Chapter 1

General introduction
PERIOPERATIVE CARDIOVASCULAR COMPLICATIONS

Annually 234 million major surgical procedures are performed worldwide.¹ The overall mortality rate following surgery is estimated at 4%, resulting in 9 million affected patients globally each year.² Cardiac complications after noncardiac surgery remain a major cause of death in the perioperative period, with an estimated prevalence of 1% (superficial surgical procedures) to more than 5% (vascular surgery) depending on the type of surgery and anesthesia.³⁻⁶ The risk of cardiovascular complications increases with the presence of comorbidities such as coronary artery disease, diabetes mellitus, renal dysfunction and previous ischemic stroke. One of the most common cardiovascular complications is the occurrence of myocardial ischemia and infarction, which significantly contribute to perioperative morbidity and usually occur within 24 to 48 hours after surgery.⁷⁻⁹ Disturbances in myocardial perfusion and blood flow leading to an imbalance in oxygen demand and delivery, or preexisting coronary artery disease are at the root of these complications.¹⁰ Accurate prediction of the risk of developing perioperative cardiovascular complications becomes more important, since age, incidence and complexity of comorbidities in surgical patients are increasing.

REGULATION OF MYOCARDIAL BLOOD FLOW

Myocardial blood flow is essential for proper cardiac function and is regulated by neurohumoral, endothelial and metabolic signals producing contraction or relaxation of smooth muscle cells in the tunica media of coronary arteries. Neurotransmitter release from the autonomic nervous system alters coronary vascular resistance via α-adrenergic vasoconstriction and β-adrenergic and cholinergic vasodilation. Local metabolic messengers like carbon dioxide, pH, adenosine and endothelial factors such as nitric oxide, endothelin and prostanoids also influence the coronary vascular resistance via vasodilator and vasoconstrictor signals.¹¹,¹² The aim of this regulatory process is to maintain blood flow to the heart over a wide range of driving pressures and under different metabolic conditions.

The aortic pressure and the pressure drop across the vascular bed are major determinants of myocardial perfusion pressure. Rises in intramyocardial pressure due to systolic contractile force development decrease the pressure drop across the vascular bed and impede myocardial blood flow during systole.¹³ Consequently, oxygen delivery to subendocardial vessels occurs particularly during diastole.¹¹ During stress, heart rate as well as myocardial compressive force increases, which decreases perfusion time and effective driving pressure. These consequences of stress may not increase the risk of myocardial ischemia in cardiovascular healthy patients; it may however impair myocardial oxygen delivery in patients with comorbidities like coronary artery disease, anemia or hypoxia.
Cardiac smooth muscle cells also regulate myocardial blood flow by responding to alterations in perfusion pressure. Stretch imposed by a rise in arterial pressure increases vessel diameter and wall stress. In response, smooth muscle contraction decreases vessel diameter thereby limiting the increase in blood flow and normalizing wall stress. The opposite myogenic response occurs with a decrease in perfusion pressure. Under physiological circumstances, myocardial oxygen delivery is meticulously matched to oxygen demand by the abovementioned endothelial, metabolic and myogenic mediated alterations in coronary vascular resistance. This phenomenon is also known as autoregulation. While the oxygen extraction rate in the myocardium is nearly maximal under normal circumstances, adaptation to a rise in oxygen demand is largely dependent on autoregulated-increases in myocardial blood flow.

MYOCARDIAL MICROVASCULAR REACTIVITY AND CORONARY FLOW RESERVE

If blood supply to the myocardium is impeded, e.g. by diseases of large coronary arteries or the myocardial microcirculation, hypotension or anemia, myocardial ischemia may develop. In coronary artery disease, stenosis of one or more of the large epicardial arteries increases the resistance to flow. In order to preserve myocardial blood flow, post-stenotic dilation of the epicardial vessel(s) occurs with an associated decrease in perfusion pressure. In these patients, basal myocardial blood flow is preserved, while maximal blood flow is diminished. In case of ischemic heart disease, perfusion abnormalities usually precede other symptoms of ischemia such as a decline in myocardial contractile function and an altered electrocardiogram. Consequently, assessing myocardial blood flow (in milliliters per minute per gram tissue) and the vasodilator capacity (coronary flow reserve) of the myocardial vascular bed instead of myocardial function yields a higher sensitivity for detection of coronary stenoses. The vasodilator capacity can be determined by measuring basal myocardial blood flow and after inducing maximal endothelium-independent vasodilation (hyperemia) by intravenous administration of adenosine or dipyridamole. Dividing hyperemic myocardial blood flow by basal flow renders the coronary flow reserve. Myocardial blood flow typically increases 3.5– to 4–fold in response to hyperemia; this response is reduced in the presence of coronary artery disease or microvascular dysfunction. The latter is characterized by abnormalities in structure and function of the microcirculation and can be present without or with underlying coronary artery or myocardial diseases. Also, exercise or sympathetic stimulation may be used for assessment of the vasodilator capacity of the myocardium. Both lead to an endothelium-dependent vasodilation of arteriolar resistance vessel and an increase in myocardial blood flow. Typically, a 2– to 3–fold increase in blood flow is observed.
ANESTHESIA AND MYOCARDIAL PERFUSION

The influence of general anesthetics on coronary arteries has been acknowledged since several decades. Already in the 1970s it was shown that halothane dose-dependently decreases myocardial function and blood flow in healthy volunteers. Isoflurane anesthesia in patients with critical coronary artery stenosis resulted in coronary vasodilation. Some years later, experimental investigations confirmed that sevoflurane, isoflurane and halothane are potent coronary vasodilators, both in vitro and in vivo. 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.

After a relatively silent decade with respect to studies concerning anesthesia and myocardial perfusion, recently the effects of xenon anesthesia on myocardial blood flow and systemic hemodynamics were studied in six healthy volunteers. Blood flow was measured using positron emission tomography at baseline (awake) and during xenon anesthesia. Mean arterial blood pressure and the rate-pressure product (heart rate x systolic blood pressure; estimate of myocardial oxygen demand) decreased during xenon anesthesia. Further, a decrease in myocardial blood flow with xenon anesthesia was observed, although not statistically significant in this small population. It was concluded that xenon anesthesia has minimal effects on coronary hemodynamics and could therefore be an attractive anesthetic 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 more than propofol anesthesia. Whether these apparent beneficial effects of xenon anesthesia translate into improved postoperative outcome remains to be established.

In this thesis we focus on sevoflurane, a well-known and widely used inhalational anesthetic, and its effect on myocardial blood flow and hemodynamic indices. Furthermore, we focus not only on overall perfusion of the myocardium as most previous studies. Instead, we particularly aim to study myocardial microcirculatory changes in a clinically relevant scenario in the absence of artificial modulation of vasomotor tone or myocardial performance.

SYMPATHETIC STIMULATION

In response to intraoperative stress, increased autonomic sympathetic activity may alter myocardial oxygen demand. Under physiological circumstances, sympathetic stimulation increases myocardial blood flow via adrenergic coronary vasodilation. However, coronary vessels contain both α- and β-adrenoreceptors, and if the coronary circulation is impaired due
to cardiovascular disease, unopposed adrenergic coronary vasoconstriction may contribute to ischemia.\textsuperscript{29} Anesthetics reduce both myocardial blood flow regulation and the sympathetic autonomic nervous activity.\textsuperscript{24,30-35} However, it is unclear whether and how anesthetic-related reductions in myocardial blood flow and autonomic sympathetic innervation are related.\textsuperscript{33,34} Moreover, studies reporting alterations in myocardial blood flow in response to sympathetic stimulation during anesthesia provide conflicting results. While Moffitt and Sethna showed that coronary blood flow decreases during sternotomy-induced sympathetic stimulation, Kirno \textit{et al.} observed an increase in coronary blood flow in a similar setting.\textsuperscript{36,37} Studies on the relation between myocardial blood flow, microvascular responses and autonomic control in anesthetized healthy humans are lacking because of the absence of reliable noninvasive measurement of myocardial blood flow. This issue is overcome by the introduction of noninvasive echocardiographic techniques using ultrasound contrast agents allowing evaluation of myocardial blood flow and its microvascular constituents.\textsuperscript{38-40}

\textbf{CARDIAC AUTONOMIC FUNCTION}

Cardiovascular autonomic function is often evaluated using the Ewing tests combined with quantitative assessment of heart rate variability. Current guidelines recommend performing these tests under standardized conditions, in a quiet ambiance at room temperature with patients refraining from smoking, eating and drinking for a considerable amount of time.\textsuperscript{41,42} The lack of uniformity in data acquisition and interpretation combined with logistical issues prevents cardiovascular autonomic function tests from gaining a place in routine pre-assessment screening. This is unfortunate since the presence of cardiovascular autonomic neuropathy, like resting tachycardia, orthostasis and alterations in heart rate variability, strongly predict abnormalities in myocardial perfusion, myocardial blood flow regulation and impaired vasodilator responses to stress.\textsuperscript{43-45} Indeed, autonomic neuropathy as determined by heart rate variability predicted mortality in patients with coronary artery disease undergoing noncardiac surgery, but the contribution of impaired coronary vasodilatory responses to these results has not been established.\textsuperscript{46} Clarification of the relation between autonomic control and myocardial blood flow during anesthesia may not only contribute to our insight in pro-ischemic processes in the heart, but may lead to changes in preoperative assessment of patients at risk for perioperative ischemia, thereby reducing perioperative complications.

\textbf{AIM AND OUTLINE OF THIS THESIS}

In this thesis we study myocardial blood flow and microvascular responses during sevoflurane anesthesia and specifically focus on the role of the autonomic nervous system. Additionally, we aim to explore whether evaluation of autonomic function in the perioperative setting is a realistic goal.
The central hypothesis in the present thesis is that sevoflurane anesthesia alters autonomic control such that perioperative myocardial blood flow is significantly disturbed. If our hypothesis is confirmed, these disturbances in myocardial blood flow could contribute to the development of myocardial ischemia in the perioperative period. Furthermore, while cardiovascular healthy patients may not directly be at risk, it could explain why patients with a cardiovascular autonomic neuropathy, e.g. patients with diabetes, are even more prone to developing perioperative disturbances in myocardial blood flow.

PART I: Evaluation of autonomic function in the perioperative setting

In chapter 2 we investigate whether heart rate variability, which is a widely used measure of autonomic function, can be substituted by pulse rate variability. The latter parameter is more useful in the operating room, since it is less influenced by environmental factors.

In chapter 3 we address the implementation of autonomic function tests in the preoperative assessment screening clinic. Specifically the reproducibility of these tests under non-standardized conditions is addressed.

PART II: Modulation of autonomic function during myocardial blood flow measurements

In chapter 4 we review the latest evidence on perioperative myocardial perfusion, influence of general anesthesia and the usefulness of cardiac biomarkers for monitoring postoperative myocardial injury.

In chapter 5 we provide an overview of the background, principles, indications and technical considerations of contrast-enhanced ultrasound for myocardial perfusion imaging.

In chapter 6 we investigate whether sevoflurane anesthesia affects myocardial blood flow and microvascular reactivity in cardiovascular healthy subjects.

In chapter 7 we analyze the effects of acute inhibition of autonomic sympathetic innervation on myocardial blood flow in cardiovascular healthy patients undergoing high thoracic epidural anesthesia. Furthermore, the additional effect of sevoflurane anesthesia on autonomic sympathetic denervation is studied in this chapter.

In chapter 8 we study patients with diabetes-related alterations in autonomic function and anesthesia-induced disturbances in myocardial blood flow.
REFERENCES