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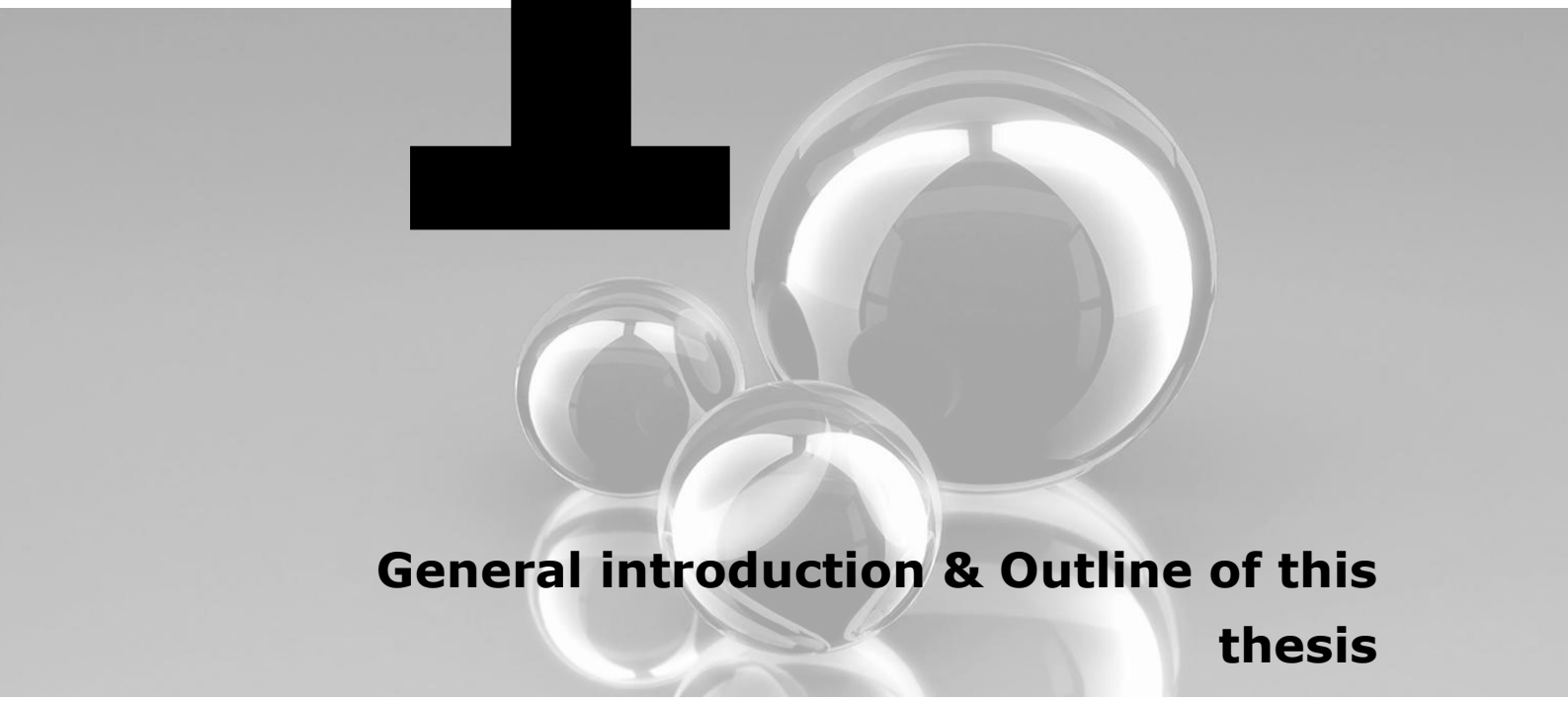

General introduction & Outline of this thesis

Perioperative cardiovascular risks

In the Netherlands, about 1.3 million surgical procedures are performed every year under general or locoregional anesthesia. Surgery and anesthesia are associated with alterations in systemic and regional perfusion and oxygenation. These alterations are due to the cardiovascular effects of anesthetics, loss and replacement of intravascular volume, mechanical positive pressure ventilation and application of vasoactive drugs. Although the mortality risk of surgery and anesthesia is nowadays considerably low, patients are still at risk for perioperative cardiovascular complications. Bainbridge *et al.* showed a total perioperative mortality of 0.12% and anesthetic-related mortality of 0.0034% in the 1990s-2000s in developed and developing countries.[1] The risk for cardiovascular complications increases with age and in the presence of comorbidities like heart disease, pulmonary disease or diabetes mellitus.[2-4] Other well-known predictors of perioperative cardiac complications are coronary disease, angina pectoris, prior myocardial infarction, heart failure, stroke/transient ischemic attack, renal dysfunction and diabetes mellitus requiring insulin therapy.[4;5] It is estimated that cardiovascular complications like myocardial infarction and cardiac arrest occur in 2-5% of all noncardiac surgical procedures, and globally affect 5-12 million patients each year.[4;5]

Myocardial ischemia and reperfusion

The most common cardiovascular complication during or after noncardiac surgery is the development of myocardial ischemia,[4;5] which is associated with a significant risk for morbidity and mortality. Myocardial ischemia occurs when coronary perfusion is inadequate to maintain a sufficient oxygen supply/demand ratio in the heart. During surgery, maintenance of the myocardial oxygen balance is challenged by anesthetics and surgical stress, which directly affect myocardial oxygen supply and consumption. This altered balance may increase the risk of myocardial ischemia.[6;7]

While the silent nature of perioperative myocardial ischemia hampers its diagnosis, Landesberg *et al.* showed that patients with a large increase in troponin following major surgery are at risk for cardiac complications and unfavorable outcome.[8] More recently, McFalls *et al.* described that perioperative elevated cardiac troponin levels strongly predict long-term mortality.[9] From these findings it might be concluded that myocardial ischemia is often present during and after surgery, and prevention of an oxygen supply/demand mismatch may contribute to improved postoperative outcome.

Volatile anesthesia

There is an ongoing debate whether the type of anesthesia could modulate the risk of perioperative cardiovascular complications. Surgical procedures under general

anesthesia are either performed using intravenous anesthetics, like propofol, or inhalational anesthesics using volatile agents like isoflurane or sevoflurane. Volatile anesthetics are acknowledged for their cardioprotective effects, which consist of preservation of cardiovascular function in case of reduced tissue oxygenation.

Volatile anesthetics exert several effects on the heart, peripheral vasculature and the autonomic nervous system. Sevoflurane alters calcium (Ca^{2+}) handling in the heart. To be more specific, sevoflurane reduces myocardial Ca^{2+} availability and increases sarcoplasmic reticulum Ca^{2+} content,[10] depresses Ca^{2+} currents,[11] reduces Ca^{2+} influx via the L-type Ca^{2+} channels[12] and increases Na^{+}/Ca^{2+} exchanger-mediated Ca^{2+} influx.[13] In addition, sevoflurane prolongs the QT interval, thereby prolonging ventricular repolarization.[14;15] Moreover, inhalation of volatile anesthetics causes a dose-dependent decrease in blood pressure, mainly due to a reduction in systemic vascular resistance.[16] In healthy humans, sevoflurane decreases myocardial blood volume and hyperemic blood flow, while myocardial blood flow during baseline conditions is not affected.[17] Further effects of volatile anesthetics on the heart are negative inotropic effects, such as depressed myocardial contractility and lusitropic effects reflected by early diastolic dysfunction.[18-20] One might expect that, due to the general effects of volatile anesthetics on the heart, anesthesia may be associated with a changed balance between myocardial pefusion and function, although this has been rarely investigated.

Cardiometabolic disease

Patients with lifestyle risk factors, such as excessive caloric intake and a sedentary lifestyle, which both contribute to the development of obesity and type 2 diabetes mellitus, even show a higher risk for postoperative morbidity and mortality in case of perioperative myocardial ischemia.[3;4;9;21] Worldwide, more that 1.4 billion adults were overweight in 2008, and of these over 500 million people were obese. Moreover, 344 million people suffer from impaired glucose tolerance, whereas 366 million patients are diagnosed with type 2 diabetes mellitus.[22] It is expected that by the year 2030 almost 400 million people suffer from impaired glucose tolerance and 552 million people from diabetes.[22]

The higher risk for the development of perioperative myocardial ischemia in patients with obesity and type 2 diabetes mellitus may partly be due to reduced coronary vasodilation in response to pharmacological stimuli, atherosclerosis, oxidative stress and insulin resistance.[23-25] With the expanding epidemic of obesity and type 2 diabetes mellitus it is therefore expected that the number of patients that are prone to develop perioperative myocardial ischemia will increase within the next decades. The number of studies focusing on the impact of cardiometabolic disease on myocardial perfusion and function during anesthesia is however limited, and the underlying pathophysiology is not well understood.

Dietary intake

While obesity and type 2 diabetes mellitus are acknowledged as factors that accelerate the risk of perioperative myocardial ischemia, there is only limited information available with respect to the association between the development of cardiometabolic disease with myocardial perfusion, function and ischemia and reperfusion injury. It is commonly acknowledged that excessive caloric intake, in combination with a sedentary lifestyle, is the main contributor to the development of obesity and type 2 diabetes mellitus. Most lifestyle programs therefore focus on changes in dietary behavior in combination with physical activity. In addition to the number of calories that contribute to the development of cardiometabolic disease, there is increasing interest in the role of dietary composition on the development of cardiometabolic disease. A western or cafetaria diet, which is characterized by a high percentage of saturated fatty acids and simple carbohydrates such as fructose or sucrose, is one of the most common causes for overweight, obesity and diabetes mellitus. Animal studies provide evidence that excessive availability of dietary lipids or simple carbohydrates leads to accumulation of metabolic intermediates, thereby inducing myocardial insulin resistance and impairment of myocardial function.[26-29] In humans, myocardial triglyceride accumulation is associated with alterations in myocardial function and has been demonstrated to occur in the diabetic heart.[30] During normal physiologic conditions the heart derives its energy requirements from fatty acid oxidation (60-70%), glucose oxidation (30-40%) and amongst others, lactate (10%). However, this process is restricted as myocardial substrate metabolism is largely determined by the availability of the substrate.[31-35] The above described observations contribute to the emerging concept that myocardial substrate metabolism is closely related to myocardial function. Moreover, in case of surgical stress and anesthesia, diet-induced alterations in myocardial substrate metabolism may become more abundant with respect to the balance between the supply and demand of oxygen and cellular nutrients. It might therefore be interesting to investigate how modulation of dietary intake influences the susceptibiltiy of the heart to injury, and whether the protective effects of anesthetic strategies may be altered by dietary composition.[31-35]

Interestingly, while the negative consequences of obesity and type 2 diabetes mellitus for the development of cardiometabolic diseases are well acknowledged, there is increasing evidence that overweight and obesity may also be protective in case of postoperative risks,[36] the so-called obesity paradox. The counterintuitive observations suggest that the unfavorable cardiometabolic effects of high intake of saturated fatty acids may shift towards a beneficial condition in case of stress. Moreover, recent studies suggest that a change in diet before surgery and anesthesia may be of influence on the risk of postoperative complications.[37] Animal studies further showed that short-term dietary restrictions before surgical stress are

associated with improved insulin sensitivity, oxidative protection and organ preservation during ischemia and reperfusion injury.[38;39] It is however unknown whether dietary changes in the period before exposure to an anesthetic procedure may alter the effects of volatile anesthetics on myocardial perfusion, function and injury.

Aim of this thesis

In the light of these considerations, the present thesis particularly focuses on the interaction of the volatile anesthetic sevoflurane with myocardial perfusion, systolic function as well as ischemia and reperfusion injury in rats exposed to a normal healthy or a western diet. Myocardial perfusion and function were studied using echocardiography as a noninvase technique for the monitoring of myocardial systolic and diastolic function. The use of a contrast agent expands the use of the technique for determination of myocardial perfusion.

We hypothesized that sevoflurane-induced changes in myocardial perfusion and function are distinctly influenced by preoperative dietary composition. Moreover, we tested the hypothesis that a high intake of saturated fatty acids in combination with simple carbohydrates alters the cardioprotective effects of sevoflurane in case of myocardial ischemia and reperfusion. The specific aims per chapter are summarized below.

Outline of the thesis

This thesis focuses on the effect of dietary changes on myocardial function, perfusion and injury during sevoflurane anesthesia. In **chapter 2** the effects of volatile anesthetics, diabetes and perioperative ischemia on myocardial substrate metabolism are reviewed.

In **chapter 3**, we studied the effect of high fat diet feeding on myocardial perfusion and function with (contrast) echocardiography. We used dipyridamole infusion to induce conditions of hyperemia. **Chapter 4** describes the effects of a more severe, western diet on myocardial perfusion and function. Additionally, the effects of sevoflurane were studied.

Furthermore, we studied the effect of changing dietary intake on myocardial function and myocardial ischemia and reperfusion injury. **Chapter 5** was designed to study the effect of dietary alterations in combination with sevoflurane exposure on myocardial function. In **Chapter 6** the hypothesis that the cardioprotective effects of sevoflurane on myocardial ischemia and reperfusion injury are reduced by western diet-feeding has been tested.

Finally, **Chapter 7** provides a general discussion of the findings presented in this thesis and places these findings in perspective.

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