ENGLISH SUMMARY

The studies described in this thesis were designed to gain more insight into alterations in myocardial blood flow and microvascular responses during anesthesia, with specific focus on the role of the autonomic nervous system. Furthermore, we explored whether evaluation of autonomic function in the perioperative setting is feasible.

I. Evaluation of autonomic function in the perioperative setting

Cardiac complications after noncardiac surgery remain a major cause of death in the perioperative period, with an estimated prevalence of 1 – 5% depending on the type of surgery and anesthesia. 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. Chapter 1 provides a general introduction on perioperative cardiac complications and current knowledge of the influence of anesthesia and cardiac autonomic dysfunction on myocardial blood flow.

In chapter 2 we describe the results of a study in healthy volunteers aimed at testing the suitability of heart rate variability measurements as test for autonomic function for the intraoperative setting. Autonomic function is usually evaluated by quantitative measurement of heart rate variability, which reflects parasympathetic and sympathetic control of the sinoatrial node. Decreased heart rate variability is associated with perioperative hemodynamic instability, increased mortality after myocardial ischemia and sudden cardiac death. R-R intervals derived from an electrocardiogram over a fixed time frame are necessary for quantification of heart rate variability. However, intraoperative electrocardiographic signals frequently interfere with diathermy or patient movement causing artifacts. In this chapter we showed that pulse rate variability, measured with a continuous noninvasive blood pressure measurement device, corresponds well with heart rate variability obtained from an electrocardiogram and is significantly less influenced by environmental factors. We concluded that pulse rate variability is a valuable marker in the perioperative setting and its use may contribute to an early recognition of patients at perioperative cardiovascular risk.

In chapter 3 we present a study evaluating the comparability of autonomic function tests (heart rate variability and Ewing tests) under both non-standardized and standardized test conditions in healthy individuals. By convention, these tests are undertaken under standard test conditions: patients should refrain from smoking, eating and drinking, and the tests are performed early in the morning in a quiet ambiance at room temperature. These conditions are however difficult to establish in a preoperative screening clinic. In this chapter we reported that non-standardized cardiovascular autonomic function tests could be used as an alternative to standardized measurements for the detection of disturbances in cardiovascular autonomic function. Considering the association between autonomic function and perioperative
cardiovascular complications, we concluded that evaluation of autonomic function at the preoperative screening clinic may yield valuable information for the clinician.

**II. Modulation of autonomic function during myocardial blood flow measurements**

In *chapter 4* an overview is given of the most recent literature on perioperative myocardial blood flow. It is discussed that general anesthetics have only a mild influence on myocardial perfusion in cardiovascular healthy patients. Furthermore, recent studies provide no convincing evidence that volatile anesthetics are preferred over intravenous anesthetics in patients at risk for cardiovascular complications undergoing noncardiac surgery. Finally, we argue that routine measurement of troponin levels should be considered in patients at-risk for perioperative cardiac events.

In *chapter 5* we provide a description of characteristics and feasibility of myocardial contrast echocardiography, the relatively new technique we employed in this thesis. Myocardial contrast echocardiography uses contrast agents consisting of small, gas-filled microbubbles for measurement of myocardial blood flow. The microbubbles remain intravascular during their transit through the myocardial microvasculature and therefore directly reflect myocardial blood flow. The resolution of myocardial contrast echocardiography is superior to other imaging modalities and patients are not exposed to radiation. Furthermore, it is a portable tool that provides exciting new opportunities for studying myocardial perfusion in the operating room. In our case, the aim to study not only overall myocardial blood flow but also the underlying microvascular parameters was decisive in our choice for this technique.

In *chapter 6* we describe a study assessing the influence of sevoflurane anesthesia on myocardial blood flow and microvascular reactivity in cardiovascular healthy patients. We reported that sevoflurane anesthesia preserves myocardial blood flow at rest and during sympathetic stimulation; the myocardial blood volume and hyperemic myocardial blood flow were reduced. We concluded that these results suggest that myocardial blood flow and its regulatory pathways are largely maintained in cardiovascular healthy subjects subjected to sevoflurane anesthesia. The decrease in hyperemic myocardial blood flow (*coronary flow reserve*) may have no direct clinical consequence in this specific population. However, it may become important in cases of a decreased arterial oxygen content, for example during hypoxemia or hemodilution, which are frequently occurring events in the intraoperative setting.

In *chapter 7* we studied myocardial blood flow and microvascular responses in patients with acute blockade of cardiac autonomic function induced by high thoracic epidural anesthesia. The results indicate that cardiac sympathetic blockade by thoracic epidural anesthesia blunts the increase in myocardial blood flow in response to sympathetic stimulation. Also, thoracic epidural anesthesia increased myocardial blood volume and hyperemic myocardial blood flow. Especially the increase in myocardial blood volume is a remarkable observation, since
this volume is expected to remain stable when coronary perfusion pressure is within the autoregulatory range and arteriolar vasomotion is intact. The reported increase in myocardial blood volume may be explained by capillary recruitment or increased myocardial capillary distensibility. The increase in hyperemic myocardial blood flow suggests that acute cardiac sympathetic blockade increases the vasodilator capacity of the myocardium. Interestingly, the abovementioned effects of acute cardiac sympathetic blockade were blunted by the combined administration of thoracic epidural anesthesia and sevoflurane. Whether these observations are purely the result of decreases in blood pressure or whether sevoflurane itself interferes with pathways responsible for regulation of myocardial blood flow cannot be concluded from this study.

The study described in chapter 8 focused on myocardial responses to anesthesia in a group of patients with a fundamentally altered autonomic nervous system. We reported that sevoflurane anesthesia decreases resting myocardial blood flow in type 2 diabetic patients compared to healthy controls; also a trend towards a decreased hyperemic myocardial blood flow was observed. These results indicate different myocardial responses in diabetic patients and expand our understanding of possible mechanisms behind increased perioperative cardiovascular complications in patients with type 2 diabetes mellitus. Knowledge of the distinct myocardial response in patients with diabetes is of critical importance, and makes us aware that these patients require a more aggressive approach to maintain myocardial perfusion in case of hypoxemia, hypotension or anemia than healthy controls.

In chapter 9 the main findings of this thesis are discussed and placed in a broader perspective. Furthermore, methodological considerations and future directions for research are discussed. In the final paragraph we conclude that sevoflurane anesthesia preserves resting myocardial blood flow as well as the increase in flow in response to sympathetic stimulation in cardiovascular healthy patients. Furthermore, sevoflurane reduces the myocardial blood volume, which resides in the capillary system. Acute cardiac sympathetic blockade by high thoracic epidural anesthesia increases myocardial blood volume, suggesting a role for the sympathetic nervous system in the recruitment and derecruitment of myocardial capillaries. In patients with type 2 diabetes, resting myocardial blood flow is reduced by sevoflurane anesthesia. Although the autonomic nervous system plays only a moderate role in the regulation of myocardial blood flow it might be useful to assess its integrity prior to allowing a patient to be anesthetized. We demonstrated that evaluation of heart rate variability as a measure of autonomic function in the perioperative setting is feasible and may be a valuable tool both at the preoperative assessment clinic and in the operating room to identify patients at risk for cardiovascular complications.