1. English summary

In this thesis we studied perioperative tissue perfusion in different stages of overweight and obesity. We studied animal as well as human subjects during general anesthesia, mechanical ventilation, laparoscopy or cardiac surgery with cardiopulmonary bypass. In addition, we studied possible minimally invasive monitoring tools for extended cardiac monitoring in obese subjects in the perioperative period.

Chapter 1 provides a general introduction describing the problem of overweight and obesity in the perioperative period. First, the pathophysiology of disturbances in microcirculation and cardiac function related to overweight and obesity is described. In addition, the effects of the perioperative stress response, surgery-related factors such as laparoscopy and cardiopulmonary bypass as well as anesthetics on tissue perfusion are described. Finally, an overview is given on current possibilities for minimally invasive perioperative monitoring in the overweight and obese patient.

In chapter 2 we studied the hypothesis that sevoflurane anesthesia has more extensive cardiodepressive effects in obese, prediabetic rats when compared to lean controls. We determined systolic function and myocardial perfusion using (contrast-enhanced) echocardiography in a western-diet induced obese, hyperglycemic and glucose-intolerant prediabetic phenotype. Compared to lean, healthy control animals, the obese prediabetic rats had diminished myocardial perfusion as well as decreased systolic function at baseline. Following exposure to sevoflurane anesthesia, hemodynamics were equally altered in both groups. In the obese prediabetic phenotype myocardial contraction was however further reduced by sevoflurane, which was not observed in the control group. In both groups myocardial perfusion was unaltered compared to baseline measurements. These findings indicate that sevoflurane anesthesia is more cardiodepressive in obese prediabetic rats, and exposure to sevoflurane anesthesia may lead to uncoupling of myocardial perfusion and function. This may predispose to an oxygen demand-mismatch and thus myocardial ischemia.

In chapter 3 we investigated the effects of isolated obesity without the possibly confounding effects of (pre)diabetes. For this purpose, we exposed mice to a western diet and induced early obesity, without alterations in metabolic characteristics such as glucose levels, glucose tolerance and insulin resistance. We assessed cardiac systolic as well as diastolic function using pressure-volume loops from a conductance catheter in the left-ventricle, and studied
myocardial perfusion with contrast-echocardiography. Under general anesthesia, obese mice had diminished systolic as well as diastolic function and impaired myocardial perfusion when compared to lean control mice. Because of the known beneficial effects of insulin on myocardial perfusion as well as reports of its positive inotropic effects, we subsequently studied whether intraoperative insulin exposure could restore alterations in myocardial function and perfusion in the obese mice. Insulin exposure decreased afterload and improved ventricular relaxation or diastolic function. However, there was no improvement in myocardial perfusion during insulin exposure, nor a beneficial effect on load-independent parameters of systolic function. These findings suggest that even isolated obesity without metabolic alterations compromises cardiac function and perfusion in the perioperative period under general anesthesia and mechanical ventilation. Perioperative insulin treatment may be beneficial to modulate loading conditions and ventricular relaxation, but has no effect on myocardial perfusion and contractility.

In chapter 4 we studied microcirculatory perfusion in obese patients undergoing cardiac surgery with the use of cardiopulmonary bypass (CPB). It is known that CPB decreases microcirculatory perfusion even after surgery and we hypothesized that this would be even more severe in obese patients. Microcirculatory perfusion was determined with sublingual Sidestream Dark Field imaging measurements before, during and after cardiac surgery with cardiopulmonary bypass. We found that microcirculatory perfusion in obese patients was not compromised at baseline when compared to lean patients. Furthermore, induction of anesthesia did not alter microcirculatory perfusion in either group. Cardiopulmonary bypass induced the same alterations in obese patients as in lean patients, and in both groups perfusion was restored to baseline values 72 hours postoperatively.

The second part of the thesis focuses on cardiac monitoring options for the obese patient in the perioperative period. In chapter 5 we propose a new method for assessment of cardiac function. Commonly used parameters for cardiac function such as ejection fraction are sensitive to changes in loading conditions, and the frequent changes in pre- and afterload that may occur during major surgery make these less suitable in the perioperative period. Therefore, we studied a method for assessment of load-independent end-systolic elastance ($E_{es}$) in patients undergoing major surgery, which is normally determined in an invasive fashion. We demonstrate the feasibility of a minimally invasive method in lean patients using transesophageal echocardiography and non-invasive continuous blood pressure measurements using the Nexfin device. We found acceptable agreement between this method of $E_{es}$ estimation and a more invasive method using an arterial line, and thus conclude that this may be a useful tool to assess cardiac function during major surgery. For
estimation of $E_{es}$ however, invasive inferior vena cava compression of occlusion is required, and we found that it could not be replaced by a pharmacological loading intervention with phenylephrine administration. This makes application of $E_{es}$-estimation limited to surgery where the vena cava can be accessed. Because of this limitation, that makes $E_{es}$-estimation highly invasive, we did not extend these findings to the obese population.

The applicability of the Nexfin device has never been studied in the morbidly obese population before. We assessed the applicability of the Nexfin device for cardiac monitoring in the morbidly obese population in chapter 6. We compared noninvasive cardiac output measurements with the Nexfin device to thermodilution cardiac output measurements with PICCO in morbidly obese patients undergoing laparoscopic gastric bypass surgery. We found an unacceptable level of agreement between the non-invasive Nexfin monitor with thermodilution, with a precision error that exceeds the Critchley criteria for agreement of cardiac output devices. Furthermore, trending of cardiac output was insufficient with the Nexfin device when compared to the thermodilution measurements. We conclude that the Nexfin device is unreliable for cardiac output monitoring in the morbidly obese population. Because of these results regarding the Nexfin device in the morbidly obese population, we did not investigate the feasibility of end-systolic elastance estimation with transesophageal echocardiography and the Nexfin (chapter 5) in morbidly obese patients.

In chapter 7 we further discuss and aimed to analyze the lack of suitability of the Nexfin device in morbidly obese patients, and more specifically looked into the algorithm used by the Nexfin to determine cardiac output and how this applies to morbidly obese patients. We describe how the Nexfin algorithm uses calculations of vascular characteristics that were based on aortic samples from healthy subjects, and hypothesize that this may not be applicable in the (morbidly) obese population. We furthermore aimed to improve the applicability of the Nexfin device in the morbidly obese population, because this population could especially benefit from extended noninvasive monitoring. Therefore, we studied different approaches of bodyweight-input in the Nexfin device. We hypothesized that bodyweight derivatives such as ideal- and adjusted bodyweight would give more reliable results, and confirmed this for adjusted bodyweight when we re-analyzed the Nexfin data of chapter 6 using adjusted bodyweight as input into the Nexfin algorithm. These data suggest that hemodynamic measurements generated by the Nexfin device could be more reliable when adjusted- instead of actual bodyweight is used as input.