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Summary

In the present thesis we investigated the impact of preoperative dietary composition on sevoflurane anesthesia-induced changes in myocardial perfusion and function. Moreover, we studied the effects of high intake of saturated fatty acids in combination with simple carbohydrates on the cardioprotective effects of sevoflurane in case of myocardial ischemia. We hypothesized that preoperative dietary intake influence sevoflurane-induced changes in perioperative myocardial function. To investigate this we studied myocardial perfusion, function and ischemic injury in diet-induced glucose intolerant or prediabetic rats.

Patients undergoing anesthesia and surgery are at risk of perioperative cardiac complications, especially in the presence of comorbidities like obesity and type 2 diabetes mellitus. A general introduction is given in **Chapter 1** on perioperative complications, myocardial performance and ischemia during anesthesia and the combination with dietary interventions and lifestyle changes.

A broader introduction on diabetes, perioperative ischemia and volatile anesthetics is given in **Chapter 2**. Several mechanisms involved in anesthesia-induced cardioprotection have been evaluated in the experimental setting. However, the existing evidence suggests that the obese and type 2 diabetic heart is less adaptable to cardioprotective interventions and that anesthesia-induced cardioprotection is just a "healthy heart phenomenon". Additionally, it is suggested that myocardial substrate metabolism is one of the underlying protective mechanisms; therefore we focused on the consequences of derangements in myocardial substrate metabolism. This overview of recent literature reveals the importance of interventional options focusing on recovery of the metabolic flexibility of the heart, especially by improving insulin sensitivity.

Myocardial perfusion during diet exposure and sevoflurane anesthesia

This thesis focused on the effect of diet-induced glucose intolerance and prediabetes on myocardial perfusion. **Chapter 3** describes the effect of high fat diet-induced glucose intolerance on myocardial perfusion and function during baseline and hyperemic conditions. High fat diet-induced glucose intolerance did not affect myocardial perfusion and function during baseline conditions. During hyperemia, we found that diet-induced glucose intolerance is associated with impaired myocardial function, but myocardial perfusion is maintained. These findings result in new insights into the effect of glucose intolerance on myocardial function and perfusion during hyperemia.

Sevoflurane is associated with myocardial depression and these effects seem more abundant during obesity and type 2 diabetes mellitus. **Chapter 4 focused on the impact of a more severe western, or cafeteria, diet on myocardial perfusion and function and the interaction with sevoflurane exposure. Western diet-induced prediabetes impaired myocardial perfusion and function.** Exposure to

sevoflurane did not affect myocardial perfusion, but impaired systolic function in healthy and prediabetic conditions. Our findings therefore suggest that sevoflurane leads to uncoupling of myocardial perfusion and function, irrespective of the metabolic state.

Effect of changing the dietary balance

Furthermore, this thesis investigated the effect of altering the dietary balance on myocardial function and ischemic injury by lowering the caloric intake. In **Chapter 5** we investigated whether lowering the caloric intake can restore the effects of sevoflurane on myocardial performance in prediabetes. Western diet-induced prediabetes impaired myocardial systolic and diastolic function, whereas sevoflurane even further impaired systolic function in prediabetes. Lowering caloric intake normalized the prediabetic phenotype, improved myocardial function and restored systolic function during sevoflurane exposure. Therefore, sevoflurane is a stronger cardiodepressant in prediabetes than in healthy conditions, which could be restored by lowering caloric intake. These results suggest that dietary changes-related normalization of the cardiometabolic profile is of direct influence on the myocardial response to sevoflurane.

Sevoflurane is known for its cardioprotective effects during myocardial ischemia and reperfusion, which seems blunted in the presence of obesity or type 2 diabetes mellitus. In **Chapter 6** we investigated whether a reduction in caloric intake reverses the deteriorating impact of western diet feeding on the cardioprotective potency of sevoflurane during ischemia and reperfusion. In contrast to our hypothesis, western diet itself protected the heart against ischemic injury, and this effect was maintained even after lowering caloric intake. Exposure to sevoflurane exerted cardioprotective effects in healthy conditions, but this effect was blunted in prediabetes. Plasma insulin levels suggested that the protective effects of diet feeding may be induced by insulin. Hyperinsulinemia was cardioprotective in healthy conditions, suggesting that the protective effects of western diet feeding or sevoflurane are mediated by insulin.

The main conclusions of this thesis are 1) sevoflurane induces cardiodepression without altering myocardial perfusion, 2) the cardiodepressive effects of sevoflurane are modulated by dietary composition, 3) the cardioprotective effects of sevoflurane during myocardial ischemia are altered by dietary intake, and 4) normalizing caloric intake reverses the cardiodepressive effects, but not the protective characteristics of sevoflurane. In **Chapter 7**, the conclusions are discussed and this chapter ends with future directions.