Title: Perioperative Management of the Severely Obese Patient - A Selective Pathophysiological Review

Short title: Perioperative care in severe obesity

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Implication Statement (25-50 words)

Obesity is a common comorbidity now recognized as a multi-system pro-inflammatory disorder, not simply a structural one. This article presents anesthesiologists with a selective synopsis of the key pathophysiological changes involved in obesity, placing up to date research in context with perioperative care of the severely obese patient.

Abstract

Purpose: Obesity is widespread, yet is often understood primarily as a disorder of body structure. The article provides anesthesiologists with a synopsis of recent research into the complex pathophysiology of obesity emphasizing the importance of this information for perioperative planning and management, and reviewing some of the major perioperative challenges in this patient group.

Principal findings: Obesity is a multi-system chronic pro-inflammatory disorder, associated with increased morbidity and mortality. Adipocytes are far more than storage vessels for lipid, and they secrete a large number of physiologically active substances called adipokines that lead to inflammation, vascular and cardiac remodeling, airway inflammation, and altered microvascular flow patterns. They contribute to linked abnormalities such as insulin resistance and the metabolic syndrome, and attract and activate inflammatory cells such as macrophages. These changes can ultimately lead to organ dysfunction, especially cardiovascular and pulmonary issues. In the respiratory system, anesthesiologists should be familiar not just with screening tools for obstructive sleep apnea, but also with the obesity hypoventilation syndrome, which is less well appreciated and carries a significant outcome disadvantage. Perioperative management is challenging, and centers around cardiorespiratory and metabolic optimization, minimizing adverse effects of both pain and systemic opioids, effective use of regional anesthesia, and an emphasis on mobilization and nutrition, given the prevalence of micronutrient deficiencies in the severely obese. There is a risk of incorrect drug dosing in obesity, which requires an understanding of the appropriate dosing weights for perioperative medications.

Conclusion: The literature clearly highlights the complexity of severe obesity as a multi-system disease, and anesthesiologists caring for these patients peri-operatively must have a sound understanding of the changes in order to offer the highest quality care to these patients.

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Key points

- Obesity is a multi-system chronic pro-inflammatory disorder, not just a structural one
- Coronary microvascular flow is abnormal in advance of demonstrable atheroma
- Left atrial dilatation and atrial fibrillation are more common in the obese
- Diastolic heart failure is often unrecognized and must be sought out
- BNP is a useful screening tool in investigating the cause of exercise intolerance
- Patients should be screened for obesity hypoventilation syndrome as well as OSA
- Anesthesiologists must be familiar with appropriate dosing weights for drugs
- Micronutrient deficiencies are common and potentially serious

Introduction

Obesity has been aptly described as an epidemic. Around 25% of Canadian adults are now obese, over 60% are within the combined classification of overweight or obese, and the trend continues upwards (1). Figures for other major developed nations are comparable, around 34% for the United States, and 24% for the United Kingdom, using measured data from 2006 and 2007 respectively (2).

Anatomically, obesity is defined by the presence of excess stored fat. Physiologically, obesity is a multi-system pro-inflammatory disorder. This article presents some of the significant advances in the understanding of organ dysfunction, cellular, and metabolic abnormalities in obesity. This knowledge underpins approaches to both preoperative optimization and perioperative organ support, and is often reported outside the mainstream anesthesia literature. Obesity is still commonly perceived as merely a disorder of body structure with attendant functional consequences. We provide anesthesiologists with a selective synopsis of the key pathophysiological changes underlying obesity, starting at the basic cellular level and leading on to associated organ dysfunction, emphasizing the pro-inflammatory nature of obesity. We link up to date information from basic science and clinical research with perioperative care of the severely obese patient, emphasizing core issues such as cardiac dysfunction, sleep-disordered breathing (with appropriate emphasis on obesity-hypoventilation syndrome), perioperative importance of nutritional deficits, pharmacology, and meeting the challenges of regional anesthesia. The particular pathophysiological and management aspects of the obese parturient are outside the scope of this particular article.

What is Obesity?

Obesity is described anatomically as an elevated level of fat storage in the form of hypertrophy (increased size) and/or hyperplasia (increased number) of fat cells, known as adipocytes. Given the complexities of body composition analysis, the body mass index (BMI) acts as a surrogate for the amount of bodily fat, and facilitates patient comparison and grouping for the purposes of research or discussion. BMI is defined as the body weight in kg divided by the square of the height in meters (kg/m^2). Obesity has been defined as a BMI > 30 kg/m^2 with morbid obesity referring to patients with BMI > 40 kg/m^2, or BMI > 35 kg/m^2 with obesity-related comorbidity (Table 1). BMI alone is not a good predictor of the distribution of excess body fat, and central obesity with elevated visceral fat levels is associated with greater metabolic impact and complications than widespread subcutaneous fat. BMI may be misleading in patients with significant muscle bulk. It is also critical to understand that patients can have elevated body fat content despite a normal BMI, so-called "normal weight obesity", and that this too has impacts on organ function (3) with the risk of metabolic abnormalities and hypertension increasing as %BF increases (4). Obesity impacts virtually all organ systems, and is an independent risk factor for both morbidity (5) and mortality (6).

Adipocytes as key effectors in the pathophysiology of obesity

A primer on the adipocyte

The fat cell, or adipocyte, is central to the pathophysiological changes terminating in obesity-associated comorbidity. Adipocytes have two main roles, the first of which is lipid handling, where adipose tissue can be viewed as an adaptive response aimed at controlling potentially toxic free fatty acids (FFA) levels. The second role is an endocrine and paracrine one, central to the adverse impact of obesity. These cells actively produce and secrete a large number of

important biologically active substances referred to as adipokines, and these include substances with metabolic and growth regulation roles as well as cytokines and collagens (See Figure 1). Pro-inflammatory substances are mainly secreted by visceral fat cells, whereas adiponectin and leptin are the key substances produced by subcutaneous adipocytes (7). These pro-inflammatory signals reach a point where they lead to macrophage and T-cell recruitment to the adipose tissue, further contributing to the inflammatory state. This adipocyte and inflammatory cell mix is the potent combination at the core of the metabolic disturbances in obesity.

Leptin is produced in proportion to triglyceride stores, and its normal physiological actions are to decrease appetite and to trigger increased sympathetic activity (to burn calories), maintaining energy intake-expenditure balance. Leptin levels are elevated in obesity, but a state of leptin resistance is seen. Adiponectin is a protective hormone with anti-atherosclerotic, anti-diabetic, anti-inflammatory, and anti-hypertensive effects. It increases free fatty acid oxidation, augments endothelial nitric oxide production, and plays a role in regulation of cyclooxygenase 2 (COX-2). Adiponectin levels fall in obesity, and this is associated with elevated risks of hypertension, pulmonary arterial hypertension, acute coronary syndrome, and airway inflammation (8). Adiponectin levels are inversely related to aldosterone (and sympathetic activity) levels (9).

Adipocytes and FFA

Elevated free fatty acid levels and uptake play an integral part in adipocyte physiology, triggering increased pro-inflammatory expression via pathways that involve Toll-like receptor 4 (TLR4) and Nuclear Factor Kappa B (NF-κB), as well as several other mechanisms (10). In addition to increased cytokine and acute phase reactant (e.g. C-reactive

protein, CRP) production, FFA levels commonly seen in plasma of obese patients and patients with type 2 diabetes mellitus lead to macrophage accumulation and contribute to insulin resistance (11). Supranormal levels of FFA also impair endothelial function and nitric oxide (NO) release, with chronic elevation impacting on pancreatic cell function and insulin secretion.

Perivascular adipose tissue

Adipocytes are also found in close proximity to blood vessels and organ vascular beds, and are thought to play a role in microcirculatory control through the action of adipokines and cytokines. As obesity progresses, elevation of FFA and the enhanced pro-inflammatory state of the adipocyte lead to a shift away from the production of adiponectin (which interferes with NF-κB signaling) and towards tumor necrosis factor α (TNF-α) mediated microvascular vasoconstriction. If unchecked, this process leads to reduced microvascular flow and contributes to organ dysfunction and ischemia (12).

Epicardial adipose tissue

Epicardial fat covers around 80% of the heart surface and can account for up to 20% of the weight of the heart. There is significantly more fat associated with the right ventricle than the left. The presence of excess fat tissue around coronary arteries is associated with increased risk of ischemic heart disease (13), and higher levels or epicardial fat are also associated with left ventricular diastolic dysfunction (14).

Adipose tissue blood flow

Adipocyte hyperplasia is not accompanied by increased vascularization of the fat tissue, and one of the features of severe obesity is a reduction in adipose tissue blood flow (ATBF) compared to the non-obese state (15). This reduction is already evident at baseline flow, but

there is also significant blunting of the usual post-prandial ATBF increase. This is important because the post-prandial rise in blood flow is essential for uptake and storage of FFA (i.e. the protective functions of adipose in lowering plasma FFA concentrations). In addition, adipocytes act as a store for FFA that can then be released as fuel during for example periods of prolonged fasting. The lower ATBF may impair this beneficial FFA release. The ultimate consequence for the obese patient is post-prandial hyperlipidemia. ATBF is controlled by the sympathetic nervous system and is increased by agents such as beta agonists. The flip side is that beta-blockade, often used for hypertension or ischemic heart disease, may further limit the post-prandial increase in ATBF and potentially aggravate post-prandial hyperlipidemia.

The metabolic syndrome (MetS)

The changes outlined above set up the necessary conditions for the development of the metabolic syndrome (MetS). Although definitions vary, for the purposes of research MetS comprises obesity, hyper- or dyslipidemia, an insulin resistant state, and hypertension, and is accompanied by an elevated level of pro-inflammatory and pro-thrombotic mediators (16). Obese patients with MetS have higher all-cause mortality and higher risk of both type 2 diabetes and cardiovascular disease (particularly coronary artery disease and heart failure) (17,18). This is at least partly due to the impact of the pro-inflammatory and pro-thrombotic state on microvascular blood flow and organ function in the heart and elsewhere.

Cardiovascular dysfunction in obesity - implications and optimization

Obesity is associated with cardiac disorders beyond "conventional" atheromatous coronary disease.

Myocardial blood flow in obesity with the metabolic syndrome

MetS is accompanied by significant alterations in myocardial blood flow, which, importantly, may predate the presence of detectable atheroma. Coronary vasodilatation in response to pharmacological or metabolic stimuli is reduced, and coronary auto-regulation is inhibited (19). The impact on myocardial oxygenation may become evident in settings where coronary flow reserve is an important defense mechanism, such as during exercise or cardiac ischemia. On the other hand, the response of the coronary circulation to vasoconstrictor agents such as angiotensin II (circulating or locally produced by adipocytes) and alpha-1 receptor agonists is enhanced in animal models of the metabolic syndrome (20), and this is in keeping with the increased activity of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system often found in MetS. This enhanced response is partly mediated through up-regulation of angiotensin receptors in the coronary circulation (21). It is unclear if this increased vasoconstrictor potential has clinical implications for the perioperative use of agents with a predominant alpha-1 receptor agonist effect, such as phenylephrine. However, it is apparent that there are abnormalities of coronary flow and flow reserve in severely obese patients that may not be evident on angiography but may become relevant during the perioperative period in response to perioperative stress or hypoxia.

Ventricular hypertrophy

Ventricular remodeling and diastolic dysfunction are both seen in obesity, and importantly they can occur independently of hypertension. Hypertrophy has been attributed to the need for increased cardiac output to meet the metabolic demand of the increased fat mass, accompanied by the impact of increased angiotensin II and RAAS activation. The conventional view has been that the additional metabolic demand leads to increased cardiac output and blood volume, and that the increased blood volume leads to hypertrophy as an adaptive response to the volume-induced tendency for ventricular dilatation. This view is under challenge, with studies showing that hypertrophy often occurs independently of

increased wall stress from dilatation (22). It is now proposed that the initial trigger for hypertrophy is exposure to elevated insulin and leptin levels, and indeed leptin may be the more important. Interestingly, the right ventricle (RV) undergoes hypertrophic change to a greater relative extent than the left in some patients, and this may reflect the presence of a greater number of leptin receptors in the right heart. These right heart changes become even more relevant in those patients who develop significant respiratory dysfunction as an added cardiac stressor, placing the RV at much greater risk of oxygen supply-demand mismatch. Another key contributor to ventricular remodeling and progression to hypertension is aldosterone. Aldosterone levels are elevated in obesity with MetS (23) and even more so in patients with obstructive sleep apnea (OSA), where levels correlate with the number of hypoxic episodes (24). Aldosterone contributes to the development of left ventricular fibrosis and decreases nitric oxide availability and endothelial function (25). On this basis, aldosterone antagonists may be a beneficial addition to conventional renin-angiotensin-system inhibition (26).

Atrial fibrillation (AF)

The individual association of obesity, metabolic syndrome, and obstructive sleep apnea with new onset atrial fibrillation is under-appreciated. The exact nature of this relationship is unclear, although there are multiple possible contributors. Obesity increases the risk of left atrial dilatation (LAD), with up to 50% of severely obese patients demonstrating LAD. Interestingly, the dilatation appears to occur more often in a longitudinal direction than in a transverse one, although how this relates to AF onset is unknown (27).The incidence and risk increases as the degree of obesity increases, and it is the left atrial dilatation and not the obesity *per se* that correlates with AF risk (28). In addition to left atrial dilatation, higher epicardial fat mass is associated with genesis of atrial arrhythmias in patients with or without

heart failure (29), although it appears that AF occurs at lower fat volumes in patients with heart failure. This may be due to the pro-inflammatory effects of perivascular fat. Naturally, obesity is also associated with comorbidities which themselves increase the risk of AF, such as hypertension, left ventricular diastolic dysfunction, and diabetes.

Cardiac failure

Obesity is an independent risk factor for cardiac failure (30). This increased risk is strongly related to the duration of obesity. Although it has been known for many years that lesser degrees of obesity are associated with increases in stroke volume and reduction in systemic vascular resistance (combining to increase cardiac output), as obesity progresses these changes put increasing stress on the cardiovascular system and are, ultimately, associated with increased left ventricular (LV) wall stress and elevated filling pressures. This is in addition to any leptin-related hypertrophic change or hypertensive changes. There follows a reduction in cardiac systolic and diastolic deficiency in severe obesity which has been linked to hypertrophy, increased cardiac fibrosis, lipotoxicity, abnormal calcium handling, oxidative stress, repeated hypoxic episodes, diabetes, and volume overload (31). In animal models there is also a strong influence of obesity on cardiac apoptosis and evidence for abnormal leptin signaling as a contributor to myocardial dysfunction (32).

Although the severest forms of obesity-related cardiomyopathy, with significant systolic dysfunction even in the absence of coronary artery disease, are usually seen in the super-obese, lesser degrees of abnormal function are likely to be present at a much earlier stage. This is especially the case for diastolic function and abnormalities of cardiac relaxation. Diastolic dysfunction occurs along a spectrum of severity from asymptomatic changes detected on echocardiography to frank episodes of pulmonary edema. Diastolic dysfunction

and heart failure with preserved ejection fraction are under-appreciated in both the non-obese and obese populations as contributors to exercise intolerance. Severe diastolic dysfunction is a risk factor for incipient cardiac failure and pulmonary edema when fluid management is not carefully monitored, since LV filling pressures, even if near-normal at rest, can rise significantly during exercise or stress (33). It should be specifically sought out in patients with severe obesity, for example by echo Doppler interrogation of the transmitral blood flow pattern (34) (Figure 1). The normal transmitral flow pattern in sinus rhythm consists of an E wave from early diastolic filling and an A wave from atrial contraction. In the normal setting the E wave is dominant and the E/A ratio is around 1.5. Diastolic dysfunction alters this ratio through a recognizable sequence of patterns dependent on severity. Further information can be gained through tissue Doppler interrogation of the mitral annulus. Anesthesiologists should not assume that exertional dyspnea is simply the result of body mass, and should have a low threshold for echocardiography.

Cardiac risk assessment and medical optimization

A detailed discussion of cardiac risk assessment for non-cardiac surgery is outside the scope of this article and readers are referred to existing reviews and guidelines (35). We will confine ourselves to additional considerations for the severely obese in this setting, as this population is often not considered separately in guidelines. In the formal evaluation of severely obese patients for the presence of cardiac ischemia, conventional exercise stress testing may be problematic due to mobility limitations, and joint dysfunction may prevent such testing even at lower degrees of obesity. The use of a stationary bicycle, rather than a treadmill, may allow some of the patients with joint issues to be tested, and if this is the case more detailed information on the nature of their exercise limitation may be obtained from formal cardiopulmonary exercise testing (CPEX), already used for integrated assessment

prior to high-risk surgery (36). It has also been suggested that dobutamine stress echocardiography (DSE) has a role in this patient population to overcome exercise limitations. Unfortunately, severe obesity presents a challenge for echocardiographers and adequate transthoracic images may not be obtainable. For patients with such poor echocardiographic windows, transesophageal DSE will facilitate testing, but may not be available in all centers (37). The role of DSE is not without controversy. A study in unselected patients with severe obesity found that only 1.7% of the patients tested had a positive DSE, and of these patients only 1 in 7 had confirmed coronary artery disease at angiography (38). The place of DSE remains unclear at present, at least in the absence of better information to guide targeting of the investigation.

Other tests may assist in risk stratification. For example, easily performed blood tests such as brain natriuretic peptide (BNP) or N-terminal-pro-brain natriuretic peptide (NTpro-BNP) are available to help identify obese patients with systolic or diastolic cardiac dysfunction. Systolic dysfunction may not be clinically evident because of a low baseline activity levels or mobility, and it can be difficult to separate out exercise intolerance symptoms due to severe obesity from those of heart failure, as discussed above. The relevance of diastolic dysfunction to anesthesia practice in major surgery is clear. Elevated BNP or NTPro-BNP levels should prompt further investigation. It is important to appreciate that obesity appears to be associated with lower baseline BNP levels, and lower levels than lean individuals with comparable heart failure severity, and there have been suggestions based on this that the threshold for abnormality in diagnosing heart failure should be lower in the obese (39). Although BNP rises in diastolic and systolic heart failure, it is also elevated in obese patients with left atrial dilatation who do not (yet) have echocardiographic evidence of LV diastolic or systolic dysfunction (40)

Obviously co-existing cardiac conditions such as hypertension, ischemia, and heart failure should be medically optimized prior to surgery, and if the family physician has not achieved this, a cardiology consult may be required. Although statins are a relatively uncontroversial therapy in patients with metabolic syndrome, the role of beta-blockade raises some issues. Perioperative beta-blockade (starting 1-2 weeks preoperatively) has been recommended for patients with risk factors for cardiac ischemia, although the benefits in terms of ischemia and cardiac event reduction have to be weighed against the potential for increased all-cause mortality and stroke (41). It also seems very likely that individual response to these agents is variable and may be significantly influenced by beta-receptor polymorphisms (42). Beta-blockade in the severely obese, particularly those with metabolic syndrome, may also have unintended and detrimental metabolic consequences that should be anticipated. Conventional beta-blocking agents can impair glucose tolerance, enhance insulin resistance, and worsen other metabolic abnormalities. This would be particularly disadvantageous at the time of a surgical insult that carries its own stress-related metabolic consequences. If beta-blockade is desired for these patients, agents such as carvedilol, which have much less of a metabolic impact (43), should be considered, although the evidence base supporting their use for perioperative protection is much less extensive.

Mineralocorticoid receptor antagonists such as spironolactone and eplerenone are beneficial in symptomatic heart failure and resistant hypertension, and indeed may be useful prior to the development of symptomatic heart failure in patients with hypertension and/or MetS who have diastolic dysfunction (44)(25). These drugs are suitable for administration in the perioperative period in many types of surgery, provided that potassium levels and renal function are monitored. They should not, however, be used concurrently with non-steroidal

anti-inflammatory drugs (NSAIDs) or where significant renal impairment is present. Although eplerenone is more expensive than spironalactone, it does not cause breast pain, gynecomastia, or menstrual irregularities, and may be a better choice in younger patients. On the basis of work in diabetic patients showing that spironolactone is associated with elevated glycated hemoglobin (HbA1c) levels, reduced adiponectin, and increased cortisol, there is reason to suspect that eplerenone may turn out to be a better choice in the obese (45), perhaps in combination with angiotensin receptor blockers (ARBs).

Respiratory dysfunction in obesity - implications and optimization

Pulmonary physiological changes

Obesity-related changes in respiratory function are, intuitively, related to the severity of the body mass increase and to the location of the excess fat deposits. Clearly, upper body (waist and above) fat will have a greater impact on diaphragmatic excursion, chest wall mechanics, and work of breathing. In addition, there will be an important superimposed impact from body position and anesthesia. The major physiological changes are listed in Table 2 (46,47). The impact of intraoperative body position on the respiratory system must be anticipated and dealt with effectively (vide infra).

Given the well-recognized additional reductions in respiratory function after surgery (especially open abdominal or thoracic surgery) in the obese, attempts have been made to mitigate the decline through preoperative respiratory muscle training programs. These interventions have been shown to reduce the magnitude of the fall in maximum inspiratory pressure, but the impact on maximum expiratory pressure, lung volumes, and diaphragmatic excursion does not appear significant (48) and their place in management is unclear. It is

more likely that other aspects of postoperative management such as continuous positive airway pressure (CPAP) will have a greater effect.

Obesity associated breathing disorders

Much of the focus on obesity-related respiratory dysfunction in the anesthesia literature has centered on the detection and management of OSA. Although OSA is both important and relatively common, we must not forget the existence of another entity known as Obesity Hypoventilation Syndrome (OHS), which has a significant attributable morbidity and mortality risk.

Obstructive sleep apnea – definitions, detection, and severity assessment

OSA refers to a period upper airway obstruction occurring during sleep. This obstruction may be partial or complete. Not surprisingly, such episodes may result in hypoxemia and hypercapnia with associated hemodynamic changes such as hypertension through the night, and commonly lead into daytime somnolence. Long-term untreated OSA results in cardiovascular complications such as hypertension and right heart strain. OSA occurs in over 70% of patients with a BMI > 35, and this is combined with OHS in around 10-20% of OSA patients (49,50). Practice guidelines have been issued on perioperative management of OSA patients (51), and readers are referred to this document for more detailed information.

The key point is that anesthesiologists select and utilize appropriate tools to risk assess obese patients for the condition, and to establish severity. This then allows for appropriate perioperative planning. In some centers, the use of in-hospital sleep studies (polysomnography) is an option to formally evaluate patients. Some experts advocate universal investigation for patients who are morbidly obese or higher. However, many centers do not offer this investigation, and a number of screening questionnaires have been

developed that are suited to the pre-operative clinic. These have been the subject of a recent systematic review (52). A good example is the STOP-BANG questionnaire developed by Chung *et al.* (53). This tool has been shown to have consistently high sensitivity for detecting OSA at different severity levels (84% in mild or above, 93% in moderate or above and 100% in severe, based on apnea-hypopnea index values of ≥ 5, ≥ 15, or ≥ 30 respectively). It consists of questions on Snoring, Tiredness, Observed apnea, high blood Pressure, combined with BMI > 35, Age > 50, Neck circumference > 40 cm and male Gender. It should be noted that, in keeping with many screening tools, the high sensitivity meets the aim of allowing users to rule out moderate to severe OSA if the scoring tool ranks them as low risk i.e. the negative predictive value is good. This may come at the cost of categorizing some patients as having higher risk levels who on further investigation do not.

Preoperative detection of OSA allows for planning for the pre- and postoperative provision of CPAP or non-invasive ventilation (NIV) devices. Without such interventions, severe OSA patients are at high risk of respiratory complications aggravated by immobility, positioning, pain, and opioid analgesia. If CPAP or non-invasive ventilation is planned postoperatively in patients who do not already use the technique, they must be familiarized and conditioned to the equipment prior to surgery. Postoperative respiratory management is considered in more detail in a later section.

Obesity hypoventilation syndrome (OHS) – definitions, etiology, and significance

The diagnostic criteria for OHS include BMI > 30 and awake $PaCO_2$ > 45 mmHg (6 kPa) without other causes of hypoventilation such as chronic obstructive pulmonary disease (COPD) or neuromuscular disorders. This occurs against a background of nocturnal hypoventilation, but notably does not require the presence of OSA, although this is present in the majority of cases. The true population incidence of OHS is unclear, although it is as high

as 50% in hospitalized patients with BMI > 50 and may be present in 10-20% of formally diagnosed OSA patients (54). OHS is a serious condition with important consequences and significant negative prognostic impact.

In terms of mechanism, there is consensus that OHS results from combined abnormalities in respiratory mechanics and central respiratory control. The exact pathophysiology behind these abnormalities remains a subject of debate. Firstly, it is clear that alterations in lung mechanics and lung volumes seen in obesity are more severe in OHS patients than BMI-matched patients without OHS, and in part this results from higher central fat deposits in the OHS patients, which disproportionately affects lung volumes and diaphragmatic excursion. OHS patients, therefore, have lower respiratory system compliance, higher airway resistance, greater expiratory gas trapping, and higher work of breathing than eucapnic obese patients. While this is evident in the sitting position, it worsens further when supine. Secondly, OHS patients suffer from nocturnal hypercapnia with or without OSA, and this leads to secondary bicarbonate retention during the night. The hypercapnia improves during daytime, with a hangover of elevated bicarbonate concentration producing a metabolic alkalosis and leading to secondary hypoventilation. Thirdly, BMI-matched obese controls that are eucapnic display an increased respiratory drive that is absent from OHS patients, and it has been proposed that OHS is partly the result of an inhibited central drive. In animal studies, leptin has respiratory stimulant actions, and in humans the severity of OHS correlates with the degree of leptin resistance and with the degree of elevation of leptin levels (55).

OHS is often absent from discussions around perioperative management of obesity, and this oversight may be clinically very significant. OHS patients have worse outcomes than BMI-matched patients without sleep-disordered breathing, or those with "simple" OSA. This impact on prognosis extends to higher risk of cardiac disease (including cardiac failure),

episodes of acute on chronic respiratory failure, need for critical care, and post-discharge mortality (56,57). Many severely obese patients do not have an arterial blood gas taken at pre-operative assessment, and conventional screening for OSA will miss a large proportion of OHS patients. A serum bicarbonate concentration is, however, frequently available on venous biochemistry profiles, and a level of $\geq$ 27 mmol/L is highly sensitive (92%) for an elevated arterial partial pressure of carbon dioxide ($PaCO_2$), which may be accompanied by a degree of hypoxemia (peripheral oxygen saturation, SpO_2, readings of < 94%) (58). Patients identified as OHS should be referred to a respirologist for consideration of positive airway pressure therapy, generally starting as CPAP but with over 20% of cases requiring up-titration to NIV/Bilevel ventilation to abolish hypercapnia. Oxygen may also be required.

Patients with unidentified OHS are at high risk of respiratory complications in the postoperative period and are more likely to suffer opioid-related side effects. If these patients are missed at pre-operative assessment and identified on the day of surgery, then the anesthesiologist and surgeon should discuss the benefits and risks of proceeding with surgery, and if proceeding, urgent arrangements should be made for postoperative monitoring and respiratory support.

Nutrition status in obesity

Despite macronutrient excess, obese patients remain at risk of perioperative nutritional deficits. This risk is amplified by inaccurate perceptions that obese patients are better able to cope with loss of nutritional intake by virtue of a "nutritional reserve". Despite a large lipid store, the stress of major surgery can result in the detrimental loss of lean body mass through the process of gluconeogenesis. This acute stress comes on top of a chronic inflammatory

state associated with severe obesity. There are clear implications for respiratory muscle and cardiac reserve and for ability to mobilize.

A particularly under-appreciated area of critical importance in the severely obese is micronutrient deficiency. Preoperative deficiencies are common, certainly in bariatric surgery candidates (59). Iron deficiency occurs in 6-29% of these patients, with 3-18% being vitamin B12 deficient (60,61). There is also a significant risk of folate, zinc, selenium, magnesium and thiamine deficiencies. Deficits of Vitamins A, D and K are also possible, although Vitamin K deficiency is not usually severe enough to cause abnormalities in the coagulation testing results. An observational study on 54 patients attending for laparoscopic sleeve gastrectomy found that, preoperatively, 51% of patients had at least one deficiency, the most common being vitamin D, iron, thiamine, and vitamin B12 (62).

Patients who have undergone weight loss surgery previously are very vulnerable to micronutrient deficits. Ideally, these deficits should be sought out and corrected in the preoperative period, but this action is all too often absent. Increased metabolic and tissue demands after surgery, combined with reduced nutritional intake, can lead to these deficits becoming clinically overt after surgery. In particular, there are reports of altered mental status or neurological changes postoperatively resulting from thiamine deficiency, and cardiomyopathy with thiamine or selenium deficiency. In addition, obese patients who have undergone weight loss surgery are at risk of metabolic bone disease because of Vitamin D deficiency (present in 45-52% of patients in some studies). The combination of obesity, impaired muscle strength, immobility, and abnormal structural bone strength places these patients in a uniquely vulnerable position for injury.

Intraoperative care

Perioperative pharmacology

Pharmacokinetic changes in severely obese patients are complex, and accurate dosing is a huge challenge since much of our understanding of drug dosing and kinetics comes from data on non-obese patients. The potential for incorrect dosing is high due to the impact of increases in cardiac output, extracellular fluid volume, fat mass, and lean body weight (LBW) on pharmacokinetics (63,64). The increase in LBW is counter-intuitive. Although the ratio of LBW to total body weight (TBW) is lower in the obese, the absolute value of LBW is higher than in non-obese subjects of the same gender and height. There is a risk of accumulation of lipid soluble drugs and the peak plasma levels of some drugs may be reduced due to higher volumes of distribution. Even if adequate peak plasma concentrations are obtained, tissue levels may be inadequate, and this has significant implications for prophylactic antimicrobial therapy.

Selection of the correct weight to use for dosing calculations can be confusing - should we be using 'ideal body weight' (IBW), 'lean body weight' or 'total body weight' to calculate drug doses? In addition, staff may simply be unfamiliar with techniques used to calculate IBW or LBW. Over 98% of metabolic activity occurs within lean body mass, and anesthesiologists should ensure that they are using the more accurate formulae for calculating LBW that have been developed that work across a wider range of BMI (65). It is also essential that anesthesia departments provide evidence-based advice on prescribing in severe obesity, along with tools to support calculation of LBW (software or paper-based nomograms). A detailed analysis of the literature on kinetics and dosing in obesity is beyond the scope of this article. Data are available to provide some guidance on appropriate dosing for common perioperative

medications (Table 3) (63,64,66-73). Table 4 outlines the calculation methods for the various dosing weights.

In general, muscle relaxant drugs should be dosed on the basis of ideal body weight with the exception of succinylcholine, which should be related to total (actual) body weight. Neuromuscular block reversal agents may be appropriately dosed based on total (actual) body weight. Induction agents and opioids should be dosed on the basis of lean body weight.

Vascular access

Poorly defined anatomical landmarks in the obese mean that vascular access can be challenging. Conventional central venous access is an option where peripheral cannulation fails repeatedly, although this too may be difficult with the internal jugular vein "hidden" below significant amounts of mobile soft tissue. Peripherally inserted central catheters may be helpful. The decision to insert a central venous catheter should be considered carefully. Patients with advanced disease and concomitant cardiac failure may decompensate if placed supine or head-down to facilitate line insertion. Even in the absence of cardiac failure, prolonged periods in the supine or head-down position can cause respiratory decompensation. It has been shown that the internal jugular vein overlaps the carotid artery to a greater extent in the obese patients than the non-obese, and this may increase the risk of inadvertent arterial puncture if landmark techniques are used. Importantly, the degree of overlap was already significant with the head neutral in the obese patients, but increased further as the head was rotated to 60 degrees (as it does in the non-obese to a lesser extent).

The use of ultrasound guidance for central venous catheter (CVC) insertion may overcome vein location issues, lower the risk of arterial puncture, and reduce the time taken for

insertion as expertise increases. It has been shown to aid in the safe placement of internal jugular lines (74), and ultrasound may also be used to guide peripheral venous access (75) and arterial access. Obesity not surprisingly can hinder the ultrasound view of the subclavian vein in comparison to non-obese patients (76), and novices should not attempt unsupervised ultrasound-guided subclavian line insertion in this patient group.

Upper GI function and risk of aspiration of gastric contents

Elevated BMI is consistently associated with higher rates of gastro-esophageal reflux disease (GERD), particularly in females where estrogen exposure is considered a factor (77). Combined with higher gastric volumes than the non-obese, this would appear to increase the risk of aspiration of gastric contents into the airways. Recent literature suggests that gastric emptying is not impaired in the obese and that this is not a primary player in aspiration risk (78). The increase in GERD occurs particularly in patients with elevated abdominal fat mass, and obesity is also associated with greater risk of hiatal hernia (79).

The function of the esophageal sphincters under anesthesia has been investigated in a study of obese and non-obese patients (80). This study found that upper esophageal sphincter pressures did not differ between obese and non-obese patients during induction (they fell equally), but lower esophageal sphincter pressures fell more in the obese group after anesthesia and the difference was statistically significant. The barrier pressure (lower esophageal pressure – gastric pressure), which is probably more relevant to anesthesia, was also significantly lower in obese patients, although it was always positive. The same group have also demonstrated that the application of PEEP during anesthesia increases the pressure in the esophagus which may act as a barrier against regurgitation (81). It should be noted that the obese patients in these studies did not have active GERD, and although this work is

reassuring with respect to the use of laryngeal mask airways in similar patients, this cannot be extrapolated to those with GERD.

Prokinetics, H_2 receptor antagonists or proton pump inhibitors should be considered in an attempt to reduce the incidence and impact of aspiration. The use of rapid sequence induction of anesthesia with cricoid pressure, positioning of the patient in the ramped position on pillows or a wedge, or techniques such as awake fibreoptic intubation, may all help to minimize the risk of aspiration at induction. At the end of surgery, extubation should not be attempted until the patient is awake and responsive with adequate airway reflexes, and is often carried out with the patient ramped or sitting.

Airway Management

Patients with obesity are more likely to suffer serious airway problems during anesthesia compared to the non-obese, and this risk may be up to four times higher in patients with severe obesity (82). Airway management, both in terms of bag-mask ventilation and intubation, is challenging in this population, and experienced staff should always be involved. Prediction tools for difficult airway have recently been compared in a clinical study and reported elsewhere (83). In addition to conventional direct laryngoscopy or flexible fibreoptic intubation (awake or asleep, but spontaneously breathing), an increasing number of airway adjuncts are available to facilitate other techniques in these difficult settings.

Pentax AWS® (Pentax Medical Company, Montvale, NJ, USA)

For example, the Pentax AWS® video laryngoscope was studied in a randomized trial in 105 obese patients (84). Using experienced laryngoscopists who had between 5 and 10 previous

uses of the device, there was no difference in success rates between Pentax AWS and conventional laryngoscope with Macintosh 4 blade. The intubation time was longer in the Pentax AWS group, a median of 38 seconds versus 26 seconds for the conventional group, although this is unlikely to be clinically significant.

Glidescope® (Verathon Medical Inc, Bothell, WA, USA)

Similarly, 75 obese patients were randomized to elective intubation with the Glidescope® video laryngoscope or oral flexible fibreoptic intubation, both under anesthesia (85). There were no differences in success rates, difficulty, number of attempts, or adverse events. The median (IQR) intubation time was 37 (IQR 25-48) seconds for the Glidescope and 43 (IQR 35-58) seconds for the fibreoptic. The Glidescope has been compared with direct laryngoscopy using a Macintosh 4 blade in a randomized study of 100 consecutive patients with BMI > 35 presenting for bariatric surgery (86). This study found that although intubation was significantly slower with the Glidescope at a median (range) of 48 (range 22-148) seconds versus 32 (range 17–209) seconds ($p = 0.0001$), views were better and intubation difficulty scores lower with the Glidescope. Again, there is no clear evidence that the additional time is of clinical consequence. The Glidescope has also been used successfully for awake intubation in morbidly obese patients, although first attempt success rate was only 54%, with 12% requiring three attempts, and a 4% failure rate (87).

Airtraq® (VYGON, Écouen, France)

The Airtraq device is an optical laryngoscope (the anesthesiologist places his eye to the viewfinder) with an optional video system. It has been compared to conventional intubation with Macintosh blade in a randomized trial of 106 morbidly obese elective surgical patients (88). In this study, the duration of tracheal intubation [mean (SD)] was significantly shorter at 24 (SD 16) seconds with Airtraq than with the Macintosh laryngoscope at 56 (SD 23)

seconds ($p<0.001$). In addition, the median (range) intubation difficulty score was significantly greater in the Macintosh group at 5 (range 2– 10) versus 0 (range 0 – 2) ($P<0.001$). The authors commented on a non-significant increase in soft-tissue trauma with the Airtraq device. The Airtraq device has also been studies alongside the CTrach® intubating laryngeal mask airway (vide infra) and conventional Macintosh laryngoscope in 318 morbidly obese patients (106 per group) (89). The mean (Standard deviation, SD) duration of tracheal intubation was shortest for the Airtraq at 29 (SD 12) seconds, followed by the Macintosh at 69 (SD 17) seconds, with the CTrach being slowest at 109 (SD 27) seconds ($p<0.05$ for Airtraq versus other groups). In addition, more patients in the Airtraq and CTrach groups maintained oxygen saturation above 92%, and fewer patients in these groups desaturated to less than 88% ($p<0.05$).

Intubation via Laryngeal Mask Airway

There are a number of laryngeal mask airways designed as conduits for endotracheal intubation. It is of course likely that intubation with such devices will take longer in the obese patient than the non-obese patient (90). A recent randomized study compared the Intubating Laryngeal Mask Airway ® (ILMA) and LMA CTrach ® (which is a modification allowing real-time visualization of the glottic opening during intubation) (both LMA North America, San Diego, CA, USA) in 80 patients with BMI > 40 (91). The median (interquartile range, IQR) total time taken for intubation was shorter at 78 (IQR 63-105) seconds in the ILMA group than the LMA CTrach group where the time was 128 (IQR 98–221) seconds ($p < 0.001$). In this study the LMA CTrach also required more manipulation to achieve glottic view and ventilation. Taken together, the ILMA performed better in this evaluation. Even if intubating laryngeal masks are not used as primary techniques, they are valuable in the setting of failed or difficult conventional intubation.

Conventional laryngeal mask airways

Not all obese patients require intubation, and laryngeal mask airways are appropriate tools where intubation can safely be avoided. The choice of device depends on local availability and individual patient fit. It has been suggested that devices without an inflatable cuff, such as the iGel® LMA (Intersurgical Inc., Liverpool, NY, USA), provides for easier insertion and a better seal in lean individuals. Weber et al compared iGel with LMA-Unique® (LMA North America, San Diego, CA, USA) (a classic LMA with inflatable cuff) in 50 patients with BMI > 25 but < 35 (92). The mean (SD) insertion time with the iGel LMA was significantly shorter at 18.3 (SD 6.5) seconds versus 24.4 (SD 7.7) seconds (p=0.0001). The mean (SD) leakage pressures, where higher pressure indicates better seal, were higher in the iGel group than the LMA-Unique group at 25.7 (SD 8.6) cmH2O versus 17.0 (SD 6.2) (p=0.0001) in patients with BMI 30-35.

Oxygenation and ventilation

1) Pre-oxygenation

The deleterious impact of obesity on lung volumes, compliance, and airway resistance are amplified under anesthesia. The fall in expiratory reserve volume (ERV) and functional residual capacity (FRC) is a very important phenomenon for the anesthesiologist, since FRC is effectively the reservoir of oxygen that the body can draw on during periods of apnea. Severely obese patients suffer earlier oxygen desaturation during periods of apnea, so it is critical to ensure that FRC is maintained during induction of anesthesia and that the available lung reserve is filled with as much oxygen as possible, through the process of pre-oxygenation. Pre-oxygenation should occur with the patient positioned as upright as possible, for example in the sitting position, or by placing the surgical table in a reverse Trendelenburg

(head-up tilt) position, or by ramping the patient with linen/pillows or a purpose-built positioning device or wedge. This will optimize the safe apnea time. Several positioning devices are available to help achieve the head-elevated laryngoscopy position (HELP), including the Rapid Airway Management Positioner (RAMP®, Airpal Inc, Center Valley, PA) and the Oxford Head Elevated Laryngoscopy Position (HELP) Pillow (ALMA Medical, Oxford, UK). Many modern operating tables will allow manipulation of body and leg portions to facilitate the beach-chair position, and this function can be used to advantage.

During pre-oxygenation, the FRC may be further augmented by the application of 5-10 cmH_2O CPAP (93) or by the use of non-invasive ventilation, for example with an inspiratory pressure of 7-10 cmH_2O above positive end-expiratory pressure (PEEP) of 7 cmH_2O. The addition of NIV is effective in reducing atelectasis formation, and a recent study again demonstrated that both CPAP and NIV improve arterial oxygenation in comparison to conventional pre-oxygenation (94). In the same study, end-expiratory lung volumes may be further enhanced in the NIV group in some patients by the application of a recruitment maneuver following intubation, although the benefit was only seen in 12 out of 24 patients.

2) PEEP and lung recruitment maneuvers

It is important to ensure that the gains in end-expiratory lung volume that may be achieved during pre-oxygenation with CPAP/NIV are not lost intraoperatively. Common sense would suggest the application of PEEP, and adding periodic recruitment maneuvers or vital capacity maneuvers has been shown to improve oxygenation over the application of PEEP alone (95,96). PEEP values of 10 cmH_2O applied after recruitment/vital capacity maneuvers produce a lower A-a gradient than the application of zero PEEP (known as ZEEP) or 5 cmH_2O PEEP in obese patients undergoing laparoscopic surgery (97). The degree of obesity,

intraoperative positioning, and the nature of the surgery (laparoscopic surgery versus open) will dictate the frequency of these maneuvers, but repeated application is more effective than a single post-induction recruitment (98). There is no benefit to the use of high tidal volumes in an attempt to maintain FRC.

3) Modes of ventilation

There is no convincing evidence of superiority of one intraoperative ventilator mode over another in elective surgery in the severely obese. Volume-controlled ventilation (VCV) and pressure-controlled ventilation (PCV) have been compared during laparoscopic gastric banding surgery in a randomized study of 24 obese patients (99). For a constant minute volume, there were no differences in airway pressures, oxygenation, or cardiovascular impact, but VCV resulted in a significantly lower arterial CO_2 level ($p<0.01$).

In contrast, another study of 36 obese patients undergoing the same surgical procedure found that despite similar tidal volumes, minute volumes, and plateau pressures, the PCV group had lower $PaCO_2$ (5.2 ± 0.4 kPa v 5.4 ± 0.3 kPa, $p=0.014$), lower expired-arterial CO_2 gradients (0.67 ± 0.27 v 0.93 ± 0.27, $p<0.01$), and better oxygenation (PaO_2/FiO_2 ratio 281 ± 107 mmHg v 199 ± 74 mmHg, $p=0.011$) (100). There were no significant differences post-operatively in either study.

Patient positioning issues

There are three important aspects to patient positioning. Firstly, appropriate positioning facilitates practical procedures, such as endotracheal intubation, regional anesthesia and central venous catheter insertion, in a way that optimizes the procedure and overcomes or at least mitigates associated physiological deterioration. Secondly, appropriate positioning

reduces the risk of perioperative nerve, joint, and soft-tissue injury. Thirdly, positioning for surgery often places the patients at a major physiological disadvantage that must be countered by the anesthesiologist. It will already be clear that positions involving elevation of the head of the bed (semi-recumbent, reverse Trendelenburg or beach-chair) are most favorable from the respiratory viewpoint (101), and these will not be discussed further in this section. This section does not cover all of the complications associated with each position, but emphasizes those related to the pathophysiology of obesity.

Supine position

This position is associated with significant reductions in lung volumes and increases in work of breathing in the severely obese. This can precipitate hypoxemia. In addition, increased venous return and preload may place stress on the cardiovascular system, although in patients with very severe central obesity venous return may actually be impeded through caval compression, analogous to the effect of the gravid uterus, and aortic compression may occur. Critical cardiorespiratory instability can occur in morbidly obese patients, and this was reported in 1979 by Tsueda et al as "Obesity supine death syndrome" (102). Lateral tilt may be required to offset aorto-caval compression. It has also been shown that prolonged supine positioning in obese patients with OSA leads to an increase in neck circumference caused by fluid shifts from the legs, although in non-operative patients this does not seem to worsen sleep apnea (103). The impact on severely obese patients who are subject to prolonged surgery in this position is unknown.

Prone position

The critical care literature has demonstrated that prone ventilation improves gas exchange. There are very limited data on intraoperative effects in the obese population. A frequently

cited paper from 1996 studied only 10 consecutive patients with BMI 30-40 but demonstrated an improvement in FRC, lung compliance, and oxygenation in the prone position compared to the supine (104). Of importance, emphasis was placed on obtaining free abdominal movement, with weight taken on chest wall and pelvis. The study used a tidal volume that would be considered high today, at 12 ml/kg, and PEEP was not mentioned. It is critical to ensure that the abdomen is free in the obese patient. Failure to do so will not only embarrass the respiratory system but also increase intra-abdominal pressure and place abdominal organs at risk of malperfusion. Displacement of airway devices is obviously of even greater concern in the obese population in this position.

Lithotomy position

The lithotomy position leads to increased venous return and cardiac output, provided cardiac reserve is adequate. The increased excursion of the diaphragm into the chest due to pressure from abdominal contents further reduces FRC and puts oxygenation at risk. The chest wall compliance may be reduced by mobile superficial adipose tissue coming to rest on the chest wall. The obese patient is at higher risk of neurological injury and compartment syndrome if the legs are not properly positioned and padded. In addition, the practice of using shoulder bars to prevent the patient sliding down the operating table risks injury to the brachial plexus if not done carefully. If anesthesia with spontaneous breathing is used, pressure support ventilation with PEEP is likely to be needed. It should also be remembered that the endotracheal tube might move distally towards the right main bronchus in this position.

Trendelenburg position

The head-down position is associated with exaggerated hemodynamic and respiratory effects with auto-transfusion of blood from the lower limbs and significant falls in lung volumes and

compliance. This position should be avoided in awake, morbidly obese, patients for all but the shortest time, although non-invasive ventilation may facilitate tolerance if necessary. The endotracheal tube may move distally towards the right main bronchus in this position.

Lateral position

Although the lateral position has the attraction of allowing the weight of the obese abdomen to be transmitted away from the diaphragm in most cases, prolonged lateral positioning can lead to vascular congestion and relative hypoventilation in the dependent lung. The use of wedges to facilitate positioning for renal surgery can lead to interference with aortic or caval flow.

Regional anesthesia in the obese patient

Regional anesthesia (RA) or neuraxial anesthesia may avoid the problems of general anesthesia altogether, contribute to reductions in opioid consumption and lessen pain-related respiratory and mobility issues. The ability of the severely obese patient to undergo surgery under RA will depend to a large extent on the position they are required to adopt for the procedure.

Obesity is an independent risk factor for failed regional anesthesia procedure, with epidural, paravertebral, continuous supraclavicular, and superficial cervical blocks having the highest failure rates (105). These techniques can obviously be more anatomically challenging in the obese patient, and such patients also have less tolerance for potential adverse effects such as excessive spread of local anesthetic leading to higher than expected spinal or epidural blocks. Given the difficulty with landmark identification, there has been a great deal of interest in

ultrasound-guided regional anesthesia (UGRA). This raises obvious questions about training, expertise, and the potential to prolong procedure times. Even if ultrasound is used, the structures of interest may be deep and a lower frequency probe may be required to achieve adequate penetration, and this will come at the expense of image resolution. Positioning the patient for block insertion so that anatomical landmarks and needle pathways are optimized, while avoiding respiratory distress, takes time and experience. Monitoring and skilled assistance during block insertion in these patients is mandatory. The clinical trial literature on regional anesthesia in severe obesity is not extensive, and a selection is presented below.

Brachial plexus block

Franco et al retrospectively analyzed data from their RA database of 455 nerve stimulator-guided supraclavicular blocks in obese patients, compared with 1565 blocks in non-obese patients (106). They reported a success rate of 94.3% in the obese group against 97.3% in the non-obese ($p<0.01$), and accidental paresthesia was more common in morbidly obese patients compared to non-obese at 9.6% versus 2.2% ($p<0.01$).

In expert hands, severe obesity does not markedly increase the time taken to perform blocks such as interscalene when ultrasound guidance is used, and ultrasound guidance may help to improve block success (107).

Hanouz et al studied nerve-stimulator guided multiple injection axillary brachial plexus block 85 obese patients and 520 non-obese patients, demonstrating success in 91% of the obese group versus 98% in the non-obese group ($p=0.003$) (108). Complications such as inadvertent vascular puncture were more common in the obese (27% versus 9%, $p<0.001$).

With respect to interscalene block (ISB), the obvious concern is the significant (almost universal) incidence of phrenic nerve block leading to partial or complete diaphragmatic paralysis and exacerbating obesity induced respiratory dysfunction. It has been suggested by that if ISB is required in a morbidly obese patient, phrenic nerve involvement may be reduced by the use of ultrasound guidance, allowing the smallest volumes of local anesthetic to be administered, followed by a continuous low volume infusion via catheter (109). Schwemmer et al studied ultrasound-guided ISB in 70 patients who were a mix of obese and normal weight individuals (107). A high-frequency probe was used and the authors found that nerve visualization in the obese group took 5 ± 1 minute versus 4 ± 2 minutes in the normal weight group ($p=0.02$). There was no statistically significant difference in block success at 94% in the normal weight group and 77% in the obese group, most likely because of the small numbers involved. In an attempt to increase the available data, Schroeder et al carried out a retrospective analysis of data from 528 ultrasound-guided ISB to determine if there was a relationship between obesity and block performance (110). They confirmed that increased BMI was associated with increased time for block placement ($p=0.018$ for univariate model and $p=0.025$ for multivariate model), as well as with pain scores and opioid consumption in the post-anesthesia care unit (PACU) (all significant at $p<0.005$ across univariate and multivariate models). There is little doubt that brachial plexus block can be successful in morbidly obese patients, but these successes requires expertise and experience that training programs must ensure that they deliver.

Neuraxial anesthesia and analgesia

One obvious difficulty with neuraxial techniques in the morbidly obese is localization of the epidural or subarachnoid space through lack of tactile identification of spinous processes. Recently there has been an upsurge of interest in the use of ultrasound to guide neuraxial

blocks (111). Much of the work in this area has been in the obstetric population, although in an orthopedic population of patients with difficult anatomy (a mixture of obese patients, those with scoliosis, or previous lumbar spine surgery) ultrasound was shown to improve first attempt success rates, reduce needle insertion attempts and needle passes, and shorten the time taken to perform spinal anesthesia (112). The ultrasound-estimated depth to the epidural space appears to correlate well with the actual needle distance, at least in obese parturients (113). Description of the US technique is beyond the scope of this article, and readers are referred to existing reviews of the topic.

Longer epidural and spinal needles will be required for some of these patients, and needle-through-needle techniques may assist when performing spinal anesthesia to maintain needle trajectory. Given the mass of subcutaneous fat, and its relative mobility, one particular problem is dislodgement of the epidural catheter as the skin surface to epidural space distance changes when for example moving a patient from lateral to supine or vice versa. Insertion technique will have to balance allowing additional catheter length to cope with this against the risks of catheter malposition. For patients at extremes of obesity, epidural catheter markings in some kits are only provided in centimeters up to 15 cm with the next marking at 20 cm. This may make recording of accurate insertion distance difficult.

Epidural analgesia after surgery may be associated with improved respiratory function in the obese and a reduction in side effects from systemic opioids. Specifically, better recovery of vital capacity and spirometric values was seen in an observational study of 84 patients undergoing midline laparotomy for gynecological surgery (114). Unfortunately, only 16 patients in the study had a BMI of over 30 and the comparison group seems to have received

as required methadone on a background of regular intravenous paracetamol, and this may not represent the best comparator technique.

Trunk blocks

Even in abdominal surgery cases where neuraxial block is contraindicated or technically impossible, techniques such as transversus abdominis plane blocks or rectus sheath blocks can significantly reduce pain and opioid consumption. There is no doubt that the techniques are challenged by excessive adipose tissue, particularly catheter insertion and maintenance within the rectus sheath, but they are feasible even if poorly studied to date in morbidly obese patients.

Postoperative management

Emergence from anesthesia

Patients should have full return of neuromuscular function and be cooperative and alert prior to extubation, with adequate spontaneous tidal volumes, especially if elective post-extubation non-invasive ventilation is not planned. Careful attention must be paid to ensure adequate doses of reversal agent are used as post-operative residual curarization has the potential to precipitate a catastrophic decline in respiratory status and acid-base in the severely obese, even in the absence of OHS or overt OSA. Gaszynski et al studied reversal of rocuronium induced neuromuscular block with sugammadex 2 mg/kg corrected body weight or neostigmine 50 micrograms corrected body weight in 70 morbidly obese patients (115). They demonstrated that time to achieve 90% train-of-four (TOF) ratio was significantly shorter in the sugammadex group at 2.7 versus 9.6 minutes ($p<0.05$) and the TOF ratio in PACU was 109.8% in the sugammadex group versus 85.5% in the neostigmine group ($p<0.05$). Care should be taken when reading studies in this area to understand the dosing weight used. Van Lecker et al studied sugammadex administered as 2 mg/kg ideal body weight, ideal body

weight + 20%, ideal body weight + 40%, and actual body weight in 100 morbidly obese patients randomly assigned to one of these four groups (68). The time from administration of sugammadex to TOF ratio > 90% was shortest in the IBW + 40% group at 112.5 seconds. Next shortest was actual body weight at 128.8 seconds, which was not significantly different from the IBW + 40% group. The reversal time for IBW and IBW + 20% were significantly prolonged in comparison to IBW + 40% ($p=0.0001$ and $p=0.003$ respectively). Interestingly, the shorter time to reversal in the IBW + 40% group came with the administration of a smaller mean dose of sugammadex, 162.3 mg versus 236.5 mg, which was not explained. There were no significant differences in extubation times or times to eye opening, and all patients were successfully reversed, with the authors recommending dosing based on IBW + 40%.

The use of sugammadex does not guarantee absence of recurarization risk, as a number of case reports have shown. Le Corre et al, for example, reported a 115 kg female who received a 1.74 mg/kg actual body weight dose of sugammadex when she had return of 2 twitches, subsequently achieved TOF ratio > 90%, and required reintubation ten minutes later with loss of neuromuscular function necessitating a further dose of sugammadex (116).

The obese patient should be positioned at least in the reverse Trendelenburg position, and preferably semi-recumbent or sitting, as soon as is practical after the end of surgery. Extubation should occur in this position.

Optimization of lung function and oxygenation

Obese patients are at high risk for postoperative oxygen desaturation and ventilatory insufficiency. The effects of postoperative sedation or poorly controlled pain compound the

reduced FRC, increased airway resistance, and reduced chest wall compliance mentioned earlier. Unfortunately, intermittent clinical observations may fail to detect even significant periods of desaturation, and continuous oxygen saturation monitoring is a useful and recommended tool. Many patients with severe obesity will suffer desaturation episodes of up to 30 minutes in duration, and it is important to note that these are not abolished by the use of supplemental oxygen alone (117,118). The need for postoperative oxygen supplementation remains one of the main barriers to day case surgery for patients with obesity (119).

Many patients with severe obesity and OSA will have their own CPAP machine, and the technique can be used successfully in the postoperative period even in CPAP-naïve patients. Elective extubation to CPAP or non-invasive ventilation has been shown to improve post-operative oxygenation and offers flexibility where extubation to conventional facemask oxygen would not succeed (120). This technique can be utilized in PACU and the patient can then either electively remain on this therapy or have a trial of weaning over a period of hours. The evidence for use in patients who were not receiving such therapy pre-operatively is tenuous, but given the additional physiological insults of surgery this approach is logical. Other options include intermittent non-invasive ventilation, with interspersed periods of oxygen by facemask, which may be better tolerated by the patient. These techniques should be considered in individual patients based on operative site, impact on respiratory mechanics and suspected risk of having OSA. Admission to step-down units facilitates closer monitoring during transition back to baseline. Surgical floor staff still need to be trained to manage patients at high risk of respiratory complications, and support from specialist respiratory teams may be required for training and follow-up. Supplemental oxygen should be provided for at least the first 48-72 hours after major surgery, guided by clinical progress and monitoring results. It should be remembered that these patients are at high risk up until their

normal sleep pattern has been fully re-established, which may take 3 to 4 days or more. Patients with OHS require particularly careful management to balance analgesic needs against their respiratory risks, and to monitor their arterial blood gases (ABGs) for progress. Higher than necessary concentrations of inspired oxygen, achieving significantly supra-physiological PaO2, may result in increases in $PaCO_2$ and reduced ventilatory drive in some OHS patients (121).

Regardless of disposition following surgery, severely obese patients should be observed for evidence of increased work of breathing and decompensation, and increases in inspired oxygen fraction (FiO_2) without addressing underlying lung pathophysiology should be avoided. Development of acute hypoxic or hypercapnic respiratory failure should prompt early and aggressive intervention, as rapid decompensation is likely otherwise.

Zoremba et al carried out an interesting study looking at the utility of short-term respiratory physical therapy, carried out in PACU, on lung function in 60 patients with BMI 30-40 undergoing minor peripheral surgery (122). The intervention consisted of repeated sets of incentive spirometry exercises every 15 minutes following extubation for the first 2 hours after surgery. The intervention group demonstrated better oxygen saturation in PACU and at 6 and 24 hours post-operatively. There were also significant differences in favor of the intervention group in forced expiratory volumes in 1 second (FEV1), forced vital capacity (FVC), and peak expiratory flow lasting up to 24 hours. There are no data on the efficacy of similar interventions for more major surgery or in higher BMI groups, but this is certainly an area that should be studied further.

Pain Control

Control of pain enables early mobilization, thus reducing the risk of pulmonary infections and venous thromboembolism. An opioid-sparing multimodal analgesia approach is most-often used. This incorporates oral (or intravenous where available) paracetamol, non-steroidal anti-inflammatory drugs (in the absence of contraindications), continuous peripheral nerve blocks, local anesthetic wound infiltration, or trunk blocks. Continuous wound infiltration techniques are also available.

If they are required, opioids should be used in the minimum effective dose. There are a number of options for adjunctive therapy to reduce analgesic requirements, with positive studies using preoperative central α-2 receptor agonists (such as clonidine and dexmedetomidine), pregabalin and gabapentin, and combined clonidine and S-ketamine (123,124,125,126). If opioid-based patient-controlled analgesia is to be used, background infusions should be avoided, and the lockout period adjusted to minimize sedation and respiratory depression.

Infection Risk

Obesity is an independent risk factor for postoperative infectious complications (127). Patients with obesity are more likely to develop bloodstream infection, skin and soft-tissue infections, wound infections, wound dehiscence, urinary infections and possibly pulmonary infections (128). This may relate to the combined effect of obesity-related immune dysfunction with altered tissue perfusion and perhaps inadequate antimicrobial dosing, but the effects of comorbidities such as diabetes should not be forgotten. Obesity, and the chronic inflammatory state that goes with it, alters the number and function of cells known as dendritic epidermal T cells, which are responsible for skin barrier functions and wound re-epithelialization, resulting in less efficient wound healing (129). These cells also play a part in regulation of wound site inflammation. Elevated free fatty acid levels suppress T cell

function and reduce the effectiveness of T-cell receptor signaling. Continuous exposure to elevated leptin levels in obesity diminishes the response of immune cells to the stimulating effect of this substance - they join other tissues and organs in becoming leptin resistant (130).

How can this increased susceptibility to infection be countered? Aside from scrupulous attention to asepsis, perioperative antimicrobial administration should be carefully timed and drug doses properly considered ensuring adequate plasma and tissue levels. High-quality studies in this area are absent. Blood glucose control should be adequate throughout the perioperative period, and hospitals should have protocols in place to determine targets and treatment regimens.

Thromboembolic Risk and Prophylaxis

Obesity is an independent risk factor for venous thromboembolism (VTE), and many of these patients have lower limb venous stasis at baseline (131). Intraoperative use of appropriately sized mechanical devices such as intermittent pneumatic compression devices will also help to improve venous return as well as lower deep vein thrombosis (DVT) risk. If a patient's bleeding risk is assessed as being low, pharmacological prophylaxis should be offered to all except those with ruptured cranial/spinal vascular malformations. With the low molecular weight heparins, the optimal prophylactic dose is unclear, although in the obese patient weight-based dosing is recommended over fixed doses (132). It may be that an enoxaparin dose of up to 0.5 mg/kg actual body weight (once or twice daily depending on VTE risk) for example is needed to achieve adequate anti-Xa levels (133,69). Anti-Xa monitoring may be beneficial in patients with very severe obesity, and target anti-Xa activity in the range of 0.2-0.4 IU/mL has been recommended (134). Hospitals should ensure that their guidance is up to date and incorporates specific advice on management of the obese patient.

Mobilization

Early mobilization is a core target of enhanced recovery programs and this should apply equally to the obese surgical patient. Mobilization will minimize respiratory complications, pressure-related skin damage, and venous thromboembolism. Epidural anesthesia should not be considered a barrier to mobilization, although patients should be supervised and an assessment made of the presence of motor blockade if local anesthetic infusions are used. Aggressive early mobilization may involve considerable manpower and resources. Patients should have clearly set and individualized daily mobilization targets. There should be objective triggers for patient review when mobilization targets are not met, as failure to mobilize may be an early sign of medical deterioration.

Nutrition support

Perioperative nutritional goals for severely obese patients include maintenance of euglycemia, provision of adequate protein and amino acid intake to minimize loss of muscle and optimize wound healing, and the provision of sufficient calories to permit utilization of endogenous fat stores without triggering severe ketoacidosis. For patients whose clinical course and surgery allow it, return to oral intake in a staged manner is appropriate, starting with clear liquids and progressing through protein-enriched liquids back to diet. For patients who are ill or requiring critical care, more formal enteral or parenteral nutrition support may be required. High protein content hypocaloric feeding is one strategy that has been successfully used in the critically ill (135). Micronutrient deficiencies may require individual treatment schedules. The use of supplementation for vitamin and trace element deficiencies around bariatric surgery has recently been reviewed (136). Of particular important for anesthesiologists is thiamine deficiency. This may present with neurological symptoms. These symptoms can be disregarded as minor side effects of regional or neuraxial anesthesia,

or indeed may divert attention away from what really is a complication of regional or neuraxial anesthesia. In general, thiamine supplementation at 50 mg/day to 100 mg/day is adequate, although higher doses will be required for Wernicke-Korsakoff syndrome.

Summary

Successful management of major surgery in the severely obese patient requires a coordinated effort across many disciplines, and well thought-out care pathways with clear expectations and guidance. These patients are medically very complex and all those involved require training and knowledge of the critical underlying pathophysiological alterations to ensure that patients receive the care and attention to detail that they deserve. Anesthesiologists have a core role in manipulating altered physiology in this patient group to help ensure the best outcomes and to minimize complications. In addition, anesthesiologists are well placed to recognize early postoperative problems and assist with their management, and to ensure appropriate referral to critical care when the perioperative course dictates. An expansion of targeted research into the perioperative pathophysiology and management of this high-risk group is needed.

Table 1: BMI Categories

Classification	**BMI (kg/m^2)**
Anorexia	<17.5
Underweight	<18.5
Normal	18.5 − 25
Overweight	25 − 30
Obese	30 − 40
Morbidly obese	40 − 50
Super morbidly obese	> 50

Table 2: Respiratory physiological changes in obesity

Component	**Impact**	**Comments**
Lung Volumes	Reduced tidal volume	
	Decreased functional residual capacity	
	Decreased expiratory reserve volume	
	Minor reductions in total lung capacity	
Compliance	Decreased chest wall compliance	Especially with truncal obesity
	Decreased lung compliance	Due to loss volume and small airway closure
Gas flow & resistance	Fall in FEV1 & FVC in morbid obesity	This is a variable finding
	Normal FEV1/FVC ratio	
	Increased airway resistance	Small airway collapse, lower volumes and potentially airway remodeling due to low adiponectin levels
Oxygenation & exercise	Mildly elevated A-aDO_2	Ventilation/perfusion mismatch
	Hypoxemia on room air	An inconsistent finding
	Increased O_2 consumption on exercise	
	Reliance on tachypnea during exercise	Due to increased consumption and limited ability to enhance tidal volumes
	Increased peak oxygen consumption and reduced anaerobic threshold in absence of overt cardiac disease	Morbid obesity and above, particularly truncal obesity
Ventilation	Increased respiratory rate	
	Increased minute ventilation	
Vascular	Potential for higher pulmonary artery pressures	
	Increased risk of primary pulmonary arterial hypertension	

Table 3: Dosing Weight Scalars for Common Perioperative Medications

Medication	**Dosing Weight**
Thiopental sodium	Lean body weight (more rapid awakening)
Propofol	Lean body weight (induction bolus) Total (actual) body weight (maintenance infusion)
Etomidate	Lean body weight
Succinylcholine	Total (actual) body weight
Pancuronium	Ideal body weight
Rocuronium	Ideal body weight
Vecuronium	Ideal body weight
Cisatracurium	Ideal body weight
Fentanyl	Lean body weight
Alfentanil	Lean body weight
Remifentanil	Lean body weight
Midazolam	Total (actual) body weight (bolus dose) Ideal body weight (infusion)
Paracetamol	Lean body weight
Neostigmine	Total (actual) body weight
Sugammadex	Total (actual) body weight or ideal body weight + 40%
Enoxaparin (VTE prophylaxis)	Total (actual) body weight 0.5 mg/kg

Table 4: Body Weight Adjustment Equations

Dosing Weight	**Calculation method (weights in kg)**
Ideal Body Weight (IBW)	45.4 + 0.89 x (height in cm - 152.4) for females 49.9 + 0.89 x (height in cm - 152.4) for males
Lean Body Weight (LBW)	**Classical equation:** (1.07 x TBW) - (0.0148 x BMI x TBW) for females (1.10 x TBW) - (0.0128 x BMI x TBW) for males **Alternative ("modern") equation:** (9720 x TBW)/(8720 + (244 x BMI)) for females (9270 x TBW)/(6680 + (216 x BMI)) for males
Predicted Normal Weight	(1.57 x TBW) - (0.0183 x BMI x TBW) - 10.5 for females (1.75 x TBW) - (0.0242 x BMI x TBW) - 12.6 for males

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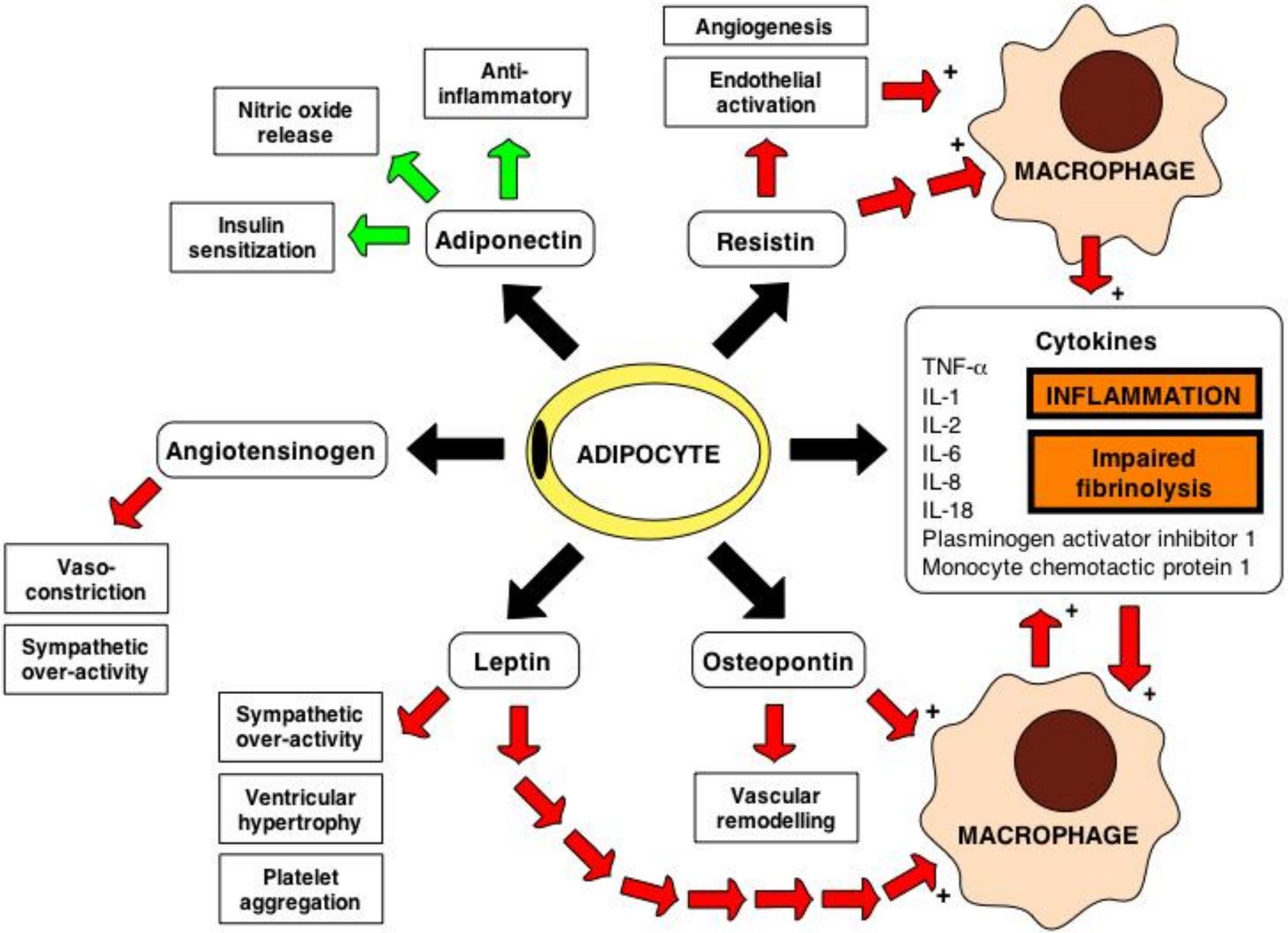
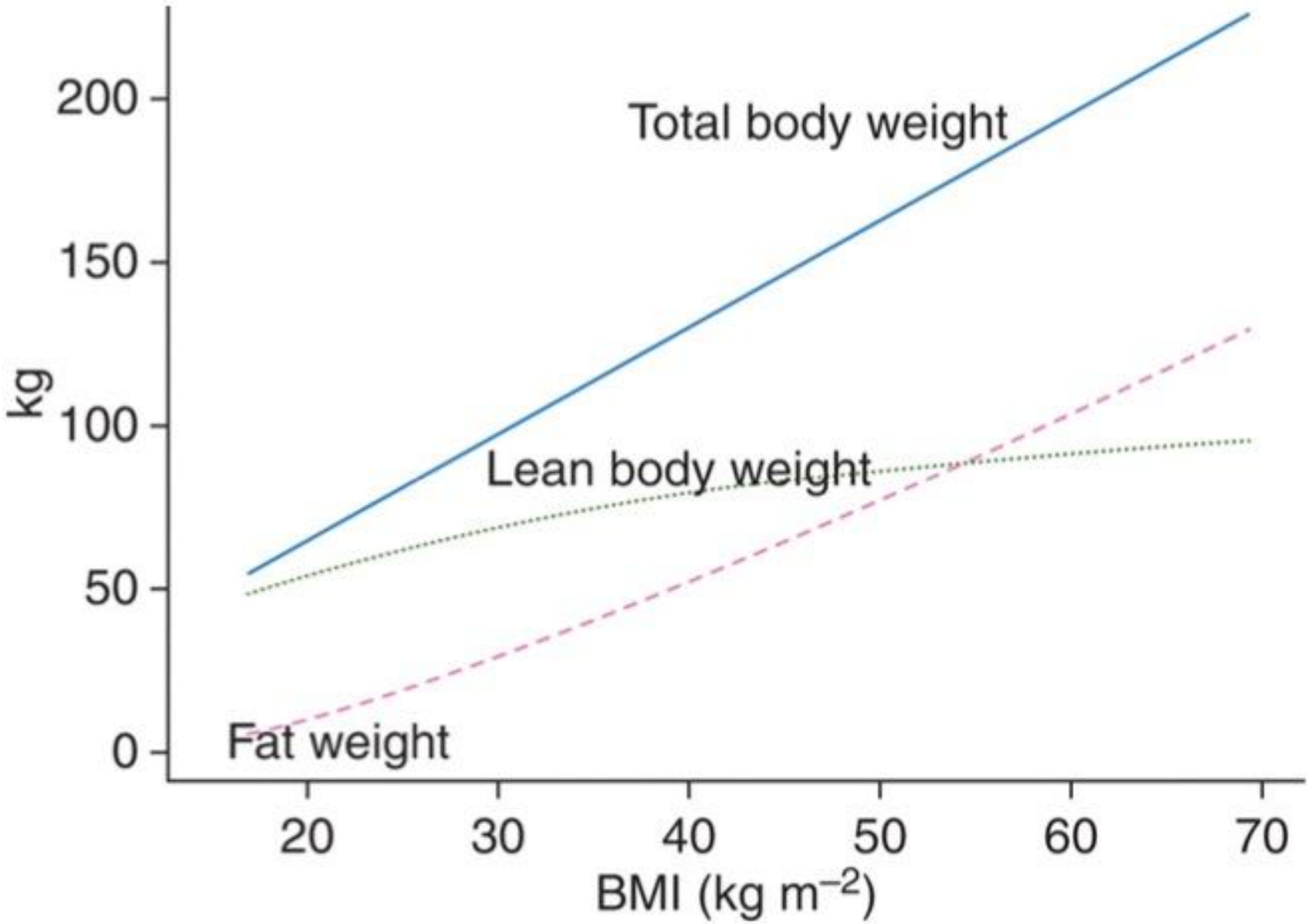

Angiogenesis
Endothelial activation
Anti-inflammatory
Nitric oxide release
Insulin sensitization
Adiponectin
Resistin
MACROPHAGE
Cytokines
TNF-α
IL-1
IL-2
IL-6
IL-8
IL-18
INFLAMMATION
Impaired fibrinolysis
Plasminogen activator inhibitor 1
Monocyte chemotactic protein 1
ADIPOCYTE
Angiotensinogen
Vaso-constriction
Sympathetic over-activity
Leptin
Osteopontin
Sympathetic over-activity
Ventricular hypertrophy
Platelet aggregation
Vascular remodelling
MACROPHAGE

Figure 2. Relationship of TBW, fat weight, and LBW to BMI in a standard height male. Reproduced from Ingrande J, Lemmens HJM. Br J Anaesth 2010; 105: i16-i23 (page i17 Figure 1) by permission of Oxford University Press on behalf of the British Journal of Anaesthesia.


200
150
100
50
0
kg
Total body weight
Lean body weight
Fat weight
20
30
40
50
60
70
BMI (kg m−2)