Chapter 8

Discussion
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This chapter discusses the results in this thesis by describing main findings, clinical implications and future perspectives, and by making conclusions.

The aims of this thesis were to improve identification of undernutrition and to explore the effect of the arginine/asymmetric dimethylarginine (ADMA) ratio and nutrition during surgery in patients with cardiovascular failure.

Main findings
In Chapter 1 the current way of screening and assessment of undernutrition in cardiac surgery is shortly described. It was stated that the identification of undernourished cardiac surgical patients has to be improved as the currently used screening tools do not accurately identify these patients. Therefore, the study described in Chapter 2 evaluated a new screening tool for undernutrition in cardiac surgery; the Cardiac Surgery-Specific Undernutrition Screening Tool (CSSUST). The CSSUST includes the aetiology-based items reduced food intake and inactivity, and turned out to be superior to the existing tools [1] in identifying undernutrition in patients undergoing cardiac surgery. When identified to be at high risk for undernutrition by a screening tool like the CSSUST, the patient is referred to the dietitian who will perform the diagnostic assessment including body composition measurements. Both a low fat free mass (FFM) (i.e. undernutrition) and a high FM (i.e. obesity) have been associated with adverse outcome in cardiac surgical patients. Chapter 3 described the results of the study in which the association between a combination of a low FFM index (FFMI) and high FM index (FMI), so-called sarcopenic obesity (SO), and adverse clinical outcome was investigated. It was shown that preoperative SO was associated with an increased occurrence of infections after cardiac surgery. It turned out that one quarter of those patients with a low FFMI are obese, patients who might not be recognised to be undernourished but are at aggravated risk of adverse postoperative outcome. Furthermore, the study described in Chapter 3 showed that SO was characterized by low handgrip strength (HGS). Especially the FFM part of SO correlated with HGS while FM did not. Finally, a low HGS was independently associated with a prolonged time of mechanical ventilation. To further improve assessment of undernutrition, we investigated whether the bioelectrical impedance phase angle (PA) could help to indentify undernutrition (Chapter 4). Indeed, this study showed that a preoperative low PA was associated with undernutrition, and an increased risk of prolonged intensive care and hospital length of stay, and could therefore be useful in the assessment of undernutrition.

In Chapter 1 we described that previous studies considered ADMA not only as risk factor of cardiovascular disease but also as indicator of clinical outcome in patients with cardiac dysfunction. This suggestion is supported by the results we found in septic and cardiogenic shock patients described in Chapter 5. In these patients, a low arginine/ADMA
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Ratio was associated with circulatory failure, organ failure, severe disease and increased the risk of mortality while arginine and ADMA separately were not. Therefore, we proposed a pathophysiological mechanism in shock: a low arginine/ADMA ratio contributes to endothelial and cardiac dysfunction resulting in poor organ perfusion and organ failure thereby increasing the risk of death. In Chapter 6, we investigated whether nutrition before, during, and after surgery could increase the arginine/ADMA ratio and amino acids and whether this increase affected myocardial glucose metabolism. In this randomized controlled intervention trial of patients undergoing CABG, it was found that enteral or parenteral nutrition before and during surgery can increase concentrations of arginine/ADMA in the human heart. In plasma, nutrition increased levels of both arginine/ADMA and branched chain amino acids (BCAA). Furthermore, an increase in plasma arginine/ADMA was associated with an increase in myocardial glucose metabolism. These findings suggested that the arginine/ADMA ratio and thus NO availability are linked to myocardial glucose metabolism. We proposed the following mechanism; revascularization in combination with the extra flow induced by a higher arginine/ADMA ratio and concomitant NO elevation further improves access of substrates to cardiac cells reflected by an increase in glucose uptake. As pre- and postoperative nutrition has been shown to diminish the inflammatory response, we investigated whether nutrition before, and during surgery could affect myocardial inflammation. Furthermore, the inflammatory response of the heart itself during (cardiac) surgery has never been described. Chapter 7 fulfilled this gap and found a minor change in the inflammatory response in myocardial atrial tissue during off-pump coronary artery bypass grafting (CABG) as only the amount of lymphocytes significantly decreased in myocardial tissue. Furthermore, we found that supplementation of nutrition during surgery did not reduce or induce an inflammatory response in myocardial tissue in patients undergoing off-pump CABG.

Clinical implications & Future perspectives
Currently, undernutrition is determined when patients are admitted for surgery or sometimes after surgery. About two weeks of nutritional treatment is advised to improve postoperative outcome in undernourished patients [2]. As most patients planned for cardiac surgery have to wait for several weeks for their surgery, there is time to start therapies to improve nutritional status preoperatively [1,3]. Therefore, a fundamental switch is needed in which undernutrition is determined at the time patients are accepted for surgery. This switch creates the opportunity to treat undernutrition during the weeks patients are waiting for their surgery. For now, we advise to use the CSSUST to correctly screen for undernutrition in all cardiac surgical patients in the preoperative period. When identified to be at high risk for undernutrition by the CSSUST, we advocate undernutrition assessment that includes BIS measurement to determine body composition (i.e. FFMI and FMI) and PA, and functional measurement by HGS. After undernutrition has been
diagnosed, nutritional intervention can be started. However, it should be mentioned that studies investigating the effect of nutritional interventions on body composition, PA and HGS in cardiac surgical patients are not performed yet. As the results of the CSSUST-study suggested that both reduced food intake and physical inactivity are involved in the aetiology of undernutrition, the combination of nutrition and physical exercise to treat undernutrition might be particularly effective in patients undergoing cardiac surgery. Indeed, nutritional interventions are shown to be most effective together with anabolic stimuli such as physical activity [4-8]. Especially for those with SO, an increase of FFM together with FM loss might be advantageous for postoperative outcome. Therefore, protein-rich supplements in combination with exercise training might induce favourable effects for cardiac surgical patients. In addition, restarting both nutritional and exercise interventions after surgery might enhance recovery. In cardiac rehabilitation and in elderly, physical exercise have already been shown to be safe [9,10]. Exercise and/or dietary interventions appeared to be effective on preventing SO in breast cancer patients [11], reduced postoperative infections in cardiac surgical patients [12], and reduced weight loss and improved HGS and quality of life in acute stroke patients at nutritional risk [13]. Unfortunately, clinical studies investigating the effect of both nutrition and physical exercise interventions on body composition and clinical outcome in cardiac surgery are absent. Future studies should investigate these important topics.

A high plasma ADMA is recognized to be a risk factor for cardiovascular disease and an indicator of clinical outcome in these patients. In addition to measuring plasma ADMA, we advocate measuring plasma arginine in order to determine the arginine/ADMA ratio as indicator of NO availability. Patients with cardiovascular dysfunction having a low arginine/ADMA ratio are more prone to have circulatory failure, organ failure, severe disease, and have an increased risk of mortality. The optimal cut-off value for a low arginine/ADMA ratio for surgical and critically ill patients has to be determined in future studies.

Our randomized controlled trial was the first study investigating the effect of nutrition before, during, and after surgery on the heart, and found increases in myocardial and plasma arginine/ADMA ratio and plasma BCAA. The increase in plasma arginine/ADMA ratio was related to improved myocardial glucose metabolism. In our study, a minor myocardial inflammatory response was seen during off-pump CABG which was not influenced by nutrition before and during surgery. We safely supplemented enteral or parenteral nutrition during surgery by which fastening was avoided. Therefore, this study paves the way to further investigate the possibilities of nutrition during surgery. Parenteral nutrition was given by a peripheral inserted central catheter which is a less-invasive alternative to other central venous catheters that can be introduced at bedside. Enteral nutrition was given by a computerized guidance system-placed nasoduodenal tube which makes an endoscopic procedures unnecessary [14]. Our study did not show relevant differences between parenteral and enteral nutrition. Compared to parenteral nutrition,
enteral nutrition maintains gastrointestinal integrity and thereby immunocompetency, and is associated with fewer infections [2]. Hence, the enteral route is preferred to the parenteral route. Therefore, in order to avoid a fastening period in surgical patients with proper gut functioning, we advise to supply enteral nutrition during surgery given by a (computerized guidance system-placed) nasoduodenal tube. Future studies should investigate whether continuing of nutritional interventions during surgery is beneficial for postoperative recovery.

In summary, future research should focus on investigating the effects of nutrition and exercise interventions before and after surgery while continuing nutrition during surgery, on clinical parameters.

General conclusion
Undernutrition is a common problem in cardiac surgery and needs to be identified and treated, as it increases the risk of worse clinical outcome. Based on the results described in this thesis, we advise to optimize screening of undernourished cardiac surgery patients by using the CSSUST. For undernutrition assessment, we recommend performing body composition analysis by bioelectrical impedance to measure FFM and the PA, and muscle function measurement by HGS, in both non-obese and obese patients. Plasma arginine/ADMA ratio can help to evaluate cardiovascular function and prognosis, and nutrition during surgery can increase this ratio in the myocardium and plasma which may improve myocardial glucose metabolism. A minor myocardial inflammatory response was seen during off-pump CABG which was not influenced by nutrition before and during surgery. Research is needed to investigate the effect of nutritional and exercise interventions, and nutritional supplementation during (cardiac) surgery on clinical outcome.
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