Assessment and management of bariatric surgery patients

Tomi Pösö
"Kaiken viisauden alku on tosiasioiden tunnustaminen.”
“The beginning of all wisdom is the confession of the facts.”

J.K. Paasikivi
The president of Finland, 1946 - 1956.

This work is dedicated to my Family.
# Table of Contents

Table of Contents  
Preface  
Abstract  
List of papers  
Abbreviations  
Sammanfattning på svenska/ Summary in Swedish  
Introduction  
Background  
Method  
The aims of the thesis  
Results  
Discussion  
Conclusions  
Future implications  
Acknowledgements  

---

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of Contents</td>
<td>i</td>
</tr>
<tr>
<td>Preface</td>
<td>iii</td>
</tr>
<tr>
<td>Abstract</td>
<td>iv</td>
</tr>
<tr>
<td>List of papers</td>
<td>v</td>
</tr>
<tr>
<td>Abbreviations</td>
<td>vi</td>
</tr>
<tr>
<td>Sammanfattning på svenska/ Summary in Swedish</td>
<td>viii</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>1</td>
</tr>
<tr>
<td>Obesity – the perioperative challenge</td>
<td>3</td>
</tr>
<tr>
<td>Background</td>
<td>4</td>
</tr>
<tr>
<td>Preoperativ surgical optimization</td>
<td>4</td>
</tr>
<tr>
<td>Impact of obesity on physiology – an anesthesiological point of view</td>
<td>5</td>
</tr>
<tr>
<td>Obesity and the respiratory system</td>
<td>5</td>
</tr>
<tr>
<td>Obesity and the cardiovascular system</td>
<td>7</td>
</tr>
<tr>
<td>Pharmacological aspects and anesthetic drugs in obesity</td>
<td>11</td>
</tr>
<tr>
<td>Airway management, positioning, preoxygenation and perioperative oxygenation</td>
<td>17</td>
</tr>
<tr>
<td>Monitoring strategies and fluid management</td>
<td>21</td>
</tr>
<tr>
<td>Intra-abdominal pressures and pneumoperitoneum in morbid obesity</td>
<td>24</td>
</tr>
<tr>
<td>Postoperative considerations in bariatric surgery</td>
<td>24</td>
</tr>
<tr>
<td>The aims of the thesis</td>
<td>26</td>
</tr>
<tr>
<td>Methods</td>
<td>27</td>
</tr>
<tr>
<td>Study design and etics</td>
<td>27</td>
</tr>
<tr>
<td>Patients and methods</td>
<td>27</td>
</tr>
<tr>
<td>Anesthesia and preoxygenation techniques used in this thesis</td>
<td>28</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>31</td>
</tr>
<tr>
<td>Fluids</td>
<td>36</td>
</tr>
<tr>
<td>Inotropic and vasoactive drugs</td>
<td>37</td>
</tr>
<tr>
<td>Paper I</td>
<td>37</td>
</tr>
<tr>
<td>Paper II</td>
<td>37</td>
</tr>
<tr>
<td>Paper III</td>
<td>39</td>
</tr>
<tr>
<td>Paper IV</td>
<td>40</td>
</tr>
<tr>
<td>Statistics</td>
<td>43</td>
</tr>
<tr>
<td>Limitations</td>
<td>43</td>
</tr>
<tr>
<td>Results</td>
<td>45</td>
</tr>
<tr>
<td>Discussion</td>
<td>56</td>
</tr>
<tr>
<td>Conclusions</td>
<td>63</td>
</tr>
<tr>
<td>Future implications</td>
<td>64</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>66</td>
</tr>
<tr>
<td>Economical support</td>
<td>67</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Permissions and reprints</td>
<td>67</td>
</tr>
<tr>
<td>References</td>
<td>68</td>
</tr>
</tbody>
</table>
Preface

Every individual has right to medical care of high quality achieved by best-practise methods regardless of age, ethnicity, race, color or body mass index (BMI). During recent decades, patient characteristics have changed significantly. The number of patients with overweight, obesity and severe obesity with concomitant comorbidities has increased substantially in anesthesia practice and intensive care. This presents a challenge for the entire perioperative staff.

The basis for an acceptable outcome is awareness of the perioperative concerns that may arise in patients with a high BMI. In severe obesity uncontrolled airway or hemodynamic instability may lead rapidly to deleterious consequences. Thus, safe, reproducible and thoroughly implemented methods for airway control, fluid management, drug dosing and monitoring are addressed in these individuals.

To manage these issues may be an awkward perioperative challenge, but is definitely a part of anesthesia practice worldwide today. With this thesis, I hope to increase knowledge and improve understanding of the key issues in morbid obesity from an anesthesiological point of view.

At last, I will express my motivation and source of inspiration for this work by quoting the words of Mark Twain: “Twenty years from now you will be more disappointed by the things you didn’t do than by the ones you did do. So throw off the bowlines, sail away from the safe harbor. Catch the trade winds in your sails. Explore. Dream. Discover.”

Luleå, Sweden, the 16th of January, 2014

Tomi Pösö
Abstract

**Background:** In morbidly obese individuals (MO) cardiorespiratory comorbidities and body habitus challenge the perioperative management of anesthesia. To implement safe and reproducible routines for anesthesia and fluid therapy is the cornerstone in order to minimize anesthesia-related complications and to meet individual variability in rehydration needs. **Methods:** Paper I: Impact of rapid-weight-loss preparation prior to bariatric surgery was investigated. Prevalence of preoperative dehydration and cardiac function were assessed with transthoracic echocardiography (TTE). Paper II: The anesthetic technique for rapid sequence induction (RSI) in MO based on a combination of volatile and i.v. anesthetics was developed. Pre- and post-induction oxygenation, blood pressure levels and feasibility of the method was evaluated. Paper III: The preoperative ideal body weight based rehydration regime was evaluated by TTE. Paper IV: Need of rehydration during bariatric surgery was evaluated by comparing conventional monitoring to a more advanced approach (i.e. preoperative TTE and arterial pulse wave analysis). **Results:** Rapid-weight-loss preparation prior to bariatric surgery may expose MO to dehydration. TTE was shown to be a robust modality for preoperative screening of the level of venous return, assessment of filling pressures and biventricular function of the heart in MO. The combination of sevoflurane, propofol, alfentanil and suxamethonium was demonstrated to be a safe method for RSI regardless of BMI. The preoperative rehydration regime implemented by colloids 6 ml/kg IBW was an adequate treatment to obtain euvolemia. In addition, preoperative rehydration seems to increase hemodynamic stability during intravenous induction of anesthesia and even intraoperatively. **Conclusion:** This thesis describes a safe and comprehensive perioperative management of morbidly obese individuals scheduled for bariatric surgery. Hemodynamic and respiratory stability can be achieved by implementation of strict and proven methods of anesthesia and fluid therapy. Much focus should be placed on feasible monitoring and preoperative optimization in morbidly obese individuals for increased perioperative safety.

**Keywords:** Bariatric surgery, morbid obesity, anesthesia, echocardiography, fluid therapy, preoperative, perioperative, venous return, rehydration, volatile rapid sequence induction, spontaneous breathing, sevoflurane.
List of papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


Abbreviations

CG, control group
CO, cardiac output
CI, cardiac index
IAP, intra-abdominal pressure
IBW, ideal body weight
LBW, lean body weight
MO, morbidly obese patients
NIBP, non-invasive blood pressure
OSAS, obstructive sleep apnoea syndrome
OHS, obesity hypoventilation syndrome
PONV, postoperative nausea and vomiting
RAP, right atrial pressure
RSI, rapid sequence induction
RYGB, Roux-en-Y gastric bypass
RWL, rapid weight loss
SAP, systolic arterial pressure
SpO2, peripheral saturation
MAP, mean arterial pressure
SV, stroke volume
ΔSV, change of stroke volume
SVV, stroke volume variation
TBW, total body weight
VC, volume challenge
VR, venous return

**Abbreviations for Echocardiography:**

A4C, apical 4-chamber projection
A2C, apical 2-chamber projection
DD, diastolic dysfunction
EF, ejection fraction
FS, fractional shortening
IVC, inferior vena cava
IVCCI, inferior vena cava collapsibility index
LV, left ventricle
LVEDA, left ventricular end-diastolic area
LVESA, left ventricular end-systolic area
LVOT, left ventricular outflow tract
LVOTd, left ventricular outflow tract diameter
PLAX, parasternal long axis projection
PW, pulsed-wave Doppler imaging
RV, right ventricle
SAX, parasternal short axis projection
TAPSE, tricuspid annular plane systolic excursion
TDI, tissue Doppler imaging
TTE, transthoracic echocardiography
Sammanfattning på svenska/ Summary in Swedish

Bakgrund
Förekomst av fetma (body mass index, BMI ≥ 30 kg/m²) och sjuklig fetma (BMI ≥ 35 kg/m²) har ökat dramatiskt globalt. Till följd av detta har överviktskirurgi blivit ett allt vanligare ingrepp. I Sverige har antalet operationer ökat tiofaldigt under det senaste decenniet, och de senaste åren har det opererats upp emot 9000 patienter nationellt. Fetma, särskilt sjuklig fetma, anses vara en viktig faktor bakom ökad morbiditet och mortalitet i kardiovaskulära och respiratoriska sjukdomar, hjärtsvikt, diabetes och njursvikt. Perioperativt omhändertagande av patienter med sjuklig fetma är utmanande på grund av ovanstående komorbiditeter samt en patologisk kroppskonstitution. Risk för hjärt- och lungrelaterade komplikationer ökar vid högt BMI jämfört med individer med ett normalt BMI vid operativa ingrepp.

Några vedertagna rutiner för optimal narkos och vätskeersättning vid överviktskirurgi finns ej i nuläget. Således, utveckling av patientsäkra metoder för både narkos och vätsketerapi är hörnstenar för att minimera perioperativa anestesirelaterade komplikationer i denna patientgrupp.

Syfte
Syftet i avhandlingen var att utveckla en hemodynamiskt och respiratoriskt stabil metod för induktion av anestesi i sjukligt obesa individer, och att etablera rutiner för att erhålla normalt venöst återflöde under en överviktskirurgisk operation.

Metoder

viii
Ett individualiserat protokoll för rehydrering ("individualized goal directed therapy") implementerades med hjälp av preoperativt transthorakalt hjärtultraljud och intraoperativt arteriell pulsvågsanalytsteknik.

**Resultat**

**Konklusioner**
Perioperativ kardiovaskulär och respiratorisk stabilitet vid sjuklig fetma kan nås genom att implementera noggranna och beprövade metoder för anestesi och vätsketerapi. Icke- eller miniinvasiv monitorering och målstyrda vätskeersättningsprotokoll bör nyttjas inom överviktskirurgi för perioperativ hemodynamisk stabilitet, och för att nå optimal grad av venöst återflöde. Stort fokus bör läggas på preoperativ optimering av cirkulation och lungfunktion för hög patientsäkerhet vid sjuklig fetma och överviktskirurgi.
Introduction

Epidemiology
Prevalence of obesity (body mass index, BMI ≥ 30 kg/m²) and morbid obesity (BMI ≥ 35 kg/m²) has rapidly increased worldwide (1, 2) in recent decades. Adult obesity in the USA has increased from 14 to 31 % in two decades (1978 - 2000) and is still increasing. In the UK, adult obesity has increased from 6 to 21 % in men and from 8 to 23.5 % in women in 20 years (1980 – 2001) (3-5). Similar trends can be seen nationally. In Sweden, the prevalence of obesity has increased in adult (25 - 64 years) men from 10.4 to 19.1 % and in women from 12.9 to 17.9 % in two decades (1986 -2004) (6).

Obesity, android distribution of excess fat in particular, is associated with increased morbidity in several comorbidities such as cardiovascular (e.g. heart failure, coronary disease, arrhythmias, venous thromboembolism) and respiratory diseases (bronchial and cardiac asthma, obstructive sleep apnoea syndrome (OSAS) and obesity hypoventilation syndrome (OHS)) in addition to diabetes mellitus, kidney failure, gastro-oesophageal reflux, infertility, urinary incontinence, chronic pain, fatigue and many types of cancer (2, 7-15) (Figures 1 and 2). Obesity is now considered the most common metabolic disease in mankind (16). In adults, obesity has frequently been a long-lasting problem (6) (I, II, III). Obesity, especially morbid obesity, is associated with reduced life expectancy of 8 - 10 years (17). Permanent weight loss has been reported to reduce incidence and severity of co-morbidities and the risk of dying prematurely (18-25). In addition, significant weight loss, after e.g. weight loss surgery, provides significant improvements in health-related quality of life (26-30).

Weight loss surgery (bariatric surgery) has proven to be an efficient way to decrease morbid obesity. In fact, surgery is the most important and best evidence-based treatment option for patients with severe obesity (26, 31-36). During the last decades the need for bariatric surgery has increased substantially worldwide. In Sweden, the number of bariatric operations has increased approximately tenfold during the last decade; approximately 9,000 patients have been operated annually during the last two years. In Sweden general indications for surgery are BMI ≥ 40 kg/m² or ≥ 35 kg/m² with significant co-morbidities, regardless of gender. Furthermore, patients must have attempted to lose weight seriously with conventional methods before considered for surgical intervention. Several surgical techniques are in daily use in the world, but in Sweden almost all patients undergo surgery by laparoscopic Roux-en-Y gastric bypass technique. In Sweden, mean time for bariatric surgery is approximately 75 minutes, length of hospital stay 2.1
days and 30-day mortality 0.05% (26, 34). In general, bariatric surgery is categorized as intermediate to high-risk non-cardiac surgery (37-39).

Prevalence of severe obesity is about as common in Swedish men as in women. However, a majority of patients that have undergone bariatric surgery are female. This may be due to that women are more active in seeking, and are remitted more often for, bariatric surgery compared to men. The majority of patients have been middle-aged adults, but also adolescents have been accepted for bariatric surgery recently even in Sweden (34, 40).

![Diagram of pathophysiological consequences of obesity]

Figure 1. Some pathophysiological consequences of obesity.

**Obesity – the perioperative challenge**

The perioperative management of patients with a high BMI is a definitive challenge not only for an anesthetist but for the entire perioperative staff. In severe obesity the amount of physiological functional reserve is narrowed due to body habitus and cardiopulmonary involvement. The hyperdynamic circulation, increased blood volume and altered lean body mass/total body mass ratio change pharmacological dosing principles considerably compared to lean individuals. Airway management may be complicated due to excess fat tissue in face and neck. In addition, appropriate positioning of severely obese individuals for surgery is a challenge. These obesity-related problems may increase risks of perioperative complications compared to individuals with a normal BMI (I-IV) (15, 42-48).
Thus, in severe obesity, thorough preoperative risk assessment and planning of the perioperative course is crucial. A detailed anesthetic plan must be made by anesthetist expertise on an individual basis (II, IV) (15, 41, 45, 49). Preoperative investigations as echocardiography, spirometry and chest X-ray are recommended (39, 50-52) to rule out severe pathologies such as restrictive respiratory impairment, obesity cardiomyopathy and/or cor pulmonale. In addition, development of safe routines for anesthesia and in-depth understanding of fluid therapy for patients with a high BMI are fundamental to minimize perioperative anesthesia-related complications (I, II, III) (41, 45). Furthermore, a good teamwork between the experienced surgeon and the anesthesia staff is essential for patient safety and adequate results (IV) (33, 38).

Background

**Preoperativ surgical optimization**

Excess epigastric and intra-abdominal fat tissue and increased size of liver (53) complicate both laparoscopic and open gastrointestinal surgery significantly. In order to facilitate bariatric surgery in general, reduce surgical complications and bleeding, several preoperative weight loss strategies with durations from two weeks to six months have been implicated. A strict preoperative “rapid weight loss” (RWL) preparation (duration 3 - 6 weeks) by very-low calorie-diet (VLCD) has been shown to diminish intra-abdominal fat deposits and liver size (54-58). To achieve optimal surgical conditions morbidly obese individuals should lose weight radically; approximately 8 - 10 % of total body weight. However, in practical terms, minimum 5 % weight loss is generally accepted. Nowadays this kind of preoperative RWL-preparation is accepted as requirement for bariatric surgery in many centres in Sweden. Even longer time with the diet has been advocated recently (26, 34).

However, preoperative physiological consequences of this very rapid, near-starvation-period are poorly studied. Long-time weight-loosing intervention has been reported to improve diastolic filling pattern and to diminish over-loading and size of the heart (59-61). In this thesis, post RWL effects on hemodynamic parameters and venous return to the heart were studied (I).
Impact of obesity on physiology – an anesthesiological point of view

Obesity and the respiratory system
Respiratory distress is considerable in obesity. In general, morbidly obese individuals have two main problems - chronic arterial hypoxia and carbon dioxide retention. Oxygenation may deteriorate already at minor distractions such as slight cold or changing a body position (43, 62). These changes will be aggravated substantially during anesthesia, major surgery and intensive care (Figure 3) (45, 63-66). Weight loss has been shown to reverse a majority of these pulmonary disturbances (21, 25, 67).

Lung volumes are reduced in obesity. The diaphragm is more cranially located. Impairment of lung function is mostly of the restrictive type and highly position dependent (21). A significant reduction in oxygen reserve exists even awake due to decreased functional residual capacity (63, 68, 69). In preoperative planning for endotracheal intubation and extubation it must be taken into account that most severe obese individuals are not able to sleep in the supine position. In addition, a high prevalence of obstructive sleep apnea syndrome in addition to obesity hypoventilation syndrome (10) makes the use of short-acting anesthetic agents necessary (II, IV) (15, 45, 47, 70, 71).

In general, the work of breathing is increased in obesity (63, 72). Both extra- and intra-thoracic factors are associated with increased respiratory resistance. Extra-thoracic factors are more evident particularly in abdominal and thoracic obesity. However, all morbidly obese individuals suffer more or less of increased airway resistance due to propensity for chronic hypervolemia, volume and pressure strain in the heart and a high venous pressure in the pulmonary circulation. This can be noticed for example as a high prevalence of orthopnea associated with morbid obesity - a clear sign of high filling pressures and decreased compliance of the left ventricle (I) (45, 73, 74) (Figures 5 and 6).

During major surgery, with or without pneumoperitoneum, high airway pressures may become problematic regardless of adequate respirator settings, anesthesia and neuromuscular blockade. This is often a major problem in gynecological/urogenital surgery where head-down position is needed frequently. In bariatric surgery, this may be a concern during supine positioning in particular (75). However, in clinical practice, during deep reverse Trendelendburg positioning and with optimimal respirator settings, these problems have been rare (76).

A supine position should always be avoided in morbidly obese individuals due to an obvious risk of desaturation. Thus, a semi-sitting position is crucial preoperatively and during the early postoperative period to avoid desaturation related complications such as problems with CNS alertness, wound oxygenation and healing, PONV, myocardial ischemia and arrhythmias (43, 77).

In addition, in morbid obesity, an incipient right ventricular failure may exist due to propensity for stressed pulmonary circulation in general, chronic arterial hypoxia and high central venous pressure. Thus, use of positive pressure ventilation during surgery may lead to significant right ventricular failure and, hence, jeopardize the cardiovascular stability (45, 60, 75, 78).
These pathophysiologic, obesity related issues are challenging to control by anesthetists and culminate at the induction of anesthesia where carelessness can easily lead to desaturation and hypoxia. Further, as a worst case scenario, ischemic arrhythmias and asystole may occur (Figure 7). These issues are explored in this thesis (I - IV).

**Obesity and the cardiovascular system**

The cardiovascular system is strained by obesity. Biventricular hypervolemic and hyperdynamic circulation with elevated filling pressures in the left and right ventricles are typical in morbid obesity. The increased blood volume usually leads to clinical consequences (45, 60, 74). Moreover, recent data indicate that diabetes mellitus, insulin resistance and sleep disordered breathing in obesity (e.g. OSAS, OHS) are associated with cardiovascular remodeling and ventricular diastolic dysfunction, that is, decreased compliance of the heart (steeper pressure-volume curve) (45, 79, 80). The most obvious pathophysiological changes can be seen in individuals with long-term obesity. Prolonged duration of morbid obesity (over 10 to 15 years) is strongly associated with increased left ventricular (LV) mass, left atrial (LA) enlargement, LV diastolic dysfunction and slight to severe systolic failure of LV (13, 45, 73, 81-83). Decreased compliance of the left ventricle complicates the management of perioperative fluid therapy (78, 84). In practice, both hyperhydration and deficient replacement of fluids may occur (85).

In obesity increased total body weight consists of both increased lean body mass (fat free body mass) and adipose tissue (Figure 8) (86). Both fat free and adipose tissues are metabolically active and, hence, the more it exists the more the intravascular blood volume is needed for adequate oxygen delivery. Increased circulating blood volume, stroke volume and cardiac output (87) are developed in response to increased metabolic demands. As a result volume and pressure overloading of both chambers of the heart occurs (45, 81). This in turn leads to hypertrophy of the left ventricle (concentric hypertrophy), increased left ventricular mass and increased filling pressures. In this phase the systolic function of the left ventricle is usually preserved, but the diastolic function of the left ventricle is clearly impaired. It should be underlined that the majority of morbidly obese individuals scheduled for bariatric surgery are operated at this phase (II-III). However, recent data indicate that comprehensive utilization of tissue Doppler imaging (TDI) can reveal signs of reduced systolic function at early obesity (88). In addition, many of these individuals meet formal criteria for diastolic heart failure (89-91).
With continued strain on circulation, obesity-related heart failure may develop into "Obesity cardiomyopathy" which is considered to be the final stage of this type of heart failure (81). This process can take over 20 years (13) (Figure 4). Now, in addition to severe reduction in diastolic function, a clear systolic left ventricular failure can be seen. The left ventricle is dilated (eccentric hypertrophy). Reduced stroke volumes and ejection fractions can be measured as signs of left forward failure. In addition, the critical involvement of the right ventricle can often be diagnosed. This can be seen as a dilated right ventricle with signs of secondary pulmonary hypertension, relaxation disturbance and impaired systolic function (45) (Figure 5).

Figure 4. The proposed progression of structural remodeling of the left ventricle (LV) with increasing duration and severity of obesity. In this short-axis view of the LV, the outer circle represents the epicardium and the inner circle the endocardium. A, Normal LV with normal LV mass and relative wall thickness. B, Increased LV concentric remodeling (increased relative wall thickness) without frank LV hypertrophy. C, LV concentric hypertrophy with increased relative wall thickness. D, LV eccentric hypertrophy (increased LV mass with decreased relative wall thickness). Reproduced and adapted from Linda R. Peterson. Obesity and Insulin Resistance: Effects on Cardiac Structure, Function, and Substrate Metabolism. Current Hypertension Reports 2006, 8:451–456 by permission of Springer and the author (13).

At present, it is unclear whether the above mentioned pathological changes are reversible with radical weight loss. However, it has been suggested that the final stage of obesity-related heart failure with the restrictive diastolic filling pattern and myocardial fibrosis is irreversible (13, 73, 82). Notably, diet probably plays an important role in the development of fibrosis. Free fatty acids (FFA) have been shown to cause a lipotoxic cascade in human heart, to be a trigger for intracellular apoptosis in the myocardium via reactive oxygen species and thus increase the risk of permanent fibrosis and cardiomyopathy (82).

Vascular dysfunction in general and conduction pathway failure of the heart may develop with prolonged obesity (92). In addition, the sympathetic nervous system is overactive in individuals with a high BMI. These features together with reduced compliance of the left ventricle are assumed to be
reasons for propensity for substantial changes in stroke volume and increased tendency for arrhythmias and bradycardia during rapid changes of body positioning. This may be a concern during laparoscopic surgery in particular (43, 45, 49, 73, 93).

Figure 6. Top, Schematic diagram of mitral inflow and mitral medial annulus velocities from normal to progressive stages of diastolic dysfunction. Mitral inflow E is sensitive to preload, becoming higher with shorter deceleration time (time from the peak to the baseline) as diastolic function becomes worse with increasing filling pressure. However, E’ is less sensitive to preload and reduced in all stages of diastolic dysfunction. In fact, reduced E’ is usually the earliest manifestation of diastolic dysfunction.

Bottom, Schematic diagram illustrating “pulling” or “sucking” of blood into the LV from LA by good relaxation in subjects with normal diastolic function (left), and “pushing” of blood into the LV by increased filling pressure in patients with abnormal relaxation due to severe diastolic dysfunction (right). A indicates late diastolic mitral flow due to atrial contraction; A’, late diastolic mitral annulus velocity; E, early diastolic velocity; E’, mitral annulus early diastolic velocity; LA, left atrium; LV, left ventricle. Reproduced and adapted from Oh, J.K. et al. Established and novel clinical applications of diastolic function assessment by echocardiography. Circ Cardiovasc Imaging. 2011; 4:444-455 by permission of Wolters Kluwer Health (84).
Knowledge and identification of these pathophysiological obesity-related changes in the heart is useful for the anesthetist. In these high-risk patients, assessment of pressure-volume relationship of the left ventricle should be performed prior to anesthesia and surgery to enable a tailored strategy for rehydration and invasive support for circulation. Consequently, a preoperative assessment of diastolic properties in addition to systolic function of the heart is addressed (15, 38, 51, 78, 84) (Figure 6). These issues were in the focus in this thesis (I, III, IV).

**Pharmacological aspects and anesthetic drugs in obesity**
The pharmacokinetics and pharmacodynamics of many anesthetic agents are altered in morbid obesity compared to individuals with normal weight. The pharmacokinetics for most anaesthetic drugs follows a three compartmental model (i.e. bolus to central compartment, elimination and transfer to tissues) (47, 94). Both dose and time course of drugs (onset and decline) are markedly altered due to the increased fat mass, total blood volume, increased cardiac output and changes in regional blood flow. The volume of distribution (V(d)) is increased for drugs that are distributed both in lean and fat tissues. Clearance for anesthetic drugs is usually increased or normal (94). In obesity, renal clearance is increased due to increased blood volume, size of kidney and glomerular filtration rate (47, 95). Hepatic clearance is usually normal or increased despite of propensity for fatty degeneration and fibrosis of the liver (47, 93, 96).

In morbidly obese subjects an adequate choice and administration of anesthetic drugs are fundamental for patient safety and effective care. Incorrect administration of anesthetics (both dosing and timing) may lead to perioperative complications such as hemodynamic collapse, intraoperative awareness, airway management problems and postoperative drowsiness (94, 97) (II, IV). Figure 7 illustrates potential difficulties during induction of anesthesia related to drug dosing.
The basis for successful dosing of drugs in obesity is knowledge of total body weight (TBW) and assessment of a fat-free body mass (i.e. lean body weight, LBW). In general, drug dosing is usually based on TBW. This is a safe approach for lean individuals due to similarity between TBW, LBW and ideal body weight (IBW). However, in morbid obesity, anesthetic dosing based on TBW may lead to overdosing and a prolonged effect. In obese population, in addition to increased fat mass LBW also increases but not in the same proportion (i.e. LBW / TBW ratio decreases) (Figure 8). Most of the cardiac output still perfuses lean tissue groups because of generally low perfusion of and low water content in excess adipose tissue. Thus, utilizing LBW for dosing of many anesthetic drugs may be the most appropriate approach (47, 86, 94).
There are several methods for assessment of the fat-free body mass. Body composition can be assessed both directly (e.g. by bioelectrical impedance analysis and dual-energy x-ray absorptiometry) and indirectly. Direct methods are not available for the majority of clinics. Consequently, many indirect measures have been utilized (BMI, body surface area, IBW, percent IBW, LBW). Whatever the modality is implemented, it is crucial to apply an estimation of fat-free body mass in clinical praxis in order to avoid incorrect dosing (Figure 7). The simple “IBW-equation” (height in cm – 100) used in this thesis is easy to implement in practice, and gives a good approximation of a fat-free mass of the body in morbid obesity equivalent to a BMI level about 24 kg/m² (II, III, IV) (45, 71). This IBW corresponds in principle to LBW that can be obtained by direct body impedance measurements or calculated using the generally recommended, but rather complicated equation (98):

\[
\text{LBW (male)} = 9.27 \times 10^3 \times \text{TBW}/6.68 \times 10^3 + 216 \times \text{BMI} \\
\text{LBW (female)} = 9.27 \times 10^3 \times \text{TBW}/8.78 \times 10^3 + 244 \times \text{BMI}.
\]
Thus, the "IBW concept" used in this thesis can be interpreted as an estimation of LBW in morbidly obese individuals.

In addition to the “right” dose per se, an appropriate speed of drug administration is essential. Too low speed of administration may lead to overdosing and undesired sub-clinical effects (II) (94, 99) (Figure 7). The LBW has been shown to correlate strongly with cardiac output (87, 99). Increased LBW leads to hyperdynamic and hypervolemic circulation (discussed in the chapter “Obesity and the cardiovascular system”). These features of circulation increase the speed of the drug wash-in and wash-out times in the brain and other high-perfusion tissues. As a consequence, a fast onset of the drug can be expected (depression of respiratory drive and sympathetic nervous system). On the other hand, risk of undesired patient intraoperative awareness associated with induction of anesthesia is increased.

So, the following issues are critical for successful implementation of induction and maintenance of anesthesia in morbidly obese individuals:

i) a knowledge of total body weight (TBW),
ii) an estimation of fat-free body weight (LBW, IBW),
iii) a calculation of a theoretical appropriate dose for anesthetics
    and
iv) an appropriate speed and timing of drug administration.

Nevertheless, despite of preoperative calculation of drug doses an anesthetist should always be alert to adapt management according to clinical responses and have inotropic and vasoactive drugs immediately available (IV).

Anesthetics, opiates and neuromuscular blockers

Volatile anesthetics: As discussed above, administration of most anesthetic drugs is altered in morbidly obese individuals compared to lean subjects. However, the uptake of volatile anesthetics (e.g. isoflurane, sevoflurane, and desflurane) is not significantly changed in morbid obesity. A low blood/gas distribution coefficient and low lipid solubility are obligate for rapid induction and recovery. In morbid obesity, the drugs of choice at the moment are sevoflurane and desflurane (II, IV) (71, 93, 97, 100, 101). In general, volatile anesthetics cause only a slight depression of respiratory drive – desflurane and sevoflurane being least depressive (102, 103). Theoretically, nitrous oxide could be an optimal choice in morbid obesity.
because of its analgesic properties and fast recovery but propensity to high oxygen demand during surgery and increased risk of PONV limits its use.

In current times, a volatile anesthetic induction can best be implemented with sevoflurane. Desflurane causes respiratory irritation, and therefore is not recommended as an induction agent. Sevoflurane can be used as an induction agent with various techniques (e.g. tidal volume, single-breath and vital capacity techniques) (II) (104, 105) for children, difficult airway, risk of desaturation and emergency surgery. Moreover, sevoflurane induction is associated with less hemodynamic perturbation compared to propofol (106). A lower MAC-value (~0.8) in combination with short acting opiates is generally recommended in bariatric surgery today (71, 97, 107) (II, IV). In addition, volatile anesthetics can be monitored reliably in all modern anesthetic workstations (with end tidal % and MAC-concept) in contrast to i.v. anesthetics. Moreover, postoperative reduction in lung function has shown to be more prominent after total intravenous anesthesia compared to conventional general anesthesia with sevoflurane (108). Thus, use of inhalation anesthetics may be motivated in morbidly obese patients in particular.

Hypnotics: Propofol is the most commonly used i.v. hypnotic drug for both induction and maintenance of general anesthesia even in bariatric surgery. Propofol is a highly lipid-soluble drug with high clearance. V(d) for propofol and clearance are propotional to TBW. The terminal elimination half-life of propofol is not altered in obesity compared to lean individuals (47, 94). With propofol, there is a delay between effective blood concentration and effective site (brain) concentration that must be taken into account during anesthesia induction. Propofol has favorable properties for induction in general. It provides good relaxation of larynx and pharynx (109). On the other hand, in morbidly obese subjects, this may be problematic during sedation and/or fiberscopic awake intubation where preserved pharynx tonus (i.e. free airway) and spontaneous breathing is desirable (110). In addition, a rapid injection of propofol needed in morbid obesity leads to early apnoea (86).

In the morbidly obese population a rapid sequence induction of anesthesia (RSI) is generally recommended (41, 45, 111). For the purpose, propofol is traditionally administered with TBW as a guideline. However, in clinical practise, a TBW-based dosing regime for induction of anesthesia results in high doses and rapid loss of consciousness, but usually inducts a significant decrease in blood pressure (99, 106, 112). Thus, LBW or its surrogates may function as more appropriate weight-based scalars for induction in severe obesity (II, IV) (71, 86, 99). However, at the moment, there is no clear
consensus for dosing scalar for induction dose of propofol in morbid obesity. The use of propofol in maintenance of general anesthesia may appear less suitable compared to volatile anesthetics. Larger doses needed during surgery may compromise hemodynamic stability in addition to costs of the drug (47, 71). Moreover, volatile anesthetics are clearly superior to propofol regarding the intraoperative monitoring of dosing.

Propofol may be used as a component in total intravenous anesthesia (TIVA) with or without target-controlled infusion systems (TCI). In morbid obesity, calculation of mathematic compartment algorithms needed for TCI-dosing is challenging due to altered LBW/TBW ratios (Figure 8), V(d) and hyperdynamic circulation (Figure 5) (97). However, recent data indicates that use of TCI systems may lead to increased hemodynamic stability and rapid recovery even in morbid obesity. An estimation of fat-free body weight (i.e. LBW) should be used for TCI induction and/or maintenance in bariatric surgery (the Schnider model) (71, 86, 113). However, the TCI concept was not used in this work, and a comprehensive review of the issue is beyond the scope of the thesis.

Other hypnotics, such as thiopental sodium or benzodiazepines, are not recommended for induction due to significantly increased volume of distribution and elimination half-life (47).

Opiates: Similar to hypnotics, short acting opiate drugs are used. Alfentanil may be the most suitable opiate for RSI-induction. This drug has a fast onset and recovery, no respiratory adverse effects in addition to the possibility for i.v. bolus administration (II) (114, 115). Optimal dose estimation should be based on lean body mass (45, 47, 86). Use of remifentanil is well documented in bariatric surgery. This drug is considered the most suitable of all opiates for maintenance of general anesthesia in morbid obesity (71, 107). However, propensity for muscle rigidity may limit its use as an induction drug in morbid obesity (115). Remifentanil is highly lipophilic but, on the other hand, is metabolized rapidly by unspecific esterases in both central and extracellular compartments. So, absolute volume of distribution of remifentanil is not significantly altered compared to lean subjects, and dosing should be based on ideal body weight (47, 71, 86, 93). After prolonged infusion of this drug, no accumulation occurs, and no risk of postoperative sedation and/or respiratory depression exists in addition to low incidence of PONV (116). However, according to recent data, ultra short acting advantages of remifentanil may not be superior to other opiates (e.g. sufentanil) if perioperative administration is implemented by TCI-systems (117).
Neuromuscular blocking drugs: Increased dose of depolarising agents (suxamethonium) is needed due to increased blood volume and pseudocholinesterase activity. Dosing scalars by total body weight has been proposed (45, 47, 118). However 120 - 150 mg (i.e. 0.7 - 0.8 mg/kg TBW) seems to be a most appropriate dose (II). Furthermore, use of suxamethonium together with opioids and hypnotics have been shown to have less undesirable effects on direct laryngoscopy circumstances compared to non-depolarising neuromuscular blocking drugs (II) (111).

Use of total body weight for dosing of non-depolarisizing neuromuscular blocking agents will result in a prolonged effect. Thus, the LBW or IBW is suggested to be most appropriate for dosing of these drugs in morbid obesity (47, 93).

Airway management, positioning, preoxygenation and perioperative oxygenation
Morbid obesity is associated with increased risk for gastric aspiration because of increased intra-abdominal pressure, gastric juice volume, incidence of gastro-oesophageal reflux, low gastric pH and a low barrier pressure (15, 45, 119, 120). In addition, gastric emptying may be slowed due to high prevalence of diabetes mellitus and possible autonomic dysfuction (i.e. gastroparesis). Hence, for these reasons, a rapid sequence induction or awake fiberoptic technique for endotracheal intubation has been recommended (45, 111).

There are three ways to obtain airway access in morbidly obese individuals: i) RSI without mask ventilation, ii) induction with mask ventilation or, iii) awake intubation. For all of these, a thorough preoperative assessment of possible airway problems must be carried out by an experienced anesthetist. Neck circumference and extension, the Mallampati score, mouth opening, tendency for airway obstruction (“snoring”) while awake (e.g. in severe OSAS) and signs of OSAS (e.g. drowsiness) should be assessed (10, 15, 45, 121, 122) (II). The inspiratory provocation test (a rapid forced inspiration, “FIV1”) may also give additional information of a possible severe airway obstruction.

Proper positioning is fundamental for all morbidly obese individuals – most important is head and shoulder positions prior to preoxygenation and induction (15, 123, 124). A “ramp” position (Figure 9) can be created with large pillows or blankets under the shoulder in addition to tilting the head part of the operation table (43), or with a “ramp” intubation device (“the AirPal RAMP®, i.e. The Rapid Airway Management Positioner). This position has been shown to facilitate circumstances for both mask ventilation
and direct laryngoscopy (DL), and is superior to a “sniffing” position (125). Moreover, a “sniffing” position may be challenging to achieve because of a heavy head-and neck region in severe obesity. Furthermore, reverse Trendelendburg positioning (a 15 - 30 degree tilt of the table) in addition to a “ramp” position is recommended to facilitate preoxygenation and optimize a position of the diaphragm and the functional residual capacity (41, 126, 127). However, a head-up position (a reverse Trendelendburg position) may compromise venous return to the heart which may be worsened in hypovolemia (II, IV) (43).

There are various protocols published on preoxygenation in morbidly obese individuals. The general aim of preoxygenation is to obtain enough time for endotracheal intubation without a risk of desaturation. This can be achieved by preoperative lung recruitment (i.e. applying continuous positive airway pressure aiming to diminish atelectasis and shunting and increase FRC), and by nitrogen washout using a high fresh inflow of oxygen. The peer-reviewed methods available vary e.g. in FiO2 applied (from 0.6 – 1.0), duration and use and level of continuous positive airway pressure (CPAP), pressure support and positive end-expiratory pressure (PEEP) (i.e. non-invasive ventilation, NIV) (II, IV) (46, 128-130). In addition, use of PEEP may decrease the risk of regurgitation (120). In any case the most crucial monitoring is end-tidal oxygen fraction (etFiO2), which should reach levels at least > 0.65. It is important to notice that extreme levels of etFiO2 may decrease the safety time for apnoea due to atelectasis formation (i.e. absorption atelectasis) (131, 132).

The BMI per se is a poor predictor of difficulties in anesthetic performance. More predictive is distribution of fat in face and around the neck and in the upper body region (45). In these individuals airway management (difficult mask ventilation (DMV) and endotracheal intubation) may be complicated in particular. Already a BMI > 26 kg/m² has been considered as an independent risk factor for DMV (44). Hence, challenging mask ventilation should be taken into account in most morbidly obese individuals. Problems with DMV may be managed by implementing a rapid sequence induction without mask-bag ventilation (II, IV) or by a four-handed technique for the mask and the bag (15). Alternatively, respirator-assisted mask ventilation, LMA or a nasopharyngeal tube can be placed for ventilation prior to endotracheal intubation (133, 134).

However, endotracheal intubation is often successful in a proper positioning (a “ramp” position) by conventional direct laryngoscopy with a short handle, a long Macintosh blade and a stiff stylett. Under these conditions, DL circumstances can be classified as Cormack-Lehane I/IV up to 75 % of
morbidly obese subjects (122). However, newer video-assisted techniques has shown to be superior to conventional DL regarding visualization of the larynx and success rate for endotracheal intubation but are more time consuming (135) and, hence, increase the risk of desaturation.

Awake fiberoptic intubation is a challenge per se in patients with a high BMI. It should be implemented only after comprehensive assessment of airways and/or in hyper morbidly obese individuals with abdominal, face and neck obesity with intolerance to lie in a supine position. Two operation tables may be needed to tolerate high body masses of these patients (43). However, in general, most patients are anesthetized and endotracheally intubated on the operating table (II, IV) (15). This practice has a key advantage: use of a table with appropriate weight limits (in this thesis ≤ 200 kg) a rapid in-need re-postitioning of morbidly obese individuals is facilitated.

After endotracheal intubation a rapid systematic collapse of alveoli, or atelectasis, occurs in morbidly obese patients. A lung recruitment maneuver and PEEP 8 - 10 cmH₂O is advocated to keep the lungs open (II, IV) (66, 136). Despite moderate levels of PEEP high supply of oxygen is generally needed during bariatric surgery.
Figure 9. A proper positioning (a “ramp” position) of a morbidly obese individual in order to facilitate mask-bag ventilation, oxygenation and endotracheal intubation. Reproduced from Brodsky J.B. Positioning the Morbidly Obese Patient for Anesthesia. Obesity Surgery 2002 Dec; 12(6): 751-758 by the permission of Springer (43).

Conclusively, the cornerstones for a safe induction of anesthesia and sufficient oxygenation during surgery are:

i) preoperative optimizing and medical treatment of respiratory and cardiac comorbidities,
ii) proper positioning (a “ramp” position) during preoxygenation,
iii) adequate FiO₂ and sufficient duration of preoxygenation,
iv) use of vital capacity breathing, CPAP and/or NIV during preoxygenation,
v) intraoperative recruitment of lungs and use of PEEP,
vi) monitoring of end-tidal FiO₂ levels and intrinsic PEEP,
vii) adjusting levels of I:E ratio, frequency and respirator mode when necessary.
Monitoring strategies and fluid management
In general, regardless of BMI, rapid treatment of hypovolemia is obligatory to re-establish and sustain blood pressure, blood flow and adequate tissue and renal perfusion. On the other hand, hyper-hydration of fluids may lead to tissue edema and impaired oxygenation and organ dysfunction. This may have clinical manifestations which include pulmonary strain with urgent need for non-invasive ventilatory support, increased risk of postoperative wound infections and prolonged length of hospital stay (85, 137, 138).

In severe obesity, perioperative fluid administration is a particular challenge because of propensity for heart failure, reduced compliance of the heart, vasomotoric dysfunction, respiratory strain and varying lean body mass (41, 45, 75). There is no clear consensus for fluid therapy in bariatric surgery at the moment. Published fluid replacement recommendations vary from liberal to restrictive approaches (III, IV) (41, 85, 93, 139). Assessment of rehydration needs is additionally complicated by non-standardized routines for preoperative weight loss preparation with a potential impact on venous return and hydration balance (I, III, IV) (55-58). In order to manage these challenges functional non- or mini-invasive modalities for cardiovascular monitoring and lean/ideal body weight estimates are addressed to meet individual variability in rehydration needs (III, IV) (85, 93, 137, 138, 140-142).

At the moment, individualized goal-directed volume therapies (IGDT), based on functional hemodynamic parameters, are generally recommended for monitoring hemodynamics and fluid therapy. Conventional, “static”, pressure-based monitoring (mean arterial pressure (MAP), central venous pressure (CVP) or pulmonary capillary wedge pressure (PCWP)) have not been shown to decrease perioperative morbidity and mortality in major surgery (137, 138, 143).

The choice of monitoring may depend on availability and user knowledge. There are several commercially available modalities that produce dynamic, flow-based on-line data; e.g. FloTrac™, LiDCO™, ccNexfin™, PICCO™, Cardio Q™ and echocardiography. It is a challenge to choose the most suitable monitoring system in terms of patient population, body habitus, clinical situation and type of surgery. Several different modalities can and should be used concomitantly. Obtained information should then be merged together to achieve the best results (Figure 10) (IV) (142, 144, 145).
There are several dynamic parameters available to assess need of rehydration and preload responsiveness. At the moment best documented parameters are stroke volume variation (SVV), systolic pressure variation (SPV), pulse pressure variation (PPV), inferior or superior vena cava collapsibility index (IVCCI and SVCCI, respectively) (137, 143-151).

In general, goal-directed protocols are usually designed to maximize stroke volume by administration of i.v. fluids, use of intropic and/or vasoactive medication aiming to increase oxygen delivery (137, 138). These protocols can be implemented preoperatively, intraoperatively and postoperatively (e.g. at ICU or recovery unit). The intraoperative approach is most often applied
because of the nature of validation studies and monitoring limitations during spontaneous breathing. However, the importance of pre-optimization (i.e. preoperative) protocols has been raised recently, but evidence for these is still sparse (I, III, IV) (137, 152). For this purpose, in fact, transthoracic echocardiography is the only modality reliable and robust enough to be used in subjects with spontaneous breathing (78, 153, 154). To my knowledge, the papers in this thesis are the first published studies in morbidly obese individuals in this context (I, III, IV).

Mini-invasive pulse-contour device FloTrac
The mini-invasive FloTrac™ device (version 3.01, Edwards Life sciences, Irvine, CA, USA) was used in paper IV only. The accuracy and reliability of the device is comprehensively validated (153, 155-159) even in laparoscopic surgery and obesity (160, 161). The device can be utilized as continuous monitoring for all kinds of surgery, but only during controlled ventilation. An arterial line is needed for measurements and analysis. The FloTrac produces continuous data on stroke volume, stroke volume variation, cardiac output, and can be extended to cover measurements of systemic vascular resistance and central venous saturation (ScVO2) with a central venous line when necessary. Potential source of inaccuracies are spontaneous breathing, arrhythmias and other non-sinus rhythms as nodal rhythm and reduced thorax wall compliance (137). The FloTrac algorithm calculates stroke volume every 20 seconds by using arterial pressure, age, gender and body surface area in the general equation SV = K x pulsatility. Body surface area is calculated by the Dubois formula. In the 3rd generation software the conversion factor Khi (K) accounting for arterial compliance is updated every 60 seconds automatically, and manual calibration is not required. Thus, the data should be registered minimum one minute from actions that might influence arterial compliance (e.g. administration of vasodilating i.v. drugs or a major change of position) (162, 163). A more detailed description of the technique applied in the FloTrac is beyond the scope of this thesis (137, 155).
**Intra-abdominal pressures and pneumoperitoneum in morbid obesity**

Increased intra-abdominal pressure (IAP) levels have been reported in morbidly obese subjects (164, 165). According to the recent consensus statement established by the World Society of the Abdominal Compartment Syndrome (WSACH) and the expert group (166) intra-abdominal pressure levels are graded as follows: i) Grade I, IAP 12–15 mmHg, ii) Grade II, IAP 16–20 mmHg, iii) Grade III, IAP 21–25 mmHg i.e. abdominal compartment syndrome, and iv) Grade IV, IAP > 25 mmHg.

Abnormal IAPs may have an impact on inferior vena cava and venous return to the heart. Hemodynamic effects of pneumoperitoneum depend on the degree of intra-abdominal pressure and the hydration balance of a patient. In euvolemic subjects, during a slight pneumoperitoneum (IAP < 10-15 mmHg) a thoracic compartment gain occurs (splanchnic blood recruitment) and, hence, venous return increases. In hypovolemia, this response is absent. A high IAP (> 15 - 20 mmHg) may compromise venous return and hemodynamic stability even in euvolemia, as well as decrease perfusion in the splanchnic region, and impair renal and lung function (93, 164-167).

Consequently, it is crucial to endeavor for IAP-levels < 15 mmHg and euvolemia during laparoscopic bariatric surgery. Euvolemia/optimal filling pressures of the heart should be reached before induction of anaesthesia and maintained at this level perioperatively to guarantee a sufficient coronary flow and organ perfusion in addition to avoid excessive/theoretical activation of the renin-aldosterone-angiotensin system (RAAS) (75). Thus, in general, functional hemodynamic monitoring for fluid therapy and IAP is recommended for subjects with increased IAP (166) (IV).

**Postoperative considerations in bariatric surgery**

The early postoperative care is critical in bariatric surgery. Rigorous monitoring of oxygenation and respiratory rate, renal function and signs of tachycardia (as a sign of anastomotic leakage and bleeding) and cardiac failure must be conducted. A standardized, but still individualized, postoperative care is addressed with focus on: i) careful fluid therapy ii) good pain control, iii) to minimize use of opioids and other sedative drugs, iv) to minimize risk of post-operative nausea and vomiting, v) to optimize patient positioning to ensure good cardiorespiratory function and, vi) early mobilization (97) (IV).

In general, postoperative lung function (both lung volumes and dynamic function) is significantly reduced after surgery and general anesthesia in morbid obesity (45, 65, 77). Prolonged invasive respirator therapy must be
avoided whenever possible and, hence, a morbidly obese patient should be extubated fully awake in the sitting/semi-sitting position as early as possible. A CPAP-apparatus intended for the care of OSAS must be at hand in the postoperative care unit (93). In risk assessment it should be taken into account that reported prevalence of OSAS/OHS is misleading and most morbidly obese individuals may have subclinical and undiagnosed OSAS or even OHS. Thus, implementing postoperative CPAP therapy must be considered if signs of airway obstruction are detected (10). Even a scheduled CPAP therapy for all morbidly obese patients has been advocated. The postoperative use of NIV and/or CPAP has been shown to be a safe approach for increasing oxygenation in bariatric surgery without increased risk for aspiration or anastomotic leakage (41, 93).

In association with these studies, a postoperative program with an overnight observation at the postoperative recovery unit is implemented. A head-up position is obligate in addition to intermittent positive pressure breathing. CPAP can be applied when necessary. The triple antiemetic prophylaxis (71, 168) (ondanzetron 4 mg, betamethasone 8 mg and dihydrobenzoperidol 0.75 mg) is given intravenously to all morbidly obese individuals. Postoperative pain control is initiated with preoperative paracetamol, intraoperative i.v non-steroidal anti-inflammatory drug (NSAID) (diclofenac 75 mg) and i.v. morphine 0.1 mg/kg IBW (injected 20 minutes before extubation). In addition to these drugs, intraperitoneal local anesthesia is administrated by the surgeon. In case of open and/or converted surgery two epidural catheters are placed in the wound bilaterally. In these catheters intermittent injections of bupivacaine may be administered. When necessary, intermittent administration of clonidine may be considered. Alternatively, if anatomic circumstances and body habitus are favorable, continuous epidural analgesia is conducted. Transversus abdominis plane (TAP) blocks (169) are not routinely used in these patients in our clinic.
The aims of the thesis

The primary aims of the thesis are:

i) to assess the prevalence of dehydration (hypovolemia) before bariatric surgery using transthoracic echocardiography (Paper I),

ii) to validate a cardiorespiratory stable combination of anesthetics to perform a controlled induction of anesthesia ("rapid sequence induction") suitable for morbidly obese individuals (Paper II),

iii) to evaluate a preoperative rehydration regime by a comprehensive protocol for transthoracic echocardiography with focus on venous return to the heart, volume responsivness and diastolic function of the left ventricle (Paper III),

iv) to evaluate need of rehydration during laparoscopic bariatric surgery using transthoracic echocardiography and an arterial pulse wave analysis technique (Paper IV).
Methods

Study design and ethics
Data collection took place between October 2009 and November 2013 in Sunderby county hospital, Luleå, Sweden. Studies I and II were consecutive, controlled, non-randomized, prospective observation studies. The design of study III was controlled (cross-over), consecutive, propective and interventional. Study IV was a consecutive, controlled, non-randomized, prospective interventional study. Ethical approvals (DNR 09-042M, DNR 2010-287-32M and DNR 2012-439-32M) by the Regional Ethical Review Board, Umeå, Sweden, were obtained for all substudies. In addition, studies III and IV were registered at the ClinicalTrials.gov database.

Patients and methods
The morbidly obese subjects studied (n = 132, mean BMI 42.2 kg/m² (36 - 56.7) were scheduled for bariatric surgery by laparoscopic Roux-en-Y gastric bypass (RYGB) and were prepared by 3 weeks rapid-weight-loss diet (RWL) before bariatric surgery. In addition, these subjects fasted six hours before surgery (a nil-per-os period). The control groups consisted of i) lean subjects (mean BMI 25.6 kg/m²) enrolled for elective general abdominal surgery in papers I and II (n = 22), and ii) morbidly obese subjects in papers III and IV. The subjects in the lean control groups underwent only six hours’ preoperative fasting. Subjects with untreated systemic or pulmonary hypertension, atrial fibrillation, pacemaker, unstable angina pectoris and significant failure of heart valves and known difficult airway (i.e. need for fiberoptic and/or video-assisted larygoscopy intubation) were excluded.

Data on diagnosed underlying co-morbidities, regular medication, patient characteristics and preoperative loss of weight were collected preoperatively. Prevalence of dyspnea and/or orthopnea was evaluated before and after the preoperative RWL-preparation (I). Frequency of cardiopulmonary investigations during the last 10 years was assessed preoperatively (III). For calculation of BMI in kg/m² patients were weighed with measurement accuracy of 100g. Primary and 30-day outcome, complications, length of stay at the postoperative recovery unit (POP) and length of hospital stay (LOS) were registered (I, III and IV). No sedative pre-medication was used due to potential risk of hypoventilation related to severe obesity (97).

Assessment of heart function, filling pressures of the left ventricle, level of venous return and rehydration was implemented by use of preoperative transthoracic echocardiography (TTE) (I, III and IV) in addition to a intraoperative mini-invasive pulse-contour device (FloTrac/Vigileo™) (IV).
Moreover, overall effects of perioperative volume therapy on intra-abdominal pressure (IAP), renal function and filling pressures and dysfunction of the heart were evaluated by intra- and postoperative IAP-measurements (Foley catheter™), and by gathering pre- and postoperative blood samples (serum electrolytes, pH, acid-base balance, creatinine, estimated glomerulus filtration rate, N-terminal prohormone of brain natriuretic peptide (NT-proBNP)) (IV) (167, 170-172). Blood samples were collected on the day of surgery and on the first postoperative day between 6 and 6.30 am. The arterial blood samples were collected and analysed immediately with a blood gas analyser (ABL 800 flex; Radiometer Copenhagen, Denmark). The supine position for 5 minutes without extra oxygen was compulsory before collecting these blood samples (II, IV).

**Anesthesia and preoxygenation techniques used in this thesis**

All subjects enrolled in substudies II and IV were preoxygenated by the same procedure and anesthetized by two different standardized protocols intended for RSI (i.e. volatile (II) or total intravenous induction (IV)). Common principles for RSI were followed – no mask ventilation was performed before endotracheal intubation. Both preoxygenation and induction of anesthesia were implemented in a “ramp” position created by one large and one small pillow in addition to a slight upwards tilt of the operation table (20 - 30°) (Figure 9) (43).

**Protocol for preoxygenation and anesthesia induction, Paper II**

The logistics of the anesthesia method used is illustrated in Figure 11. One minute prior to the preoxygenation period atropine 0.5 mg and propofol 20 mg were administered i.v. Atropine was used mainly for vagolysis and propofol as a sedative and anxiolytic drug (i.e. to facilitate breathing through the facemask system and decrease sympathetic tone (99, 173). The Kion SC9000 XL anesthetic workstation (Siemens Elema, Solna, Sweden) was used in this study. All subjects were preoxygenated for 2 minutes with a tight face mask with FiO2 0.9, a fresh gas flow of 10 l/min and a continuous positive airway pressure (CPAP) of +8 cmH₂O. Two vital capacity breaths with a 3 seconds inspiratory pause were mandatory during the preoxygenation period. Next, still keeping the face mask tight, the sevoflurane vapouriser was opened to 8 %. All subjects were then asked to take 3 vital capacity breaths, now with sevoflurane 8 %, without inspiratory pauses and unchanged FiO2 and fresh gas flow (104, 105). If the breaths were clinically evaluated as too small, a fourth breath was requested. In each subject, the sevoflurane vapouriser was altered to 3 % after 30 s. At this point, propofol 1.5 mg/kg, alfentanil 20 µg/kg and suxamethonium 1 mg/kg were administered intravenously as a rapid sequence bolus (approximately 1 ml/second of respective medicine) (94, 99). Dosing of propofol and
alfentanil was based on the IBW and doses of suxamethonium on the TBW (47, 86, 115, 118, 174). The scavenging facemask system (Medivent, Westfield, Massachusetts, USA) was used for possible volatile gas spill.

Clinically sufficient stage of anesthesia (i.e. loss of consciousness and onset of effect of alfentanil) was determined by absence of the eyelash reflex and presence of miosis. In addition, an appropriate level of muscle relaxation for laryngoscopy was determined as when fasciculations in the face disappeared and the jaw felt relaxed. The face mask was released and a direct laryngoscopy was performed with a laryngoscope (a Macintosh blade and a short handle). A stiff stylet was used in all endotracheal tubes. In order to ensure optimal venous return all subjects were repositioned to a 5 - 10° reverse Trendelenburg position immediately after a successful endotracheal intubation (43).

During general anesthesia all subjects were slightly hyperventilated using a pressure or volume controlled mode, positive endexpiratory pressure (PEEP) +8 cmH2O, inspiration/expiration ratio to 1:1, tidal volume approximately 7 ml/kg IBW. The lung recruitment manoeuvre was implemented to all subjects ten minutes after intubation by holding +30 cmH2O pressure for 10 seconds. Anesthesia was maintained by sevoflurane (0.8 - 0.9 minimum alveolar concentration, MAC), an infusion of remifentanil (0.20 - 0.35 µg/kg IBW per minute) and vecuronium bolus 0.1 mg/kg IBW (71, 86, 97).

Protocol for preoxygenation and anesthesia, Paper IV

Preoxygenation was performed as described above. The Primus anesthetic workstation (Dräger, Lübeck, Germany) was used in this substudy. A standardized total intravenous rapid sequence induction of anesthesia was implemented in both groups. Anesthesia was induced with atropine 0.5 mg, propofol 2 mg/kg IBW, alfentanil 20 µg/kg IBW and succamethonium 1 mg/kg total body weight (II). Anesthesia was maintained with sevoflurane, infusion of remifentanil and rocuronium or mivacuronium after endotracheal intubation. Train-of-four monitoring was used in all subjects. Dosing scalars for rocuronium and remifentanil were based on the IBW approximation and clinical course (II). Bolus of remifentanil was administered if necessary 1 µg/kg IBW. The perioperative infusion rate of remifentanil was 0.20 µg - 0.35 µg/kg IBW. Sevoflurane was administered by age-justed MAC-values. The target MAC-value was 0.8 - 0.9. No EEG-based monitoring for depth of anesthesia was used. All subjects were ventilated with tidal volume 8 - 9 ml/kg IBW, minute ventilation approximately 95 ml/kg IBW, PEEP +8 cmH2O and I:E ratio 1:2. An identical recruitment manoeuvre as in paper II was performed. A volume-controlled respirator mode was used primarily. If problems with high airway pressure occurred despite an adequate general anesthesia and neuromuscular blockade, the following were considered i) pressure-controlled ventilation mode, ii) I:E ratio 1:1 (if no auto-PEEP was observed), iii) smaller tidal volumes and higher frequency to maintain desired minute volume. However, tidal volumes was kept ≥ 8 ml/kg IBW to maintain accuracy of the FloTrac-device. If the above steps did not reduce airway pressure as desired, a reverse Trendelenburg position by 20 degree was established (43, 127).
Echocardiography

Protocols for TTE
In this thesis two different investigation protocols were implemented for transthoracic echocardiographic scanning. The “rapid” TTE protocol was designed to be implemented with focus on fast and reproducible assessment of venous return and left ventricle filling pressures regardless of body habitus or BMI. This protocol could be used in any clinical situation with need of rapid evaluation of the circulation. The “rapid” protocol was utilized once in papers I and IV before surgery. In paper III, the more time-consuming “comprehensive” protocol was implemented before surgery.

The transthoracic echocardiographic investigations were conducted by ultrasound devices Sequoia-512 (Acuson-Siemens, Mountain View, CA) in papers I, III and IV, in addition to Vivid 6 (GE, Vingmed, Horten, Norway) in paper IV. All investigations were performed in accordance with current guidelines (84, 175-177) by one experienced sonographer (cardiac physiologist) to minimize investigation bias and maximize the level of standardization of signal acquisition and analysis of echocardiographic data. The mean values of three consecutive end-expiratory cardiac cycles were analysed and used for statistic analysis. 2-D, M-mode, pulsed-wave (PW) continuous, and colored Doppler were used (I, III and IV). In addition, tissue Doppler imaging (TDI) was applied in paper III. Investigations were done with subjects in a supine position at a preoperative room.

2-D and M-Mode measurements
Standard acquisition projections were implemented (parasternal long axis (PLAX), short axis (SAX), apical 4-chamber (A4C) and subcostal projections) (I, III and IV) (Figure 12). Apical 2 (A2C) and 3 chamber projections were used for visual assessment of left ventricular contractility only. The left ventricle (LV) measurements and visual evaluation were made perpendicular to the ventricular long-axis at the level of the mitral leaflet tips from PLAX windows with 2-D. Left atrium anterior-posterior diameter in end-systole (LAd) was measured from PLAX and was indexed to the total body surface area (BSA). Also, LAd, left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter (LVESd), end-diastolic wall thickness in left ventricle (septal and posterior walls) and right ventricular end-diastolic diameter (RVEDd) were recorded from the 2-D images with electronic caliper assuring an optimal orientation for measurements.

Maximum inferior vena cava diameter (IVCmax), minimum inferior vena cava diameter (IVCmin) after a rapid sniff was recorded with 2-D images assuring an optimal measurement orientation. The IVC collapsibility index
(IVCCI) was calculated by formula: IVCCI % = 100 % x (IVCmax – IVCmin)/IVCmax. The IVC measurements were obtained from subcostal windows approximately two centimetres from the junction of the IVC and the right atrium, perpendicular to the IVC’s long-axis taking care of true IVCmax and that IVCmin was not measured at another plane (149, 178, 179).

Left ventricular systolic function was assessed visually at all acquisition windows and by left ventricle fractional shortening (FS) (I, III, IV). In addition, ejection fraction (EF) was calculated from SAX areas (III). Left ventricular end-diastolic (LVEDA) and end-systolic (LVESA) areas were traced at mid-chamber level in SAX windows. A conventional formula for EF calculation was applied: EF % = 100 % x (LVEDA – LVESA) / LVEDA (177).

In paper III, stroke volumes (SV) were measured by the left ventricular outflow track (LVOT) method. Left ventricular outflow track diameter (LVOTd) was measured in PLAX windows by 2-D only before volume-challenge to minimize bias in statistic comparison of ΔSV. Mean values of 3 separate LVOTd were used in SV calculation. Right ventricular (RV) systolic function was assessed visually if possible, and by measuring tricuspid annular plane systolic excursion (TAPSE) with M-mode. A value < 16 mm of TAPSE was used as cut-off indicating a global systolic RV impairment (176).

Conventional and Tissue Doppler imaging measurements
Transmitral inflow and pulmonary venous inflow velocities were gathered with PW from A4C projections. The PW-derived transmitral inflow pattern was used in fast visual evaluation (I, IV) and for a comprehensive analysis (III). Measurements were obtained with the sample volume at one centimeter inside of LV and in the middle of the mitral annulus. The maximum velocities Early (E) and late (A) velocities were measured at an end-expiratory phase of the cardiac cycle. E/A ratio, deceleration time (Dt) of E-wave and E/Dt ratio were measured and calculated. A Valsalva manoeuvre was performed if signs of pseudo-normalized diastolic function based on the transmitral flow pattern were detected (84, 175). In paper III, tissue Doppler (TDI) velocities; systolic (Sm), E’- and A’- wave; were collected from A4C projections at the mitral annulus. The E/E’ septum-ratio was calculated (84).

Velocity time integrals of the left ventricular outflow track (VTI LVOT) were obtained with PW from apical 5 chamber windows (A5C) (Figure 13). Mean values of three consecutive end-expiratory VTI LVOTs were used for a stroke volume calculation. Stroke volumes of the left ventricle in ml were calculated by formula: \( SV = 0.785 \times LVOTd^2 \times VTI \text{ LVOT} \) (78, 180). Continuous Doppler was used to measure velocity of a possible tricuspid valve insufficiency for calculation of a pressure gradient between the right
ventricle and the right atrium by the modified Bernoulli equation ($\Delta P = 4 \times V^2$) (176).

**Evaluation of left ventricular filling pressures and pressure dynamics**

Left ventricular filling pressures (LVFP), measured by estimated pulmonary capillary wedge pressures (ePCWP), were assessed non-invasively by combining IVCmax and IVCCI (I). Elevated ePCWP $\geq 15$ mmHg was supposed to exist with $> eRAP$ 10 mmHg. Ordinary LVFP, that is, ePCWP < 15 mmHg, was stated with eRAP-values $\leq 10$ mmHg (181, 182).

In addition, evaluation of the compliance of the left ventricle (pressure-volume relationship) was conducted (I, III). Signs of possible pathological instability in filling pressures and decreased compliance of LV were assessed by merging gathered information of diastolic properties of LV, level of venous return and TDI measurements (Figure 6) (84).

**Echocardiographic assessment and criteria for hypovolemia**

A conventional assessment of level of venous return (VR) to the heart was made by combining size of IVC (IVCmax) and IVCCI. IVCmax and IVCCI were converted to estimations of right atrial pressure (eRAP) (178, 179) as following:

i) The conventional definition for eRAP 0 to 5 mmHg was used, i.e. IVCmax $\leq 15$ mm with concomitant high IVCCI ($> 50\%$),

ii) eRAP 5 - 10 mmHg was stated with IVCmax values between 15 to 21 mm regardless of IVCCI,

iii) IVCmax size $> 21$ mm and low IVCCI ($< 50\%$) was interpreted as eRAP $> 10$ mmHg,

iv) IVCCI $\geq 80\%$ (considered as IVC collapse) and IVCmax < 15 mm was interpreted as eRAP -2 to 3 mmHg.

The criteria for the hypovolemic state, based on a low level of venous return, were the presence of estimated right atrial pressures $< 5$ mmHg. Euvolemia was stated with eRAP 5 - 10 mmHg and hypervolemia when eRAP was $> 10$ mmHg (I, III, IV).
Data analysis

The echocardiographic data obtained were processed and analysed both on-line and off-line. The rapid on-line analysis was implemented in papers I and IV including an analysis of: IVCmax, IVCmin, IVCCI, LAd, LVEDd, FS, visual assessment of left ventricular systolic function, visual assessment of the pulsed-wave Doppler velocities of transmitral flow, both visual and TAPSE-based assessment of systolic function of the right ventricle. Off-line processing (I, III and IV) consisted of a comprehensive assessment of diastolic function (Dt, E and A wave max velocities, E/A, E/Dt, E/E´ ratios), measurement of stroke volumes and LV areas and calculation of ejection fractions of LV. This process was carried out with commercially available software (EchoPac, GE, Healthcare, Horten, Norway) and/or with the Sequoia-512 device.

For overall evaluation of the usefulness of TTE as a preoperative modality, feasibility, on-line time consumption and acquisition circumstances in both morbidly obese and lean subjects were assessed. Time consumption for the on-line process was measured by a timer (I, IV) (183). In addition, the intra-observation bias for echocardiographic measurements was controlled (I).
Figure 12. The subcostal projection of the inferior vena cava and surrounding tissues obtained by transthoracic echocardiography.
Figure 13. The apical 5 chamber (A5C) view of the heart. The pulsed wave (PW) obtained flow curve of the left venricular outflow track (LVOT) for calculation of stroke volumes of the left ventricle.

**Fluids**

In this thesis both crystalloid and colloid fluids were administered. Products used were: 6 % hydroxyethyl starch 130/04 balanced (Volulyte™, Fresenius Kabi, Sweden) as colloid fluid and Ringer's solution (Fresenius Kabi, Sweden), NaCl 0.9 %, (Fresenius Kabi, Sweden) and buffered glucose solution (25 mg/ml, Fresenius Kabi, Sweden) as crystalloids.

In preoperative (II, III, IV) and intraoperative (IV) rehydration, only colloid fluids were infused. Antibiotics were mixed with NaCl 0.9 % or administrered directly in their commercially available form. In addition, minor amounts of fluids were administered as i.v. anesthetics, intropic and vasoactive drugs, NSAIDs and PONV prophylaxis.
**Inotropic and vasoactive drugs**
Perioperative ephedrine and/or phenylephrine were used as intermittent i.v. injection when necessary to ensure adequate tissue perfusion (MAP ≥ 65 mmHg), cardiac index (≥ 2.0) and heart rate (≥ 50/min) (II, IV) (184). Furthermore, if systolic left ventricular failure was detected in preoperative TTE, infusion of dobutamine 3 - 4 µg/kg IBW was started preoperatively (IV).

**Paper I**
Twenty eight morbidly obese subjects scheduled for bariatric surgery (the morbidly obese group, MO) and 19 lean subjects (the control group, CG) were consecutively enrolled in this observational study. CG consisted of subjects scheduled for elective general abdominal surgery. The aim of the study was to assess prevalence of preoperative hypovolemia and filling pressures of the left ventricle in morbidly obese subjects that have been prepared preoperatively by the rapid weight loss (RWL) diet, and compare this to lean controls with conventional preoperative fasting. This assessment was conducted by transthoracic echocardiography, with focus on the protocol’s rapidity and reproducibility. (See the detailed description of the TTE-protocol above in “Methods- Echocardiography”). All echocardiographic investigations were performed prior to surgery. The supine position was used during the TTE-scanning. Otherwise a semi-sitting position was applied preoperatively.

**Main outcome measures**
The main outcome measures were: i) level of preoperative venous return, ii) level of LVFP, iii) assessment of biventricular systolic function, iv) assessment and prevalence of impaired diastolic function in the left ventricle, and v) evaluation of feasibility, time consumption and acquisition quality for transthoracic echocardiography implemented by the study protocol.

Moreover, prevalence of dyspnea and/or orthopnea before and after the preoperative rapid-weight-loss preparation was assessed in order to evaluate significance of the RWL-diet to left ventricular filling pressures.

**Paper II**
Thirty four morbidly obese subjects scheduled for laparoscopic bariatric surgery were included consecutively. The control group (CG) consisted of 22 lean subjects enrolled for elective abdominal surgery. The ideal body weight was estimated with an equation height in cm - 100 for administration of anesthetics drugs in both groups. All subjects were anesthetized by the same
anesthetist and nurses in order to maintain a high level of standardization and avoid an inter-investigator bias.

In this study the technique for a rapid sequence induction of anaesthesia for morbidly obese patients was developed and evaluated. The technique was based on a combination of volatile and i.v. anesthetics (sevoflurane, propofol, suxamethonium and alfentanil) and was designed to do the following:

i) minimize risk for desaturation and hypoxia, i.e. maintain spontaneous breathing as long as possible and to keep the period of apnoea as short as possible before endotracheal intubation,

ii) enable sustained lung recruitment during induction as long as spontaneous breathing continued,

iii) assure hemodynamic stability, i.e. post-induction MAP goal ≥ 70% of the baseline,

iv) generate good circumstances for endotracheal intubation,

v) minimize risk for post-induction awareness.

The detailed logistics of the method is described earlier in the chapter “Anesthesia and preoxygenation techniques used in this thesis” and in Figure 11.

Before induction of anesthesia an infusion of glucose solution (25 mg/ml) at 1.5 ml/kg IBW per hour was initiated and approximately 500 ml colloid fluids were infused in both groups. In morbidly obese subjects a continuous, invasive blood pressure measurement was implemented (BD Arterial Cannula and Transducer Blood Sampling Set). In CG an automatic non-invasive blood pressure measurement was used. Arterial blood samples were gathered and analysed immediately. Peripheral oxygen saturation (SpO2) was registered directly after the preoxygenation and 1 minute after endotracheal intubation. Blood pressure levels were registered before the preoxygenation period and 3 minutes after the endotracheal intubation in a 5 - 10° reverse Trendelenburg position.

The anesthetic machine integrated timer was utilized to measure the time periods of interest in the process of induction. Three periods were measured: the spontaneous breathing time (SBT), the apnoea time (AT) and the total time (TT). The definition for the SBT was the time from the beginning of the administration of sevoflurane to the disappearance of spontaneous breathing. The apnoea was detected by clinical signs and with the
capnograph. The AT was defined as the time from disappearance of spontaneous breathing to a successful endotracheal intubation (AT = TT – SBT) (Figure 11).

The definition of a successful endotracheal intubation was the sensation and/or a clear visualisation of the endotracheal tube crossing the glottis and/or as the first signs of expiratory flow in the capnograph (for the subjects with the Cormack-Lehane scale 3 - 4).

Main outcome measures
Time relationships for spontaneous breathing and apnoea in addition to systolic and mean arterial blood pressures were measured for statistic analysis as described above. Pre- and post-induction SpO2, frequency of desaturation and MAC value after endotracheal intubation were registered. The Mallampati and Cormack–Lehane scales were used for assessment of the intubation circumstances between the groups. The suitability and feasibility of the study method for RSI were evaluated from both anesthetist’s and patients’ point of view.

Paper III
Thirty four preoperatively RWL-prepared morbidly obese subjects scheduled for bariatric surgery were consecutively enrolled in this substudy. The aims of the study were to implement and evaluate effects of the preoperative, individualized and ideal body weight (IBW) based volume challenge (VC) on hemodynamics, stroke volume, and the level of venous return to the heart. Effects of VC were evaluated by the comprehensive TTE-protocol preoperatively. (See the detailed description of the TTE-protocol above in “Methods”). All TTE investigations were performed in the awake state before and after standardized intravascular volume challenge of 6 ml coloids/kg ideal body weight (138, 185). The IBW was estimated with an equation height in cm – 100. The volume challenge was implemented to all study subjects for thorough assessment of the safety of the rehydration protocol.

Main outcome measures
The main outcome measures were: i) level of venous return before and after VC, ii) volume responsiveness; an increase of stroke volume ≥ 13 % was considered to be a volume responder (137, 180, 186), iii) biventricular systolic function before and after VC, iv) impact of VC on diastolic function and the filling pressures of the left ventricle, and v) to evaluate feasibility of dynamic and non-dynamic echocardiographic indices for VC in morbidly obese subjects.
**Paper IV**

Fifty morbidly obese subjects scheduled for bariatric surgery were consecutively enrolled for the study. The aim of the study was to evaluate need of perioperative hydration during laparoscopic bariatric surgery by comparing conventional monitoring to a more advanced approach (individualized goal-directed therapy, IGDT) (143, 146). A non-blinded allocation of the subjects to the intervention group (n = 30) and the control group (CG, n = 20) was conducted. The IBW was estimated with an equation height in cm - 100 for administration of anesthetics drugs and fluids in both groups.

In addition to pre- and/or intraoperative volume challenges, infusion of buffered glucose solution (25 mg/ml) at a rate of 1.5 ml/kg IBW/h and i.v. antibiotics (in total 550 ml crystalloids) were administrated after induction of anesthesia, before pneumoperitoneum in both groups. Postoperative fluid therapy during the stay at the postoperative recovery unit was identical between the groups, that is, 850 ml crystalloids (antibiotics, paracetamol and NSAIDs) and buffered glucose solution (50 mg/ml) at a fixed rate of 100 ml/h. Postoperative renal function, electrolyte and acid-base balance and levels of pro-natriuretic peptides (N-terminal prohormone of brain natriuretic peptide, Nt-proBNP) were analyzed in both groups (170, 171, 187). Urinary output was measured at POP only. Moreover, intra-abdominal pressures were monitored in the intervention group. The first IAP measurement was conducted in a supine position, before pneumoperitoneum in general anesthesia ensuring zero train-of-four ratio, zero PEEP and an expiratory pause of ten seconds. The pubic bone was used as a reference level. The second measurement was conducted 4 hours postoperatively without significant PONV and pain (visual analog scale, VAS ≤ 3/10) in a supine position. The perioperative logistics of the study is summarized in the study flow chart (Figure 13).

In the control group a standardized conventional cardiovascular monitoring was conducted (ECG, heart rate, non-invasive blood pressure measurements and peripheral saturation (Sp02)). No preoperative rehydration was applied. The intraoperative goals (MAP > 70 % of the pre-induction baseline and/or ≥ 65 mmHg, heart rate ≥ 50/min) were obtained by i.v. administration of colloids 3 ml/kg IBW and/or ephedrine and/or phenylephrine.

In the intervention group, IGDT and conventional cardiovascular monitoring similar to CG were implemented. Preoperative transthoracic echocardiography (TTE) and perioperative mini-invasive pulse-contour device (FloTrac/Vigileo™, Edwards Life sciences, Irvine CA, USA) were used to obtain functional hemodynamic parameters needed for IGDT in two steps.
First, preoperative TTE scanning and rehydration was performed 45 minutes before surgery. Second, maintained perioperative guidance of the fluid therapy was conducted using the FloTrac-device. The preoperative rehydration was implemented by 6 ml colloid fluids/kg ideal body weight if low level of venous return was detected by TTE (III). The second TTE investigation was performed to check the level of venous return. If remaining hypovolemia was found additional colloids 3 ml/ kg IBW was infused. Moreover, infusion of dobutamine 3 – 4 µg/kg IBW was initiated before induction of anaesthesia if systolic left ventricular failure was detected in the preoperative TTE. Stroke volume variation ≥ 12 % was used as a threshold (137, 143, 146, 160, 188) for administration of additional colloids 3 ml/kg/ IBW during surgery (138). In addition to fluids, i.v. ephedrine and/or phenylephrine were used when necessary to ensure adequate tissue perfusion (MAP > 70 % of the baseline and/or ≥ 65 mmHg, cardiac index ≥ 2.0 and heart rate ≥ 50/min) (184).

The data gathering
The baseline for MAP and heart rate was registered in a supine position before induction of anaesthesia in both groups. 5 minutes after intubation, before pneumoperitoneum and i.v. antibiotics the conventional and the first FloTrac-derived functional hemodynamic parameters (SVV, SV, cardiac output and cardiac index) were collected. From then on, registration of hemodynamic parameters was performed every 5 minutes. During pneumoperitoneum, IAP levels were kept at approximately 12 – 14 mmHg (always < 15 mmHg) to minimize risk of hemodynamic compromise (75, 93, 167). The FloTrac-guided fluid administration and monitoring was finished in the end of surgery. Conventional monitoring was implemented at the postoperative recovery unit in both groups.

Main outcome measures
Mean arterial pressures and heart rates were measured before and after induction of anaesthesia and during surgery for statistic comparison between the groups. A comparison of fluids infused was conducted. Postoperative urinary output and renal function were compared between the groups. Analysis of effects of volume therapy on NT-proBNP-levels, intra-abdominal pressures and functional hemodynamic parameters was conducted in the intervention group.
Figure 13. The flow chart of the perioperative logistics in paper IV.
Abbreviations: IGDT, individualized goal-directed therapy; *, conventional monitoring was conducted by ECG, heart rate, SpO2 and blood pressure measurements (non-invasively in the control group and invasively in the intervention group); TTE, transthoracic echocardiography; MAP, mean arterial pressure; SVV, stroke volume variation; CO, cardiac output; SV, stroke volume of the left ventricle; RSI, rapid sequence induction; IAP, intra-abdominal pressure; IBW, ideal body weight; ECG, electrocardiogram; POP, a postoperative recovery unit.
**Statistics**

The data processing was done with Statistical Package for Social Sciences (SPSS) version 18.0 (I and II) and with version 20.0 (III and IV). All data are expressed as mean values ± SD if not otherwise stated. Levene’s test was used to assess equality of variances of the data. Kolmogorov–Smirnov tests for normality were performed. Two-tailed Student’s test and/or Mann-Whitney U test were used for comparisons of mean values. Mann–Whitney U test was used as a non-parametric test whether the variables were not perfectly normally distributed and the number of cases was limited. When appropriate, Chi-squared and/or Fisher’s Exact Tests were performed for comparison of binominal data. Two-tailed p-values less than 0.05 were considered statistically significant. The sample sizes for each sub-study were calculated to achieve power at 0.8 minimum (Power = 1 − β = 0.8) with α level 0.05, β 0.2. The standard deviations of the primary variables that were used for sample size calculations were estimations if relevant values could not be found from the published data available.

**Limitations**

This thesis has several limitations. The settings of the substudies per se (single centre, not randomised, not blinded) may have been a potential confounder. In addition, anesthesia was standardized per se, but neither target controlled infusions (TCI) nor objective modalities for anesthesia depth monitoring (for example bispectral index (BIS) monitoring) were used. On the other hand, the experienced staff in bariatric surgery took care of all subjects in the studies. IBW was estimated by a simple calculation because of clinical simplicity of the equation. Thus, LBW was neither determined by objective (direct) measurements, for example body-impedance measurement, nor by more complicated equations intended to estimate the LBW.

Transthoracic echocardiography is subject to significant limitations in obese patients because of body habitus. In order to minimize investigator bias an experienced sonographer for the subject is obligate and all investigations were made by a single sonographer. Abnormal intra-abdominal and intrathoracic pressures in obesity may have an impact on measurements of inferior vena cava size and venous return to the heart (I, III, IV) (93).

The FloTrac-device is not validated in extreme obesity where reduced thorax wall and pulmonary compliance and propensity for increased stiffness of the left ventricle may have an impact on reliability of the FloTrac-data. Increased intra-abdominal pressures may also jeopardize reliability of stroke volume variation measurements but on the other hand IAPs were not significantly
increased in the substudy IV population. Furthermore, the intraoperative invasive monitoring was implemented by a single modality. This may increase a risk of incorrect decision making and fluid therapy during a possible system failure in the FloTrac-device.

Statistical comparison of effects of fluid therapy on heart and renal function between the intervention group and the control group could not be conducted due to many drop offs in controls (IV). In addition, intra-abdominal pressures were not measured in controls. In order to assess fluid therapy and cumulative balance more comprehensively a comparison of pre- and postoperative weight should have been valuable. Unfortunately, this was not conducted in this thesis.
Results

**Paper I:** In the morbidly obese subjects (MO, n = 28) mean BMI was 41.8 kg/m² (37 – 50.3) compared to lean individuals (CG, n = 19) with mean BMI 25.6 kg/m² (20.8 - 29). Most morbidly obese subjects had been severely obese over 20 years (20/28). Hypertension, asthma bronchiale, diabetes mellitus, obstructive sleep apnea syndrome/obesity hypoventilation syndrome (OSAS/OHS) and ischemic heart disease (IHD) were more frequent in the morbidly obese group compared to lean controls. In the morbidly obese group, prevalence of dyspnoea and/or orthopnea was higher before the RWL-period compared to that on the day of surgery (i.e. post RWL); 46.4 % and 10.7 % respectively. Preoperative loss of weight was 8.3 ± 2.1 % (4.4 - 12.2) and 11.1 ± 3.4 kg (5 - 18). No dyspnoea/orthopnea was found in CG. These findings may depend on potential existence of pre-RWL hypervolemia and high filling pressures of the heart (Table 1).

Low level of venous return was more common in the morbidly obese group compared with the control group, that is, 71.4 % of MO were hypovolemic vs. 15.8 % of lean controls; p < 0.001, odds ratio (OR) 13.3. In addition, diameters of left atrium (PLAX) were shorter in the morbidly obese group compared to CG. E/Dt ratios were not elevated. Left ventricular filling pressures were elevated in few subjects in the morbidly obese group (3/28) (Table 2). Left ventricular dysfunction was more frequent in MO. Impaired diastolic function of the left ventricle were more commonly detected in the morbidly obese group (57.1 %) than in controls (15.8 %); p = 0.006. Conventional systolic failure was rare; one in MO had impaired systolic LV function (ejection fraction of LV < 50 %). Right ventricular systolic function and pulmonary pressures appeared to be within normal limits in all patients.

The acquisition quality of echocardiography was poorer in MO compared to CG. PLAX and SAX were considered as the most feasible projections in MO. The most difficult to visualize was the right ventricle in A4C. The time-consumption for the on-line investigation in MO was longer vs. the control group (6.1 ± 1.97 minutes and 4.3 ± 1.1 minutes, respectively). Despite these acquisition challenges, the assessment of preload and heart function could be completed in 100 % of the patients. Reproducibility and intraobserver variation (calculated for LA, IVC, E-wave and Dt) were adequate.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>MO</th>
<th>CG</th>
<th>pT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.6 ± 10.5</td>
<td>50.1 ± 12.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, Female (%)</td>
<td>57.1</td>
<td>63.0</td>
<td>NS*</td>
</tr>
<tr>
<td>BMI (kg/m(^2)) on the day of surgery</td>
<td>41.8 ± 3.8</td>
<td>25.9 ± 2.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight (kg) on the day of surgery</td>
<td>123 ± 17.9</td>
<td>70.3 ± 10.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Preoperative dyspnea and/or ortopnea</td>
<td>13/28</td>
<td>0</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>136 ± 15.7</td>
<td>ND</td>
<td>NA</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16/28</td>
<td>3/19</td>
<td>ND</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9/28</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>OSAS/OHS</td>
<td>3/28</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>4/28</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>8/28</td>
<td>1/19</td>
<td>ND</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>11/28</td>
<td>3/19</td>
<td>ND</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2/28</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>2/28</td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbrivations: BMI, body mass index; BSA, body surface area; NA, not applicable; ND, not done; NS, not significant; T, independent sample t-test, equal variances not assumed; *, Fisher’s exact test; OSAS, Obstructive sleep apnoea syndrome; OHS, Obesity hypoventilation syndrome; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; SD, standard deviation of mean values; p, a p-value. The morbidly obese group (MO), n = 28; the control group (CG), n = 19.
Table 2. Estimated right atrial pressures and left ventricular filling pressures (number of cases and % of all cases)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MO</th>
<th>CG</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>eRAP -3 to 2 or 0 to 5 mmHg</td>
<td>20/28 (71.4%)</td>
<td>3/19 (15.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eRAP -3 to 2 mmHg</td>
<td>5/28 (17.9%)</td>
<td>1/19 (5.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>eRAP 5 - 10 mmHg</td>
<td>5/28 (17.9%)</td>
<td>11/19 (57.9%)</td>
<td>0.005</td>
</tr>
<tr>
<td>eRAP &gt; 10 mmHg</td>
<td>3/28 (10.7%)</td>
<td>5/19 (26.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>ePCWP &lt; 15 mmHg</td>
<td>25/28 (89.3%)</td>
<td>14/19 (73.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>ePCWP &gt; 15 mmHg</td>
<td>3/28 (10.7%)</td>
<td>5/19 (26.3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Prevalence of

<table>
<thead>
<tr>
<th>Condition</th>
<th>MO</th>
<th>CG</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia (%)</td>
<td>20/28 (71.4%)</td>
<td>3/19 (15.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Euvolemia (%)</td>
<td>5/28 (17.9%)</td>
<td>11/19 (57.9%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypervolemia (%)</td>
<td>3/28 (10.7%)</td>
<td>5/19 (26.3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: eRAP, estimated right atrial pressure; ePCWP, estimated pulmonary capillary wedge pressure;*, Fisher’s exact test; p, a p-value; NS, not significant. The morbidly obese group (MO), n = 28; the control group (CG), n = 19. Reprinted from Pösö T. et al. Rapid weight loss is associated with preoperative hypovolemia in morbidly obese patients. Obes Surg. 2013 Mar; 23(3):306-13 by the permission of Springer (I).

Paper II: The mean BMI was 42.4 (36 - 56.7) kg/m² in the morbidly obese group (n = 34) and 25.6 (19.5 - 30.4) kg/m² in the control group (n =22). The mean age was 43.5 (18 - 63) years in morbidly obese subjects and 49.1 (20 - 68) years in controls. Most subjects were women: 61.8 % and 86.4 % in the morbidly obese and control groups respectively.

The study protocol (Figure 11) implemented for preoxygenation and induction of anesthesia was considered to be feasible, reproducible and safe. No problems with compliance in vital capacity breathing with a tight facemask were noticed. The induction of sleep was smooth, without muscle twitches or undesirable movements in both groups. For most subjects, three to four vital capacity breaths of sevoflurane were enough for disappearance of the eye flash reflex. The circumstances for direct laryngoscopy were good and all the endotracheal intubations were successful at the first attempt. No aspiration was observed. No periods of desaturation or hypoxia were
registered; in fact, SpO2 was 100 % before and after endotracheal intubation in all subjects in the study (Table 3).

Table 3. Summary of process parameters (mean values and range)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MO</th>
<th>CG</th>
<th>pT</th>
<th>pMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous breathing time</td>
<td>67.0 (48 - 91)</td>
<td>70.7 (50 - 88)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Apnoea time</td>
<td>44.8 (21 - 65)</td>
<td>45.7 (23 - 61)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SpO2 pre intubation</td>
<td>100</td>
<td>100</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>SpO2 post intubation</td>
<td>100</td>
<td>100</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>MAP pre intubation</td>
<td>94.2 (74 - 120)</td>
<td>95.7 (73 - 124)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MAP post intubation</td>
<td>74.3 (58 - 120)</td>
<td>77.8 (53 - 111)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>MAC value post-intubation</td>
<td>0.8</td>
<td>0.8</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: MAC, a minimal alveolar conservation value (MAC); SpO2, peripheral saturation; MAP, mean arterial pressure; NA, not applicable; ND, not done; NS, not significant; T, independent sample t-test, equal variances not assumed; p, a p-value; MW, a non-parametric Mann-Whitney U test. All post values were measured 3 minutes after intubation of trachea. The morbidly obese group (MO), n = 34 and the control group (CG), n = 22.

The RSI-method implemented resulted in short apnoea times (AT) and long spontaneous breathing times (SBT) in both groups. In the morbidly obese group the AT was 44.8 (21 - 65) sec and the SBT was 67 (48 - 91) sec. In the control group the AT was 45.7 sec (23 - 61) and the SBT was 70.2 sec (50 - 88). No significant differences in measured time periods were found. All subjects were hemodynamically stable. An acceptable decrease in mean arterial blood pressure from the pre-induction baseline was registered (21.2 % in morbidly obese group and 18.8 % in the control group). No significant differences between the groups were registered in hemodynamic parameters. In addition, the first age-adjusted MAC-values after endotracheal intubation were measured to 0.8 indicating an appropriate level of general anesthesia and, thus, a low risk of post-induction awareness (Table 3).
Paper III: Thirty-four morbidly obese subjects (mean BMI 41.8 ± 4.6 kg/m², body surface area (BSA) 2.3 ± 0.2 m²) were enrolled in the study. Most subjects were women (23/34) with mean age of 42.8 ± 8.8 years. Preoperative loss of weight in three weeks was 8.3 ± 1.9 % (11.3 ± 3.6 kg) of TBW. Severe obesity had been long-lasting (≥ 15 years) in most patients (24/34). Patient characteristics, comorbidities and medications are summarized in Table 4. Preoperative risk assessment conducted with objective methods was not comprehensive, that is, cardiac and pulmonary investigations in the last 10 years before surgery were rare (Table 5).

Table 4. Patient characteristics, comorbidities and anti-hypertensive medication (% number of cases or mean values ± SD). The morbidly obese group (MO), n = 34.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>136 ± 14.7</td>
</tr>
<tr>
<td>BMI (kg/m²) at the day of surgery</td>
<td>41.8 ± 4.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.8 ± 8.7</td>
</tr>
<tr>
<td>Weight (kg) at the day of surgery</td>
<td>122.5 ± 17.9</td>
</tr>
<tr>
<td>Smoker (n)</td>
<td>12/34</td>
</tr>
<tr>
<td>Dyspnoea (in MET &lt; 4) (n)</td>
<td>13/34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (n)</td>
<td>17/34</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>12/34</td>
</tr>
<tr>
<td>Bronchial asthma/COPD (n)</td>
<td>14/34</td>
</tr>
<tr>
<td>OSAS/OHS (n)</td>
<td>9/34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>4/34   (11.8 %)</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>9/34   (26.5 %)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4/34   (11.8 %)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8/34   (23.5 %)</td>
</tr>
<tr>
<td>Combination therapy (consisting ≥ 2 of medications above)</td>
<td>9/34   (26.5 %)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; OSAS, Obstructive sleep apnoea syndrome; OHS, Obesity hypoventilation syndrome; COPD, chronic obstructive pulmonary disease; MET, metabolic equivalent of task; SD, standard deviation of mean values; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.
Table 5. Preoperative cardiac and pulmonary investigations in the last 10 years (number of cases). The morbidly obese group (MO), n = 34.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography/Dobutamine stress echocardiography</td>
<td>3/34</td>
</tr>
<tr>
<td>Spirometry/lung function testing</td>
<td>4/34</td>
</tr>
<tr>
<td>Exercise testing / cardiopulmonary exercise testing</td>
<td>2/34</td>
</tr>
<tr>
<td>Single-photon emission computed tomography (SPECT)</td>
<td>0/34</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (PCI)</td>
<td>1/34</td>
</tr>
</tbody>
</table>

Conventional systolic failure in LV and RV was infrequent; 2/34 and 0/34 respectively. Diastolic dysfunction (DD) of the left ventricle was commonly seen; 64.7 % (22/34) of MO were classified into DD-grades I to III of IV. Decreased dynamics of E/A-ratio were seen in association with a post VC Valsalva manoeuvre (p = 0.016). Increased post-VC E-wave and A-wave velocities were detected compared to baseline before VC (p < 0.001 and p < 0.001 respectively). No significant changes in E/A-ratios could be found. Increase in E/E’-ratios were seen post-VC (p = 0.025), but these ratios still remained below 10 (8.7 ± 2).

Preoperative hypovolemia (i.e. low level of venous return) was detected in most subjects (24/34, 70.6 %). The hypovolemic state was more frequently associated with female gender (p = 0.036), use of diuretics (p = 0.031) and no use of ACE/ARB (p = 0.009). The post volume challenge hypovolemia was rare; 5.9 % (2/34) patients were hypovolemic and 23/34 (67.6 %) of patients were euvoletic. The post-VC hypervolemia was seen in 26.5 % (9/34) of subjects. In these subjects diastolic dysfunction (p = 0.013), use of calcium channel blockers (p = 0.048), male gender (p = 0.033) were more frequent findings compared to post-VC euvoletic and hypovolemic subjects. In addition, post-VC hypervolemia was associated with pre-VC hypovolemia (p = 0.009) but not with pre-VC euvoletic (Table 6).

Most subjects were volume responders (29/34, p < 0.001). The preoperative state of venous return was not associated with volume-responsiveness in this study population. Medication with calcium channel blockers and systolic LV failure were more frequently seen in non-volume responders (5/34) compared to volume responders (p = 0.006, p = 0.015 respectively).
Table 6. Summary of hemodynamic parameters (% or number of cases or mean values ± SD) before and after volume challenge.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MO pre</th>
<th>MO post</th>
<th>pT/Chi-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>91 ± 14.4</td>
<td>86.4 ± 9.5</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>73.2 ± 13</td>
<td>74.1 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>66.1 ± 12.2</td>
<td>79.5 ± 14.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ΔSV (%)</td>
<td>NA</td>
<td>16.6 ± 7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Volume responder (%)</td>
<td>NA</td>
<td>29/34 (85.3 %)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Prevalence of hypovolemia</td>
<td>24/34 (70.6 %)</td>
<td>2/34 (5.9 %)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Prevalence of euvolemia</td>
<td>7/34 (20.6 %)</td>
<td>23/34 (67.6 %)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Prevalence of hypervolemia</td>
<td>3/34 (8.8 %)</td>
<td>9/34 (26.5 %)</td>
<td>NS*</td>
</tr>
</tbody>
</table>

Abbreviations: MAP, mean arterial blood pressure; ΔSV, change of stroke volume; T, independent sample t-test; *, Chi-Square or Fischer's exact test; NS, not significant; NA, not applicable; SD, standard deviation of mean values; n, number of cases; p, p-value; MO pre, the morbidly obese group before volume challenge; MO post, the morbidly obese group after volume challenge. The morbidly obese group (MO), n = 34.

Paper IV: Patient characteristics were similar in both groups. In the intervention group BMI was 42.7 ± 5.3 kg/m², age 43 ± 14 years and 16/26 were women. In the control group BMI was 41.8 ± 4.3 kg/m², age 46 ± 11 years and 11/20 were women. Equal to other papers in this thesis, hypertension, diabetes mellitus and bronchial asthma were common co-morbidities. In the intervention group prevalence of preoperative hypovolemia was 13/26, euvolemia 12/26 and hypervolemia 1/26 (Table 9). Preoperative loss of weight (% of TBW) was similar between the groups (8.8 ± 1.8 in the intervention group compared to 8.5 ± 2.0 in CG, NS).

No differences in time for surgery, consumption of anesthetics, length of stay at POP, length of hospital stay and thirty-day mortality were found between the groups. No pre- or postoperative renal failure was found. In the intervention group postoperative Nt-proBNP levels were higher compared to the preoperative baseline (280.4 ± 263.3 vs. 112.5 ± 157.7, respectively); p = 0.007. Intra-abdominal pressures were not elevated at OR nor at POP. The perioperative data is summarized in Table 7.
In the intervention group, more preoperative colloid fluids were administered compared to no preoperative rehydration in CG; \( p < 0.001 \). During surgery there was no difference in fluids administered between the groups. In total, more fluids were administered in the intervention group compared to the control group; \( p = 0.009 \). Overall, more colloid and crystalloid fluids were infused in the intervention group compared to CG (\( p = 0.007 \) and \( p = 0.039 \), respectively) (Table 8).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IG</th>
<th>CG</th>
<th>( p )T</th>
<th>( p )MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min)</td>
<td>79.5 ± 15</td>
<td>86.6 ± 49</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>MAC value intraoperatively</td>
<td>0.85 ± 0.1</td>
<td>0.83 ± 0.1</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Remifentanil (mg) infused</td>
<td>2.14 ± 0.54</td>
<td>2.0 ± 1.3</td>
<td>NS</td>
<td>0.035</td>
</tr>
<tr>
<td>Time at POP in hours</td>
<td>18.1 ± 1.6</td>
<td>18.2 ± 2.3</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Diuresis at POP</td>
<td>1683 ± 741</td>
<td>1478 ± 331</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Cumulative fluid balance in ml without perspiration</td>
<td>2298 ± 892</td>
<td>2013 ± 371</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Creatinine preoperatively</td>
<td>70 ± 19.6</td>
<td>76 ± 24.8</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Creatinine postoperatively</td>
<td>65.7 ± 18.1</td>
<td>72 ± 18.6</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>2.4 ± 2</td>
<td>1.7 ± 0.7</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>0/26</td>
<td>0/20</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Intra-abdominal pressure</td>
<td>9.52 ± 2.6</td>
<td>9.46 ± 3.8</td>
<td>NS</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation of mean values; n, number of cases; mg, milligrams; min, minutes; POP, the postoperative recovery unit; MAC, a minimal alveolar concentration of sevoflurane; p, a p-value; T, an independent sample T-test; MW, a non-parametric Mann-Whitney test; NS, not significant; ND, not done. The intervention group (IG), n = 26; the control group (CG), n = 20.
Table 8. Summary of fluids infused (in ml) in the intervention group (IG) and the control group (CG) (mean values ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IG</th>
<th>CG</th>
<th>pT</th>
<th>pMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fluids</td>
<td>4053 ± 734</td>
<td>3499 ± 342</td>
<td>0.002</td>
<td>0.009</td>
</tr>
<tr>
<td>Total fluids (crystalloids)</td>
<td>3403 ± 752</td>
<td>3036 ± 396</td>
<td>0.039</td>
<td>0.07</td>
</tr>
<tr>
<td>Total fluids (colloids)</td>
<td>657 ± 263</td>
<td>463 ± 203</td>
<td>0.007</td>
<td>0.007</td>
</tr>
<tr>
<td>Colloid fluids infused preoperatively</td>
<td>213 ± 204</td>
<td>0</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation of mean values; n, number of cases; ml, milliliters; p, a p-value; T, an independent sample T-test; MW, a non-parametric Mann-Whitney test; NS, not significant. The intervention group (IG), n = 26; the control group (CG), n = 20.

Mean arterial blood pressure levels were higher in the intervention group compared to the control group both after induction of anesthesia (76 ± 15 and 62 ± 11 mmHg respectively); p = 0.001 and during surgery (78 ± 11 and 68 ± 10 mmHg, respectively); p = 0.001. Drop in blood pressure after induction of anesthesia was 20.8 % in the intervention group and 38 % in the control group. No tachycardia was registered (Table 10). More phenylephrine was used in the intervention group vs. CG, 0.21 ± 0.22 and 0.12 ± 0.27 mg respectively; p = 0.011. Dobutamine infusion was used for one patient in the intervention group.

In the intervention group heart rate (68 ± 11) and SVV (8.7 ± 2.9) were lower after endotracheal intubation compared to mean intraoperative values (heart rate 78 ± 11, SVV 11.5 ± 2; p = 0.002 and p = 0.001, respectively). In addition, lower stroke volumes (66 ± 16 ml), higher heart rate (75 ± 14) and higher SVV (15.7 ± 4.8) were registered after reverse Trendelenburg positioning and pneumoperitoneum compared to post-intubation values (SV 78 ± 20 ml, heart rate 68 ± 11, SVV 8.7 ± 2.9; p = 0.022, p = 0.001, p = 0.017, respectively). No statistical change in cardiac index was registered (Table 9).
Table 9. Summary of perioperative hemodynamic parameters in the intervention group (IG) (mean values ± SD or n).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IG preop</th>
<th>IG post intub</th>
<th>IG post rT</th>
<th>IG intraop</th>
<th>pT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>96 ± 11</td>
<td>76 ± 15</td>
<td>75 ± 14</td>
<td>75 ± 9</td>
<td>0.001†</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>74 ± 12</td>
<td>68 ± 11</td>
<td>75 ± 14</td>
<td>78 ± 11</td>
<td>0.017‡ 0.002‡‡</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>NA</td>
<td>78 ± 20</td>
<td>66 ± 16</td>
<td>70 ± 14</td>
<td>0.022‡</td>
</tr>
<tr>
<td>SVV</td>
<td>NA</td>
<td>8.7 ± 2.9</td>
<td>15.7 ± 4.8</td>
<td>11.5 ± 2</td>
<td>0.001‡‡</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>NA</td>
<td>5.2 ± 1.3</td>
<td>5.0 ± 1.5</td>
<td>5.4 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>NA</td>
<td>2.3 ± 0.6</td>
<td>2.2 ± 0.6</td>
<td>2.4 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>eRAP &lt; 5mmHg</td>
<td>13/26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>eRAP 5 - 10 mmHg</td>
<td>12/26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>eRAP &gt; 10 mmHg</td>
<td>1/26</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: MAP, mean arterial blood pressure; SVV, stroke volume variation; eRAP, estimated right atrial pressure; T, independent sample t-test; rT, a reverse Trendelenburg position; IG preop, preoperative baseline mean values in the intervention group; IG post intub, post intubation mean values in the intervention group; IG post rT, mean values in the intervention group 5 minutes after re-positioning to rT; IG intraop, intraoperative mean values in the intervention group; p, a p-value; †, a p-value between preoperative baseline and post intubation mean values; ‡, a p-value between post intubation and post rT mean values; ‡‡, a p-value between post rT and intraoperative mean values; NS, not significant; NA, not applicable; SD, standard deviation of mean values; n, number of cases. The intervention group (IG), n = 26.
Table 10. Summary of perioperative hemodynamic parameters in the intervention group (IG) and the control group (CG) (mean values ± SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IG</th>
<th>CG</th>
<th>pT</th>
<th>pMW</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP T0</td>
<td>96 ± 11</td>
<td>100 ± 12</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>MAP T1</td>
<td>76 ± 15</td>
<td>62 ± 11</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>MAP T2</td>
<td>74 ± 11</td>
<td>69 ± 15</td>
<td>NS</td>
<td>0.051</td>
</tr>
<tr>
<td>MAP T3</td>
<td>78 ± 11</td>
<td>68 ± 10</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate T0</td>
<td>74 ± 12</td>
<td>74 ± 14</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Heart rate T1</td>
<td>68 ± 11</td>
<td>66 ± 7</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Heart rate T2</td>
<td>75 ± 11</td>
<td>78 ± 15</td>
<td>NS</td>
<td>ND</td>
</tr>
<tr>
<td>Heart rate T3</td>
<td>79 ± 11</td>
<td>75 ± 11</td>
<td>NS</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: MAP, mean arterial pressure; T0, preoperative baseline mean values in a supine position as awake; T1, mean values 5 minutes after endotracheal intubation; T2, mean values 5 minutes after re-positioning to a reverse Trendelenburg position; T3, intraoperative mean values; SD, standard deviation of mean values; n, number of cases; p, a p-value; T, an independent sample T-test; MW, a non-parametric Mann-Whitney test; NS, not significant; ND, not done. The intervention group (IG), n = 26; the control group (CG), n = 20.
Discussion

This thesis describes a comprehensive perioperative management of morbidly obese individuals scheduled for bariatric surgery. In morbid obesity perioperative cardiovascular and respiratory stability and, hence, enhanced recovery, can be achieved by implementing strict and proven methods of anesthesia (97) and fluid therapy (III, IV) (41, 85).

The key messages of papers I, III and IV were that i) the RWL-preparation prior to bariatric surgery may expose morbidly obese patients to significant dehydration (I), ii) the preoperative rehydration regime implemented by colloids 6 ml/kg IBW was found to be a suitable treatment to obtain optimal levels of venous return (III) and, iii) preoperative rehydration may increase hemodynamic stability during intravenous induction and even maintenance of anesthesia without risk of postoperative complications. In addition, conventional intraoperative cardiovascular monitoring seems to be a sufficient approach in non-complicated bariatric surgery (IV).

Much focus should be placed on cardiovascular assessment and optimization of morbidly obese patients (I, III, IV) (38, 41, 45, 93). Non- and/or mini-invasive cardiovascular monitoring in combination with targeted IBW-based rehydration should be considered to increase thorough perioperative hemodynamic stability. Cardiovascular optimizing of morbidly obese individuals should be initiated already before anesthesia induction and surgery (III, IV) (185). Preoperative screening of a level of venous return, assessment of filling pressures in the left ventricle, biventricular function of the heart should be included in management of these high-risk patients to increase perioperative safety. For this purpose, transthoracic echocardiography was shown to be a feasible preoperative modality, even in morbid obesity (I, III, IV). Monitoring of preoperative level of venous return and cardiac function has several potential advantages: i) judgment of individual targets without bias of anesthetic vasodilatation is facilitated, ii) instability during induction of anesthesia is minimized, iii) possibility for more precise planning of vasoactive/inotropic medication and additional volume therapy during surgery is generated and, iv) intraoperative monitoring is facilitated with “the preoperative data” in mind (IV) (152, 154).

Stable biventricular filling pressures are fundamental throughout the perioperative period in bariatric surgery in order to reduce the physiological stress of anesthesia and surgery (41, 97). Hemodynamic instability may occur particularly during induction of anesthesia and pneumoperitoneum (38, 75, 93). The results of paper IV may indicate that not only the amount of
fluids but the timing of rehydration may play a key role for cardiovascular intraoperative stability - both post-induction and intraoperative mean arterial blood pressures were higher in the intervention group with preoperative rehydration vs. the control group. Thus, euvolemia is advocated in bariatric surgery (41, 75, 93) and should be reached before induction of anesthesia (I - IV).

In morbidly obese individuals scheduled for general surgery, overreplacement of fluids may lead to respiratory complications, including pulmonary strain/edema that necessitates non-invasive ventilatory support and monitoring at a higher level of care than an ordinary postoperative recovery unit (41). In addition, hypervolemia may increase perioperative bleeding (189). On the other hand, insufficient volume therapy may lead to organ hypoxia and acute renal failure. Hence, proper monitoring of rehydration is crucial for highest perioperative safety for this patient group (I, III, IV) (45, 85, 185, 190).

However, at the moment, publications concerning perioperative fluid therapy regimes in severe obesity are few and are not based on general consensus (41, 85). To my knowledge, papers I, III and IV are the first works available with focus on preoperative hydration balance and fluid management in this patient population. This lack of published information was reflected in a recent consensus statement for bariatric anesthesia management (97) where fluid management is not mentioned at all. Nevertheless, based on the results of paper IV, the perioperative need of fluids was approximately 800 ml per hour (11 ml/kg IBW/h) during surgery plus preoperative colloid fluid bolus 6 ml/kg IBW. These results are in concordance with a recent work by Jain et al. (85) indicating that “liberal” rehydration (190, 191) in bariatric surgery may not be needed.

In patient populations with propensity for heart failure, e.g. individuals scheduled for bariatric surgery, the fluid therapy should be implemented preferably with on-line knowledge of volume responsiveness, diastolic properties and compliance of the left ventricle. This kind of information during rehydration can be achieved by echocardiography and Doppler indices (Figure 6) (III) (78, 154). In this context, assessment of diastolic properties of the left ventricle, evaluation of E/A-ratio dynamics is a robust, reproducible and rapid way to obtain on-line information of pressure-volume relationship of LV (III) (78, 84). Tissue Doppler imaging is a useful modality in comprehensive cardiac diagnostics. However, monitoring volume challenge by use of TDI gives no additional information with a critical impact for bed-side decision making. Thus, monitoring conventional dynamic transmitral indices together with change of stroke volume (ΔSV)
provides sufficient information about pressure–volume relationship in LV, volume responsiveness and limitations in global stressed volume (III) (78, 192). In addition, it was confirmed that where there are physical limitations for signal acquisition related to body habitus as in morbid obesity, detailed comprehensive assessment of filling pressures can be difficult and time-consuming (III).

In addition, echocardiography can also be applied preoperatively during spontaneous breathing (154). Most modalities that produce dynamic data of hemodynamics (e.g. FloTrac, PiCCO, Cardiac Q) are validated only for use during mechanical ventilation with sufficient tidal volumes and, hence, cannot be utilized in preoperative optimizing protocols during spontaneous breathing (IV) (144). However, assessment with echocardiography is a single assessment compared to other available modalities that are designed to gather continuous data. Thus, the best results may be reached by a combined and strategic use of these modalities (IV) (144, 145, 153) (Figure 10). Continuous cardiovascular monitoring allows an anesthetist to react on hemodynamic instability promptly and precisely. Traditional perioperative “in need” approach for volume therapy with conventional intermittent monitoring may lead to fluctuating hemodynamics, suboptimal organ perfusion, and potential over-replacement of i.v. fluids with risk of postoperative respiratory distress during prolonged surgery in particular (137, 193).

The FloTrac was the modality of choice in this thesis due to existing validation data, availability in our clinic, relative feasible and rapid set-up (only an arterial line needed). However, invasive intraoperative monitoring by the FloTrac-device gave no additional information on hemodynamics with critical impact in our practice, where no difference in fluids administered during surgery was found. There was no difference in length of stay at POP, length of hospital stay or postoperative complications between the groups in paper IV (Table 7). On the other hand, time for surgery was relatively short in this study population. Thus, it should be kept in mind that the value of continuous cardiovascular monitoring may be augmented during prolonged or complicated surgery (85, 137). In addition, when comparing set-up times of the FloTrac to assessment by transthoracic echocardiography, the TTE is clearly superior. The time spent for obtaining hemodynamic data by TTE was $6.4 \pm 2.3$ minutes compared to $18.6 \pm 3.3$ minutes for the FloTrac device ($p < 0.001$). From the economical point of view, TTE is even cheaper in everyday practice without catheter costs.

The volume therapy used to obtain euvolemia in this thesis was based on the standardized combination of crystalloid and colloid fluids. Colloids were
used in volume challenges only (II, III and IV). In fact, this kind of combination has shown to increase the glomerular filtration rate and the clearance of crystalloids (194) and, hence, may protect individuals with narrowed cardiorespiratory limits against hyper-hydration. Thus, combined administration of these fluids in general may be motivated despite of somewhat restrictive recommendations for use of colloids at the moment (195). This subject should be studied further in morbidly obese subjects scheduled for general surgery in particular.

Table 11 summarizes some essential hemodynamic issues that bariatric anesthetists and surgeons should take into account for increased safety and to cut complication rates and length of hospital stay in morbidly obese individuals.
<table>
<thead>
<tr>
<th>Point of interest</th>
<th>Principles</th>
<th>“Caution”</th>
<th>Methods</th>
<th>Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of venous return and biventricular filling pressures of the heart</td>
<td>Venous return stability</td>
<td>Optimal positioning</td>
<td>Preoperative volume challenge</td>
<td>Preoperative TTE</td>
</tr>
<tr>
<td></td>
<td>Afterload stability</td>
<td>Avoid hypo/hypervolemia</td>
<td>Intraoperative volume challenge</td>
<td>Intraoperative non/min invasive monitoring, (TEE)</td>
</tr>
<tr>
<td></td>
<td>Pressure-volume stability of LV</td>
<td>Avoid excessive vasodilatation</td>
<td>Vasoactive medication</td>
<td>Foley/direct measurement by the surgeon</td>
</tr>
<tr>
<td></td>
<td>Euvolemia</td>
<td>Level of IAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractility</td>
<td>Preserved/ increased contractility</td>
<td>Arrhythmias</td>
<td>Low-dose inotropic medication (dobutamine)</td>
<td>Preoperative TTE</td>
</tr>
<tr>
<td></td>
<td>Optimal biventricular filling pressures</td>
<td>Avoid excessive vasoplegia</td>
<td>Perioperative inodilators in case of severe HF (levosimendan, milrinone)</td>
<td>Intraoperative non/min invasive monitoring, (TEE)</td>
</tr>
<tr>
<td></td>
<td>Slight pulmonary vasodilatation</td>
<td>Avoid hypoxia and hypercapnia</td>
<td>Adequate intraoperative administration of anesthetics</td>
<td>Consider PA in severe RV failure</td>
</tr>
<tr>
<td></td>
<td>RV failure</td>
<td>Moderate decreased sympathetic activity only</td>
<td></td>
<td>Assessment of IBW, LBW</td>
</tr>
<tr>
<td>Renal function</td>
<td>Stabile RAAS</td>
<td>Avoid excessive hypotension</td>
<td>Preoperative volume optimizing</td>
<td>Preop TTE, Intraop non/min invasive monitoring, Foley catheter</td>
</tr>
<tr>
<td></td>
<td>Euvolemia</td>
<td>Avoid high IAPs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; HF, heart failure; RV, the right ventricle; PA, a pulmonary catheter; RAAS, the renin-aldosterone-angiotensin system; IBW, ideal body weight; LBW, lean body weight; IAP, intra-abdominal pressure; preop, preoperative; intraop, intraoperative.
As discussed earlier in the Background part of the thesis (“Obesity and the respiratory system”), risk of desaturation is increased in morbidly obese individuals during induction of anesthesia in particular. Thus, most effective and safe techniques for preoxygenation and anesthesia induction are addressed. In the anesthesia technique described in paper II, sevoflurane was combined with propofol, alfentanil and suxamethonium, and was demonstrated to be a safe method for rapid sequence induction regardless of BMI without episodes of desaturation. In addition, minimal compromise of hemodynamics was attained (II) (Table 3, Figure 11).

To maintain spontaneous breathing as long as possible during induction of anesthesia may be fundamental regarding to prolong “the safety time period” for laryngoscopy (i.e. decrease risk of desaturation). This can be resolved in different ways, including the use of volatile anesthetics during induction (II) or other i.v. drugs that have minor depressive impact on the respiratory drive (196, 197). Volatile induction conducted by sevoflurane may have several advantages in morbidly obese individuals in particular. Sevoflurane causes bronchodilatation and decreases respiratory resistance (198). In addition, in morbid obesity efforts to improve or even normalize ventilation/perfusion ratio before surgery may be fundamental for adequate oxygenation. Therefore, as described in this thesis, utilizing sevoflurane together with high FiO2 and vital capacity breathing in the beginning of a RSI sequence allows continued recruitment of lungs during induction of sleep and, hence, may increase the quality of preoxygenation (II) (Figure 11). This procedure may have major advantages in patients with excessive body mass, particularly for abdominal, thoracic or face obesity, especially in obese patients with concomitant pulmonary pathology such as bronchial asthma and/or chronic obstructive pulmonary disease (199). In addition, accordingly to the results of paper II, use of sevoflurane during the induction process may reduce risk of post-induction awareness (post-intubation MAC 0.8) (Table 3).

Moreover, it is clear that prevalence for cardiovascular co-morbidities is increased in morbidly obese individuals (38, 41). This should be taken into account regarding the choice of anesthetics. Volatile anesthetics, e.g. sevoflurane, have cardioprotective properties that should be utilized in management these individuals with increased risk of perioperative cardiovascular adverse events (200, 201). Thus, use of volatile anesthetics already in induction of anesthesia (II) may function as volatile preconditioning and, hence, reduce cardiovascular adverse events.

As discussed earlier in this thesis, a proper choice, dosing and speed of administration of opiates, hypotics and neuromuscular blocking agents are the cornerstones for safe induction of anesthesia at the moment (Figure 7).
An anesthetist must secure sufficient speed for injection to avoid awareness and, on the other hand, overdosing. The hyperdynamic circulation in addition to possible pre-induction anxiety in morbidly obese individuals should be taken into account before administration of hypnotics (86, 94, 99). In general, sedatives are not recommended as premedication due to respiratory co-morbidities (41, 45, 93). In this thesis (II), as a substitute of sedative premedication, a bolus of propofol was given before pre-oxygenation (20 mg i.v.). This may facilitate induction of sleep in morbidly obese individuals due to reduction of sympathetic activity and hyperdynamic circulation by the drug. In addition, 30 sec vital capacity breathing with sevoflurane may have had equivalent effects as propofol (Figure 11).

Necessity of RSI in morbidly obese individuals has been questioned in recent guidelines (33, 97) for bariatric surgery, and is recommended only with history of gastrooesophagal regurgitation. Regardless to the approach chosen for induction (i.e. RSI or pre-intubation mask-bag ventilation) an early injection of neuromuscular blocking agents during the induction process may be advocated for easier mask ventilation and/or rapid endotracheal intubation. In many severe obese individuals proper mask ventilation is possible only after i.v. injection of these drugs (II) (97).

Nevertheless, RSI can also be conducted in other indications than increased risk of endotracheal aspiration. In addition to the obvious risk of difficult mask-bag ventilation per se, it must be underlined that morbidly obese individuals have considerably increased risk of rapid desaturation and hypoxia during hypoventilation and/or apnoea due to decreased functional residual capacity, increased intra-abdominal pressure, cranial displacement of diaphragm, increased tendency to atelectasis and shunt fraction (II) (45). Moreover, in contrary to common difficulties in face mask ventilation, endotracheal intubation has been shown to be relatively easy (II) (122). For these reasons, in my opinion, mask-bag ventilation should be avoided when possible and a straightforward rapid sequence induction is advocated in proper positioning (a “ramp” position) and adequate preoxygenation (125). Thus, in this thesis (II, IV), RSI was implemented in all study subjects to avoid mask-bag ventilation in addition to conventional indications for RSI (111).
Conclusions

**Paper I:** Low level of venous return and impaired diastolic function of the left ventricle was more common in the RWL-prepared morbidly obese group compared to the lean control group with ordinary preoperative fasting. Caution must be taken regarding the level of venous return in subjects scheduled for bariatric surgery with significant preoperative weight loss. Preoperative transthoracic echocardiography is a robust modality for assessment of level of venous return and cardiac function even in morbid obesity.

**Paper II:** The combined RSI-technique conducted by sevoflurane, propofol, alfentanil and suxamethonium was found to be a cardiorespiratory stable and practical method for RSI regardless of BMI. In addition, minimal risk of awareness and good circumstances for endotracheal intubation by direct laryngoscopy were established by the method.

**Paper III:** IBW-estimates and appropriate monitoring are the key issues for feasible and safe fluid management in severe obesity. The standardized volume challenge of 6 ml colloids/kg IBW was shown to be suitable for preoperative rehydration of RWL-prepared morbidly obese individuals. Euvolemia was achieved in most subjects. No association between the preoperative state of venous return and volume-responsiveness was found. Majority of the morbidly obese subjects were volume responders. In this patient population, use of conventional Doppler indices were more suitable compared to tissue Doppler, giving sufficient information on pressure-volume correlation of the left ventricle during rehydration.

**Paper IV:** Increased perioperative cardiovascular stability may be reached by preoperative rehydration. The management of rehydration should be individualized. Preoperative screening and optimizing of the level of venous return may be needed in morbidly obese individuals scheduled for bariatric surgery. Invasive perioperative monitoring may provide additional information of hemodynamics, but is without critical impact in uncomplicated bariatric surgery. Thus, conventional intraoperative approach for cardiovascular monitoring seems to be sufficient for the purpose.
Future implications

At the moment, in modern anesthesia management, both volatile anesthetics and i.v. hypotics are usually administered in combination with opiates. However, opiate drugs have undesired side-effects as respiratory depression and increased risk of post operative nausea and vomiting (116). When used as a single drug and low-dose (e.g. fentanyl < 1-2 µg/kg IBW) these side effects are minimal. But, in combination with other drugs (e.g. midazolam, propofol and/or sevoflurane), opiates cause significant respiratory depression due to synergistic physiological effects (110). Thus, to diminish these concerns and to optimize postoperative recovery period, use of opioids should be reassessed and perhaps minimized. Even an opiate free multimodal approach for induction and maintenance of anesthesia in morbidly obese individuals has been described. In this concept, several non-opiate drugs in various combinations can be applied. Most useful and promising drugs are α₂ agonists (for example clonidine and dexmedetomine), ketamine, lidocaine, corticosteroids and beta-blockers (such as esmolol) (86, 196, 197, 202-205). In future, beta-blockers may also play an important role in postoperative pain management and, hence, contribute in the concept of “the opiate free perioperative approach” as a standard drug (203).

Nevertheless, a multimodal opiate-free approach for induction of anesthesia without a hypnotic-opiate synergy may be a challenge regarding to e.g. awareness, circumstances for laryngoscopy and cardiorespiratory responses. On the other hand, to minimize synergistic effects of drug combinations (such as fentanyl or remifentanil plus propofol or midazolam) on respiratory drive and, hence, maximize ability for spontaneous breathing (II) (106, 110, 197), may be a cornerstone for increased patient safety in morbidly obese individuals in particular. However, at the moment, the evidence may be too sparse to implement opiate-free approaches for induction and maintenance of anesthesia in clinical practice (202, 206). Prospective randomized studies in this concept are warranted.

In addition, routine use of body impedance measurements for more precise assessment of lean body mass, TCI-models that are adjusted for severe obesity may be essential for increased patient safety and enhanced recovery (97). Moreover, reliable, feasible and economical non-echocardiographic modalities for standardized scanning of venous return (112) and function of the heart are needed. Continuous non-invasive cardiovascular monitoring that is user-friendly and easy to implement in practise without need of systematic education initiative is addressed.
In general, it should be underlined that morbidly obese individuals may appear as three different categories in need of surgery: i) in non-bariatric surgery, ii) in bariatric surgery, and iii) in general surgery after bariatric surgery. All these patient categories have different hemodynamic, respiratory and gastrointestinal characteristics and, hence, challenging the anesthesia praxis further. At the moment, the evidence of potentially altered physiological characteristics in post-bariatric surgical individuals from an anesthesiological point of view is very sparse (207). More studies comparing these patient categories with each other are needed for better understanding of impact of obesity and bariatric surgery in particular.
**Acknowledgements**

First, I would like to show my greatest acknowledgements to my supervisor Doris Kesek and to co-supervisors Ola Winsö and Roman A’roch. Most of all I appreciate the thorough confidence on my development during this project and capacity to complete the issues needed.

I also wish to show my appreciation to Michael Haney for showing me “the straightforward academic attitude” and for excellent language support.

In addition, I would thank the administration staff at Umeå University, Ullagreta Gidlund and Göran Johansson in particular, for all necessary work that you have done for this PhD project.

The paper II is dedicated to the memory of my colleague and first supervisor for this project, Staffan Andersson, who died suddenly in December 2010. In addition, I would thank the staff at Luleå University of Technology for the work done during the first steps of this project.

Thanks to all colleagues at Sunderby hospital. You have given me more ”spirit” to finish this work both by your encouraging comments and (constructive) criticism.

Thanks to the FoU-unit at Norrbotten County Concil (NLL) for both economical and scientific support for carry out this work. Thanks to Robert Lundqvist for statistical support. Karin Zingmark and Mats Eliasson – you have encouraged me to believe that the clinical research in the field of anesthesiology and “the academic sprit” can and must be established at Sunderby hospital.

And, at last but not least - the major appreciation and thanks to my family, Kajsa, Astrid, Johan and Karl, for giving me endless support and opportunity to complete this work.
Economical support
The research was supported by the Norrbotten County Council and Arnerska Research Fund.

Permissions and reprints
Some of the images, tables, and part of the text of this thesis are reproductions from the original articles. The adequate permissions for reuse of the material used in this thesis have been acquired from the publishers concerned.
References


97. Bellamy JC, Margarson MP. Designing intelligent anesthesia for a changing patient demographic: a consensus statement to provide guidance for specialist and non-specialist anesthetists written by members of and endorsed by the Society for Obesity and Bariatric Anaesthesia (SOBA). Perioperative Medicine 2013;2(12).


