On the other hand, a pilot study in patients with type 2 diabetes mellitus showed a decrease in resting myocardial blood flow under sevoflurane anesthesia compared to awake.\textsuperscript{16} Also, a trend towards a lower vasodilator capacity was observed. Overall, general anesthetics have mild influences on myocardial perfusion in a clinical setting with cardiovascular healthy patients. Effects of anesthesia in cardiovascular-compromised populations require further investigation.

\textit{Choice of anesthetic and disturbances in myocardial perfusion}  
Is the choice of the administered anesthetic important in patients with cardiovascular risk factors undergoing major noncardiac surgery? A retrospective study was recently published in which the association between etomidate and 30-day mortality after noncardiac surgery was studied.\textsuperscript{17} The authors hypothesized that the adrenal suppression following an induction with etomidate may lead to a higher mortality rate. The final study sample comprised 2144 patients receiving etomidate and 5233 matched patients receiving propofol; all patients were ASA class 3 or 4. The authors found an increased risk of mortality and cardiovascular morbidity, and longer length of hospital stay in patients receiving etomidate. These results emphasize that etomidate should be used with caution in ASA class 3 and 4 patients.

The latest version of the ACC/AHA guidelines on perioperative care for noncardiac surgery dates back to 2007 and recommends volatile agents for anesthesia maintenance in patients at risk for myocardial ischemia.\textsuperscript{18} Is this advice still up to date? A randomized multicenter clinical trial addressed the effects of sevoflurane versus propofol anesthesia on cardiac morbidity and mortality after major noncardiac surgery.\textsuperscript{19} Patients with a history of myocardial infarction or signs of coronary artery stenosis $>$50\% on angiography were included (N=385). Interestingly, the incidence of myocardial ischemia (continuous ECG and cardiac biomarkers) on the 1\textsuperscript{st} or 2\textsuperscript{nd} postoperative day did not differ between the sevoflurane (40.8\% of patients) and propofol group (40.3\% of patients). Also, NT-proBNP release was not different between groups. Follow-up after 12 months postoperatively revealed 14 patients (7.6\%) with a major adverse cardiac event in the sevoflurane group versus 17 patients (8.5\%) in the propofol group, which was not significantly different. The authors concluded that sevoflurane did not reduce the incidence of myocardial ischemia in high-risk patients undergoing noncardiac surgery.
The article instigated a widespread discussion amongst researchers in the field of anesthetic preconditioning. Criticism included lack of information on mean alveolar concentration of sevoflurane and incidence of myocardial ischemia on the 3rd – 7th postoperative days, inclusion of diabetic patients and patients using β-blockers (both negative influences on preconditioning) and the underpowered character of study. The ABSENT-trial was designed to answer a similar question: a randomized clinical trial comparing troponin-T release with fentanyl – sevoflurane versus remifentanil – propofol anesthesia in major vascular surgery. Of the 193 included patients, 64% were American Society of Anesthesiologists class 3 or 4 and 36% had coexistent coronary artery disease. Postoperative troponin-T levels did not differ between the two groups. Also, no differences in postoperative complications, coronary events or mortality were observed.

A third randomized clinical trial also failed to show any advantage for using volatile compared to intravenous anesthetics in noncardiac surgery. A total of 88 patients (73% were ASA class 3 or higher) were randomized to sevoflurane or propofol anesthesia. No differences in postoperative troponin-I level could be detected: in the sevoflurane group 27.3% of patients had detectable postoperative troponin-I levels compared to 20.5% in the propofol group which was not significantly different.

The myocardial protective characteristics of isoflurane were recently addressed in a meta-analysis. A total of 37 randomized trials in both cardiac and noncardiac surgery were included. Outcome parameters included rate of myocardial infarction and all-cause mortality. In 55% of the studies, isoflurane was compared to a nonvolatile anesthetic. A high level of heterogeneity was present in this meta-analysis due to differences in dose of isoflurane, comparators, surgery and length of follow-up. Overall, no difference in rates of myocardial infarction or mortality could be found between isoflurane and any comparator. When only high-quality trials were used for analysis (studies with a low risk of bias), isoflurane was associated with a significant reduction in mortality. High-quality trials included 4 cardiac and 6 noncardiac studies and 5 nonvolatile and 5 volatile agents as comparators. No difference in risk of myocardial infarction was found in this subanalysis. Overall we must conclude that isoflurane is comparable to other anesthetic drugs with respect to incidence of myocardial infarction and all-cause mortality. In conclusion, recent publications do not show any benefit for use of volatile over intravenous anesthetics for at-risk patients. These findings are in contrast with recommendations in the ACC/AHA guidelines.

**Factors affecting myocardial perfusion**

**Decreased perfusion pressure**

The association between mean arterial pressure and risk of myocardial injury was studied in a retrospective cohort of 33,330 noncardiac surgery cases. Myocardial injury was defined as an elevated postoperative troponin-T and creatinine kinase-MB within 7 days of surgery.
The mean arterial blood pressure was recorded every 2 – 5 minutes (noninvasive blood pressure) or every 1 – 2 minutes (invasive blood pressure). The total number of minutes spent with a mean arterial blood pressure less than 55, than 60, than 65, than 70 and less than 75 mmHg was calculated for every case. In total, 770 cases (2.3%) of myocardial injury were documented. The risk of myocardial injury was greater if mean arterial pressure was below 55 mmHg. No significant association was found between myocardial injury and other ranges of blood pressure. When compared to patients who spent no time with a mean arterial blood pressure less than 55 mmHg, increased risk of myocardial injury varied from 1.30-fold (1 – 5 minutes MAP < 55 mmHg) to 1.82-fold (> 20 minutes MAP < 55 mmHg). Whether quick restoration of mean arterial pressure improves the risk of myocardial injury cannot be concluded from this study.

Lowering myocardial oxygen demand
Perioperative β-blocker use remains a controversial issue in the field of anesthesiology. European guidelines recommend perioperative continuation of β-blockers for ischemic heart disease, arrhythmias or hypertension. Furthermore, β-blockers should be considered in patients with signs of myocardial ischemia during preoperative stress testing or patients scheduled for high-risk surgery. Whether use of β-blocker on the day of or following noncardiac surgery is actually associated with a decrease in 30-day all-cause mortality and cardiac morbidity was recently evaluated in a retrospective cohort study.28** A total of 37,805 matched pairs of patients exposed and not-exposed to β-blockers were used for analysis. Overall, exposure to β-blockers was associated with lower all-cause mortality, with a number needed-to-treat of 241 patients. Also, β-blocker administration resulted in a lower rate of nonfatal Q-wave infarction or cardiac arrest with a number needed-to-treat of 339 patients. After stratifying patients by cumulative numbers according to Revised Cardiac Risk Index factors (high-risk surgery, diabetes mellitus, cerebrovascular incident, ischemic heart disease, congestive heart failure and renal insufficiency), significantly lower mortality rates were found in patients with 2 factors, 3 factors and 4 factors or more. Patients with none or 1 risk factor appeared not to benefit from β-blockers. Interestingly, no significant associations between β-blocker exposure and outcome could be detected in patients undergoing vascular surgery. The overall incidence of postoperative stroke was 0.3% in this study; no association with β-blocker use could be demonstrated.

Impaired oxygen delivery
The effect of pre- and postoperative hemoglobin concentration on the occurrence of cardiovascular events in elective vascular surgery patients was studied retrospectively.29** Patients underwent open or endovascular repair of an aortic aneurysm, lower extremity arterial repair or carotid surgery. In 221 (21%) out of 1041 patients a cardiovascular event
occurred within 30 days postoperatively: 103 (10%) cases of nonfatal myocardial infarction, congestive heart failure, arrhythmias or stroke; 98 (9%) cases of asymptomatic troponin-T release and 20 (2%) cases of cardiovascular deaths. Patients suffering a cardiovascular event were older, were more likely to have coronary heart disease, renal dysfunction, heart failure, diabetes mellitus or hypertension compared to patients without perioperative cardiovascular event. The presence of preoperative anemia was more common in patients with a cardiovascular event. After adjusting for confounders, it was observed that a low preoperative or postoperative hemoglobin level was associated with an increased risk of cardiovascular events within 30 days of surgery. Also, every 1.0 g dl⁻¹ decrease in hemoglobin level (preoperative – postoperative) was associated with a 20% increased risk of developing a cardiovascular event within 30 days. If patients with red blood cell transfusions were excluded from analysis, only low postoperative hemoglobin levels were associated with increased risk of events. The latter suggests that low postoperative hemoglobin level is the strongest predictor of cardiovascular events in vascular surgery patients.

Perioperative monitoring of myocardial perfusion
Are cardiac biomarkers useful for monitoring intraoperative disturbances in myocardial perfusion? Van Waes et al. investigated the predictive value of postoperative troponin elevation as marker of myocardial injury in relation to 30-day mortality. Patients aged ≥60 years scheduled for intermediate- to high-risk noncardiac surgery were included and troponin-I levels were measured on the first 3 postoperative days. In 19% of patients, myocardial injury was detected by elevated troponin-I levels; all-cause mortality was 3%. Further, 0.6% of patients were diagnosed with a myocardial infarction. Postoperative myocardial injury was found to be an independent predictor of mortality with a relative risk of 2.4 in case of a minor increase in troponin level and 4.2 in case of a ≥10-fold increase in troponin levels.

In a similar study, troponin-T levels were measured on the first 3 postoperative days in patients aged ≥45 years and scheduled for noncardiac surgery. Inclusion of 15133 patients resulted in a 30-day mortality rate of 1.9%, with a significant association with increased troponin-T levels. Furthermore, higher peak troponin-T levels were associated with greater 30-day mortality rates. Based on the same population, the investigators showed in a more recent publication that a peak troponin-T level ≥0.03 ng/ml without any further feature of myocardial ischemia is also an independent predictor of 30-day mortality. Whether preoperative troponin-T levels are also associated with long-term mortality after noncardiac surgery was investigated in the VINO-trial. In a prospective cohort of 608 patients with multiple risk factors for coronary artery disease scheduled for major cardiac surgery, troponin-T and -I together with a 12-lead electrocardiogram were obtained before and immediately after surgery and on the first 3 postoperative days. During the first 3 postoperative days, patients with high preoperative troponin-T levels developed significantly more acute myocardial infarctions
(8.6%) compared to patients with a low preoperative troponin-T level (2.5%). After a follow-up of 3 years, patients with preoperative high troponin-T levels were more likely to have died (25% mortality rate) versus patients with low preoperative troponin-T levels (11%).

The potential of B-type natriuretic peptide (BNP) and NT-proBNP in predicting cardiovascular complications after noncardiac surgery was studied in a recent meta-analysis.\(^{34}\) In 18 studies with a total of 2051 patients, (NT-pro-) BNP was measured up to 7 days postoperatively and primary outcome measures were (cardiac) mortality, nonfatal myocardial infarction, coronary revascularization or heart failure within 30 days and ≥180 days after noncardiac surgery. The authors concluded that increased (NT-pro-) BNP levels were significantly associated with increased risk of mortality, nonfatal myocardial infarction and cardiac failure after both 30 days and ≥180 days follow-up. These studies suggest that monitoring cardiac biomarkers in the postoperative period is useful for predicting occurrence of cardiac complications.

CONCLUSION

Disturbances in myocardial perfusion in the perioperative period remain a major cause of cardiac complications. Recent evidence shows that general anesthesia only mildly influences myocardial perfusion in cardiovascular healthy patients. Convincing evidence for use of volatile over intravenous anesthetics in patients at-risk for cardiac events is lacking, which is in contrast with the recommendations in the ACC/AHA guidelines. Low perfusion pressure and an impaired oxygen delivery capacity were associated with perioperative disturbances in myocardial perfusion. Routine measurement of postoperative troponin levels may be indicated in at-risk patients since increased troponin levels were independently associated with mortality.

KEY POINTS

- General anesthetics have a mild influence on myocardial perfusion in cardiovascular healthy patients.
- Recent studies provide no convincing evidence that volatile anesthetics are preferred over intravenous anesthetics in patients undergoing noncardiac surgery.
- Routine measurement of troponin levels should be considered in patients at-risk for perioperative cardiac events.
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34.* Rodseth RN, Biccard BM, Chu R, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. Anesthesiology 2013;119:270–283. Also increased levels of NT-proBNP are predictive of increased postoperative mortality after 30 and 180 days. Routine measurement of NT-proBNP may be advocated in at-risk patients.