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Conclusions & General discussion

Patients undergoing surgery and anesthesia are at risk for perioperative cardiac complications, especially in the presence of comorbidities like obesity and type 2 diabetes mellitus. The inhalational anesthetic sevoflurane has been shown to have cardioprotective as well as cardiodepressive properties, which might be affected by metabolic alterations in the heart. While the cardioprotective effects are reduction of ischemia and reperfusion injury, the cardiodepressive effects are negative inotropic and lusitropic effects. In the present thesis we investigated the impact of dietary intake on perioperative myocardial perfusion, function and ischemia and reperfusion injury, thereby focusing on the interaction of dietary intake and sevoflurane anesthesia. We specifically hypothesized that anesthesia-induced changes in perioperative myocardial function are influenced by preoperative dietary alterations.

Critique of methods

We tested our hypotheses in instrumented, anesthetized rats. These rats received a standardized diet with a high concentration of saturated fatty acids and different percentages of simple carbohydrates to induce an obese/type 2 diabetic phenotype as a surrogate model for the human setting. This standardized diet improved the comparability of diet interventions within our studies. Overall, 4 weeks of high fat diet (HFD) feeding resulted in glucose intolerance with decreased HDL cholesterol (chapter 3), while 4 weeks of western diet feeding, a diet consisting of HFD with additional sucrose, resulted in obesity, hyperglycemia, hyperinsulinemia and hyperlipidemia, going from a glucose intolerant to a prediabetic rat model (chapter 5). Furthermore, these characteristics were extravagated when the duration of feeding was doubled from 4 to 8 weeks (chapter 4, 5 and 6). From these data we can conclude that western diet feeding simulates the human phenotype better than high fat diet feeding in rats.

Diet-induced models of obesity and diabetes are more human-like than other models, because obesity is based on excessive caloric intake.[1-3] Models such as the genetic Zucker or Zucker Diabetic Fatty rat are not representative for the human pathogenesis of obesity and type 2 diabetes mellitus due to a deficient leptin system, which is uncommon in humans.[4] Besides, it is important to realize that untreated type 2 diabetic patients are rare, and that most patients receive medication leading to mild or absence of hyperglycemia. The translational character of diet feeding in rats to humans is still under discussion. There is a large variation in content of the diet, time of feeding and strain used. Diets can vary in the source and percentages of fat and carbohydrates. However, in the present thesis western diet feeding represents a prediabetic phenotype in rats and closely mimics the human diet.

Our studies were performed in instrumented rats. Rats were anesthetized, endotracheally intubated and mechanically ventilated. During the experiments, ECG was recorded and arterial blood pressure was measured invasively. Moreover,

interventional techniques such as an oral glucose tolerance test to determine glucose tolerance, hyperinsulinemic euglycemic clamping to induce hyperinsulinemia, coronary occlusion to induce ischemia and reperfusion injury, and (contrast) echocardiography to determine myocardial perfusion and diastolic and systolic function have been performed. These techniques allowed standardized study conditions such as preservation of hypoglycemia during hyperinsulinemia.

All our results were obtained under strictly standardized conditions with respect to timing and composition of diet feeding. Nevertheless, as with all animal experiments extrapolation to the human setting has to be done with caution.

Major findings

Sevoflurane induces cardiodepression without altering myocardial perfusion

Under physiological conditions, myocardial blood flow and systolic function are in balance.[5] The supply of oxygen to the heart depends on the oxygen content in the blood and coronary blood flow. While oxygen content remains mostly constant, regulation of coronary blood flow is responsible for matching oxygen supply with metabolic demands. Major determinants of myocardial blood flow are perfusion pressure and coronary vascular resistance.

Under pathophysiological conditions, such as obesity and type 2 diabetes mellitus, the balance between energy supply and demand could be altered. The present thesis focused on the evaluation of dietary alterations on myocardial systolic function and blood flow. In high fat diet-induced glucose intolerant rats, myocardial perfusion and systolic function are not affected (chapter 3), whereas in western diet-induced prediabetic rats, myocardial perfusion and function are both declined when compared to control animals (chapter 4). This clearly suggests that the stage of diabetes plays a role in the development of cardiovascular alterations and that a reduction in myocardial contractility coincides with a reduction in coronary blood flow. In the context of these findings the question remains whether these myocardial alterations in prediabetic rats are additionally associated with changes in myocardial oxygen demand and supply. It is known that substrate metabolism of diabetic hearts shifts toward fatty acid utilization, which is paralleled by a decrease in glucose metabolism.[6] However, the consequence of increased use of fatty acids is a higher demand of ATP which requires more oxygen. In addition to possible alterations in oxygen supply and demand in the heart of prediabetic rats there are other pathophysiological mechanisms that may underlie the reduction in myocardial perfusion and function in our animal model. At first, cardiometabolic alterations may affect myocardial calcium handling.[7-10] The consequent reduction in contractility of the heart may also lead to alterations in myocardial blood flow. Secondly, myocardial relaxation is impaired in prediabetic rats, which might result in impairment of coronary perfusion. As shown in patients undergoing biventricular pacing, coronary

perfusion is dependent on a suction like effect during diastole, the so-called backward-traveling decompression effect.[11]

The present thesis showed that sevoflurane did not affect myocardial perfusion, while systolic function was decreased in healthy and prediabetic animals (chapter 4). This suggests that sevoflurane uncouples myocardial perfusion and function irrespective of the metabolic state of the heart. The uncoupling of perfusion and function is also observed after prolonged ischemia, which has been describes as a perfusion-contraction mismatch.[5] Moreover, sevoflurane exerts vasodilating properties, and is known to reduce coronary vascular resistance and perfusion pressure in addition to myocardial depression.[12-14] In addition, the vasodilating properties of sevoflurane are influenced by vasoactive mediators, such as nitric oxide.[15] Sevoflurane activates nitric oxide; however, altered nitric oxide availability can significantly impair myocardial perfusion-contraction matching.[16] Thus, sevoflurane seems to uncouple myocardial perfusion and contraction, however, up to now the mechanisms are unclear.

The cardiodepressive effects of sevoflurane are modulated by dietary composition

Sevoflurane exerts cardiodepressive properties in healthy subjects, therefore its perioperative use may cause hemodynamic alterations. It has been suggested that the interaction of sevoflurane with the heart is additionally altered by cardiometabolic diseases. With the growing epidemic of obesity and type 2 diabetes mellitus it is important to understand the influence of this condition on the interaction of sevoflurane with myocardial function. We found that high fat diet-induced glucose intolerance did not affect myocardial function during baseline conditions, whereas myocardial function was impaired during conditions of hyperemia (chapter 3). When prediabetes was induced in rats exposed to a diet high in saturated fatty acids and simple carbohydrates, a so-called western diet, we observed impairment of myocardial systolic and diastolic function (Chapter 4 and 5). Moreover, we found that sevoflurane is a stronger cardiodepressant in prediabetic rats than in control rats (chapter 4 and 5), which could be restored by lowering caloric intake (chapter 5). Suggested mechanisms are myocardial substrate metabolism and calcium handling. Proteins related to myocardial substrate metabolism, such as the protein kinase Akt[17] and glucose transporter 4[18] are increased by sevoflurane after ischemia and reperfusion, resulting in increased glucose and decreased fatty acid oxidation.[18] Moreover, sevoflurane reduces myocardial calcium availability[7] and affects sarcoplasmic reticulum calcium content.[7;19] These results suggest that normalization of the cardiometabolic profile by dietary changes are of direct influence on the myocardial response to sevoflurane in rats.

The cardioprotective effects of sevoflurane during myocardial ischemia are altered by dietary intake

Western diet, in combination with a sedentary lifestyle, is an important cause for overweight, obesity and type 2 diabetes mellitus.[1] Interestingly, while the overall negative consequences of western diet feeding for the development of cardiometabolic diseases are well acknowledged, there is increasing evidence that diets containing a high percentage of saturated fatty acids and simple carbohydrates may also be protective during stressful conditions, like surgery and anesthesia.[20]

In the present thesis we observed that western diet feeding itself exerted cardioprotective effects in the ischemic heart (Chapter 6). In animals, feeding a diet high in saturated fatty acids after myocardial ischemia showed preserved myocardial function even in the presence of insulin resistance, suggesting a possible protective effect of high fat diet feeding.[21;22] Interestingly, it has been suggested that overweight and obese patients exert a more appropriate inflammatory and immune response to stress, and have a better outcome that their lean or morbid obese counterparts.[20] However, it should be kept in mind that, despite macronutrient excess, obese patients remain at risk for perioperative nutritional deficits, such as iron deficiency, and the development of cardiovascular diseases.[20]

Moreover, we showed that sevoflurane exerted cardioprotective effects during myocardial ischemia and reperfusion in healthy rats. In agreement with our expectations, western diet feeding blunted the protective effects of sevoflurane during ischemia and reperfusion (Chapter 6). Western diet-induced cardioprotection was associated with a rise in plasma insulin levels, suggesting that insulin levels may be involved in the protective response of this diet (chapter 6). Besides a more appropriate inflammatory and immune response to stress, a possible mechanism might be hyperinsulinemia. Hyperinsulinemia is cardioprotective during ischemic stress.[23-28] Moreover, high fat diet feeding induces hyperinsulinemia as a compensatory mechanism. This hyperinsulinemia in the early phase of diabetes may therefore be a protective mechanisms during conditions of stress. Our experiments showed that hyperinsulinemia induced by a hyperinsulinemic euglycemic clamp mimicked the cardioprotective response as observed after western diet feeding (Chapter 6). These exciting and potentially also clinically relevant findings warrant future studies in humans.

Normalizing the caloric intake reverses the cardiodepressive effects, but not the protective characteristics of sevoflurane

Perioperative cardiac complications are an economical, medical and social burden that warrants optimization of perioperative health and cardiovascular care to improve patient outcome and reduce health care costs. Preoperative treatment of obesity and type 2 diabetes mellitus may reduce perioperative cardiac complications. Current therapies directed at reducing these risk factors focus on weight loss. Weight

loss is induced by a negative energy balance, such as dietary interventions, physical activity, pharmacotherapy and surgery.[29] Lifestyle interventions, such as changing dietary intake and increasing physical activity to improve insulin sensitivity and glucose control in obese and type 2 diabetic patients is an important part of these treatments.[30;31] The evidence for their benefits is nowadays growing and might reduce perioperative complications and improve short and long-term outcome.

Hyperglycemia, which may be triggered by the stress condition of anesthesia and surgery, is a strong predictor for morbidity and mortality after non-cardiac procedures, while high perioperative glucose variability enhances this risk even further.[32-34] Lowering of the incidence of perioperative hyperglycemia in obese and type 2 diabetic patients may therefore contribute to improved patient outcome and reduced health care costs after surgery.[35] Although the benefits of lifestyle interventions to improve the incidence of intraoperative hyperglycemia are increasingly acknowledged, it may be expected that these interventions also modulate anesthesia-related physiological alterations.

The present thesis showed that lowering caloric intake improved myocardial systolic and diastolic function (chapter 5 and 6) and that the cardioprotective effect of western diet feeding during ischemia and reperfusion is sustained (chapter 6). Further, sevoflurane induced cardiodepression was normalized (chapter 5), whereas sevoflurane had no additional cardioprotective effect on ischemia and reperfusion injury (chapter 6). Although studies focusing on preoperative dietary changes in humans are limited,[36] the overall idea is that weight loss reduces risk factors such as diabetes and cardiovascular disease and extends lifespan and reduces mortality. Besides the possibility of the sustained cardioprotective effect of western diet feeding, it is also known that caloric restriction protects against ischemia and reperfusion injury.[36] Mitchell *et al.* reviewed the feasibility and benefits of caloric restriction and concluded that caloric restriction has a wide range of benefits against surgical stress in the experimental setting, which might also account in the human setting.[36] One of the suggested underlying mechanisms is reduced insulin signaling. Improvement of insulin signaling by caloric restriction results in improved insulin sensitivity. This might also be an underlying mechanism in improved cardiometabolic state of western diet-induced prediabetic rats. Overall, dietary modulation by lowering caloric intake may have a wide range of benefits including improved insulin sensitivity, altered cardiometabolic state and reduced injury during stress.

Future directions

Laboratory investigations already studied the cardioprotective properties of volatile anesthesia for many years.[37] However, the clinical applicability in modulating the risk of perioperative cardiovascular complications by volatile anesthetics is still an ongoing debate.[38] Several experimental studies showed the protective effects of volatile anesthetics in human heart tissue. However, recent clinical studies suggest that propofol and volatile anesthetics are associated with a comparable incidence of cardiac events. Therefore further research based on large clinical trials is necessary to conclude on the possible beneficial effects of volatile anesthesia on the heart and outcome. Moreover, clinical studies need to be performed to investigate the effects of volatile anesthetics during myocardial infarction in obese and/or type 2 diabetic patients.

Secondly, drugs might modulate the sensitivity of the heart for ischemic injury, such as drugs for improvement of insulin sensitivity by glucagon-like peptide 1 (GLP-1) or metformin. GLP1 is a gut incretin hormone that is released in response to nutrient intake, stimulates insulin secretion and exerts insulinotropic and insulinomimetic properties. Metformin is a biguanide with antihyperglycemic properties and exerts its actions by enhancing insulin sensitivity. Improvement of the diabetic phenotype might improve the cardioprotective effects of volatile anesthesia during ischemia and reperfusion.

Thirdly, we found the protective effects of western diet feeding on ischemia and reperfusion injury. One of the suggested mechanisms is the presence of metabolic alterations, such as hyperinsulinemia, during ischemic stress. Several studies showed a cardioprotective effect of insulin in healthy animals and patients with myocardial infarction. However, the question remains if insulin administration has protective effects in the diabetic heart, due to the presence of insulin resistance. Future studies using insulin blockers need to be performed to prove the beneficial effects of hyperinsulinemia during ischemia and reperfusion in the prediabetic heart.

Conclusions

Patients with obesity and/or diabetes are at increased risk for perioperative cardiovascular complications. Moreover, the choice of anesthetic may modulate the risk of these perioperative cardiovascular complications. In the present thesis we focused on the modulation of dietary intake on sevoflurane-induced alterations in myocardial perfusion and function in rats. Moreover, we investigated whether the cardioprotective effect of sevoflurane is altered by diet composition, and whether changing the dietary balance by lowering fat and sucrose intake could be useful as an intervention to influence the effects of sevoflurane on the heart.

Sevoflurane induces cardiodepression without altering myocardial perfusion

In healthy control rats, sevoflurane resulted in reduced systolic function without altering myocardial blood flow, leading to uncoupling of cardiac systolic function and perfusion (Chapter 4).

The cardioprotective effects of sevoflurane are modulated by dietary composition

Rats exposed to a diet high in saturated fatty acids (HFD) developed glucose intolerance, however this phenotype was not associated with alterations in myocardial perfusion and function (Chapter 3). Though, after induction of hyperemia, we observed a reduction in myocardial systolic function in rats fed a high fat diet (HFD) without alterations in myocardial perfusion when compared to control animals (Chapter 3). When rats were exposed to a diet high in saturated fatty acids and simple carbohydrates, a so-called western diet (WD), we observed glucose intolerance and impairment of myocardial perfusion and function at baseline when compared to control animals (Chapter 4 and 5). In the presence of sevoflurane, the reduction in myocardial systolic function in rats fed a western diet (WD) was even more pronounced, while sevoflurane did not alter myocardial perfusion (Chapter 4 and 5).

The cardioprotective effects of sevoflurane during myocardial ischemia are altered by dietary intake

Sevoflurane exerted cardioprotective effects during myocardial infarction and reperfusion in healthy rats. In agreement with our expectations, western diet feeding blunted the protective effects of sevoflurane during ischemia and reperfusion (Chapter 6). More interestingly, western diet feeding itself exerted cardioprotective effects in the ischemic heart (Chapter 6). Western diet-induced cardioprotection was associated with a rise in plasma insulin levels, suggesting that insulin levels may be involved in the protective response of this diet. Separate experiments showed that hyperinsulinemia induced by a hyperinsulinemic euglycemic clamp mimicked the cardioprotective response as observed after western diet feeding (Chapter 6).

Normalizing the caloric intake reverses the cardiodepressive effects, but not the protective characteristics of sevoflurane

Rats subjected to diet reversal, which comprised a period of normal healthy diet following western diet feeding, showed normalization of their prediabetic phenotype. (Chapter 5) This was associated with improvement of cardiac systolic as well as diastolic function (Chapter 5) and a reduction in the cardiodepressive effects of sevoflurane (Chapter 5). While western diet had a protective effect against ischemia and reperfusion injury, lowering caloric intake did not alter the cardioprotective effect of western diet feeding during ischemia and reperfusion (Chapter 6). Moreover, the absence of sevoflurane-induced cardioprotection during myocardial infarction in western diet fed rats could not be restored by diet reversal (Chapter 6).

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