Can J Anesth/J Can Anesth (2012) 59:974–996
DOI 10.1007/s12630-012-9760-2

REVIEW ARTICLE/BRIEF REVIEW

Perioperative management of the severely obese patient: a selective pathophysiological review

Prise en charge périopératoire des patients présentant une obésité majeure - Une analyse physiopathologique sélective

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Received: 18 June 2012 / Accepted: 12 July 2012 / Published online: 26 July 2012

Abstract

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

Principal findings *Obesity is a multisystem chronic pro-inflammatory disorder associated with increased morbidity and mortality. Adipocytes are far more than storage vessels for lipids. They secrete a large number of physiologically active substances called adipokines that lead to inflammation, vascular and cardiac remodelling, airway inflammation, and altered microvascular flow patterns. They contribute to linked abnormalities, such as insulin resistance and the metabolic syndrome, and they attract and activate inflammatory cells such as macrophages. These changes can lead ultimately 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 obesity hypoventilation syndrome, which is less well appreciated and carries a significant outcome disadvantage. Perioperative management is challenging. It is centred 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 multisystem disease, and anesthesiologists caring for these patients perioperatively must have a sound understanding of the changes in order to offer the highest quality care to these patients.*

Résumé

Objectif *L'obésité est très répandue et elle est néanmoins vue principalement comme un trouble de la structure corporelle. Cet article fournit aux anesthésiologistes une synthèse des récents travaux de recherche sur la physiopathologie complexe de l'obésité en insistant sur l'importance de cette information pour la planification et la prise en charge périopératoire; il passe également en revue un certain nombre des principaux défis périopératoires dans ce groupe de patients.*

Constatations principales *L'obésité est un trouble chronique pro-inflammatoire touchant plusieurs systèmes de l'organisme qui est associé à une augmentation de la morbidité et de la mortalité. Les adipocytes sont beaucoup*

Author contributions *Aiden Cullen* and *Andrew Ferguson* were responsible for the conception and design of the manuscript. They contributed to the literature search and screening of the resulting papers, and they both contributed to the original draft. *Andrew Ferguson* further revised the article critically for important intellectual content.

Electronic supplementary material The online version of this article (doi:10.1007/s12630-012-9760-2) contains supplementary material, which is available to authorized users.

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plus que des réservoirs à lipides, car ils secrètent un grand nombre de substances physiologiquement actives appelées adipokines qui conduisent à une inflammation, un remodelage vasculaire et cardiaque, une inflammation des voies aériennes et à des perturbations de la circulation capillaire. Ils contribuent à des anomalies associées comme la résistance à l'insuline et le syndrome métabolique; enfin, ils attirent et activent des cellules inflammatoires telles que les macrophages. À terme, ces modifications peuvent aboutir au dysfonctionnement d'un organe, et plus particulièrement à des problèmes cardiovasculaires et pulmonaires. Concernant l'appareil respiratoire, les anesthésiologistes doivent connaître non seulement les outils de dépistage du syndrome d'apnée-hypopnée du sommeil, mais également le syndrome d'hypoventilation de l'obésité qui est moins bien évalué et est porteur d'une évolution significativement plus sombre. La prise en charge périopératoire est un défi et se concentre sur une optimisation cardiorespiratoire et métabolique en limitant les effets secondaires et de la douleur et des morphiniques systémiques, sur l'utilisation efficace de l'anesthésie régionale, et sur une attention particulière à la mobilisation et la nutrition (considérant la prévalence des déficits en micronutriments chez les patients présentant une obésité morbide). Il existe un risque de mauvais dosage des médicaments dans l'obésité qui nécessite une connaissance des posologies appropriées en fonction du poids pour les médicaments en période périopératoire.

Conclusion *La littérature insiste nettement sur la complexité de l'obésité sévère en tant que pathologie multisystème. Les anesthésiologistes qui ont la charge de ces patients dans la période périopératoire doivent avoir une bonne compréhension des changements afin d'offrir à ces patients des soins de la plus haute qualité.*

Table of contents

Infection risk
Thromboembolic risk and prophylaxis
Mobilization
Nutritional support

Summary

Key points

- Obesity is a multisystem chronic pro-inflammatory disorder, not just a structural condition
- 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
- Patients should be screened for obesity hypoventilation syndrome as well as for obstructive sleep apnea
- Anesthesiologists must be familiar with appropriate dosing weights for drugs
- Micronutrient deficiencies are common and potentially serious
- Preoxygenation can be enhanced using a ramped position and techniques, such as continuous positive airway pressure or noninvasive ventilation
- Care must be taken during and after positioning to avoid nerve or soft tissue injury
- Video laryngoscopes and intubating laryngeal mask airways (ILMA^{TM}) are useful adjuncts to airway management

PART 1

Introduction

Obesity has been aptly described as an epidemic. About 25% of Canadian adults are now obese, more than 60% are within the combined classification of overweight or obese, and the trend continues upwards.[1] Figures for other major developed nations are comparable, about 34% of adults in the United States and 24% in 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 multisystem pro-inflammatory disorder. This article presents some of the significant advances in the understanding of organ dysfunction and cellular and metabolic abnormalities in obesity. This knowledge reinforces approaches to both preoperative optimization and perioperative organ support and is often reported outside 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. We begin at the basic cellular level, lead on to associated organ dysfunction, and emphasize 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 and emphasize 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 (RA). The particular pathophysiological and management aspects of obese parturients are outside the scope of this 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. Body mass index is defined as the body weight in kg divided by the square of the body height in metres ($kg{\cdot}m^{-2}$). Obesity has been defined as a BMI > 30 $kg{\cdot}m^{-2}$, and morbid obesity has been referred to as a BMI > 40 $kg{\cdot}m^{-2}$ or a BMI > 35 $kg{\cdot}m^{-2}$ with an obesity-related comorbidity (Table 1). Body mass index alone is not a good predictor of the distribution of excess body fat; central obesity with elevated visceral fat levels is associated with greater metabolic impact and complications than widespread subcutaneous fat. Body mass index 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 this too can have an impact on organ function,[3] with the risk of metabolic abnormalities and hypertension increasing as the percent of body fat (%BF) increases.[4] Obesity

Table 1 Body mass index categories

Classification	Body mass index ($kg{\cdot}m^{-2}$)
Anorexia	< 17.5
Underweight	< 18.5
Normal	18.5-25
Overweight	25-30
Obese	30-40
Morbidly obese	40-50
Super morbidly obese	> 50

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 that terminate in obesity-associated comorbidity. Adipocytes have two main roles. The first role is lipid handling, where adipose tissue can be viewed as an adaptive response aimed at controlling the potential toxicity of free fatty acid (FFA) levels. The second role is an endocrine and paracrine function central to the adverse impact of obesity. These cells actively produce and secrete a large number of important biologically active hormones referred to as adipokines, which include substances with metabolic and growth regulation roles as well as cytokines and collagens (see Fig. 1). Pro-inflammatory substances are secreted mainly 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. Its normal physiological actions decrease appetite and trigger increased sympathetic activity (to burn calories), maintaining the 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 FFA oxidation, augments endothelial nitric oxide production, and plays a role in the regulation of cyclooxygenase 2 (COX-2). Adiponectin levels fall in obesity. This decline 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 FFA levels and uptake play an integral part in adipocyte physiology. They trigger increased pro-inflammatory expression via pathways that involve Toll-like receptor 4, nuclear factor kappa B (NF-κB), as well as

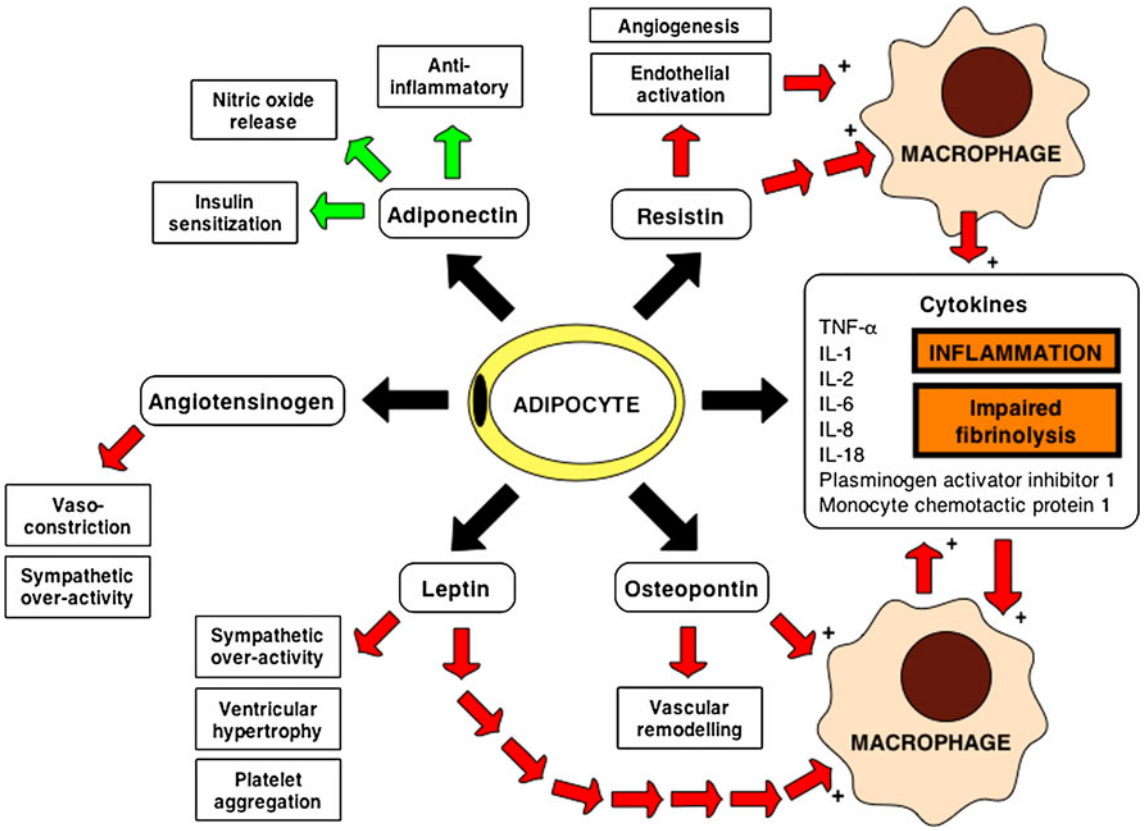

Fig. 1 Selected adipokines secreted by the adipocyte/inflammatory cell complex. TNF-α = tumor necrosis factor α; IL = interleukin

several other mechanisms.[10] In addition to increased cytokine and acute phase reactant (e.g., C-reactive protein) production, FFA levels commonly seen in the 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 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 they 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 adipocytes lead to a shift away from the production of adiponectin (which interferes with NF-κB signalling) and towards tumor necrosis factor-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 about 80% of the surface of the heart and can account for up to 20% of the heart's weight. Significantly more fat is associated with the right ventricle (RV) than with the left. The presence of excess fat tissue around coronary arteries is associated with an increased risk of ischemic heart disease,[13] and higher levels or epicardial fat are also associated with left ventricular (LV) diastolic dysfunction.[14]

Adipose tissue blood flow

Adipocyte hyperplasia is not accompanied by increased vascularization of the fat tissue, and compared with the non-obese state, one of the features of severe obesity is a reduction in adipose tissue blood flow (ATBF).[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, e.g., during periods of prolonged fasting. The lower ATBF may impair this beneficial FFA release. The ultimate consequence for the obese patient is post-prandial hyperlipidemia. Adipose tissue blood flow 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 establish 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. The MetS is accompanied by an elevated level of pro-inflammatory and prothrombotic mediators.[16] Obese patients with MetS have higher all-cause mortality and a 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 prothrombotic 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

Metabolic syndrome 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 autoregulation is inhibited.[19] The impact on myocardial oxygenation may become evident in settings where coronary flow reserve is an important defense mechanism, e.g., 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 the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system often found in MetS. This enhanced response is partly mediated through upregulation 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, e.g., phenylephrine. It is apparent, however, 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 remodelling 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, which in turn leads to hypertrophy as an adaptive response to the volume-induced tendency for ventricular dilatation. This view is being challenged by 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 leptin may indeed be the more important mechanism. Interestingly, in some patients, the RV undergoes hypertrophic change to a greater relative extent than the left ventricle, 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 a much greater risk of an oxygen supply-demand mismatch. Another key contributor to ventricular remodelling 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 LV 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, MetS, and OSA with new onset AF is underappreciated. 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 exhibiting LAD. Interestingly, the dilatation appears to occur in a longitudinal direction more often than in a transverse direction, although it is unknown how this factor relates to AF onset.[27] The incidence and risk increases as the degree of obesity increases, and it is the LAD and not the obesity *per se* that correlates with the risk of AF.[28] In addition to LAD, higher epicardial fat mass is associated with the 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, such as hypertension, LV diastolic dysfunction, and diabetes, which themselves increase the risk of AF.

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 a reduction in systemic vascular resistance (combining to increase cardiac output), as obesity progresses, these changes put increasing stress on the cardiovascular system and, ultimately, are associated with increased LV wall stress and elevated filling pressures. These changes are in addition to any leptin-related hypertrophic change or hypertensive changes. There follows a reduction in cardiac systolic and diastolic function 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 of abnormal leptin signalling 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 underappreciated as contributors to exercise intolerance in both the non-obese and obese populations. 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] Diastolic dysfunction should be specifically sought out in patients with severe obesity, e.g., by echo Doppler interrogation of the pattern of transmitral blood flow.[34] The normal pattern of transmitral blood flow 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 about

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 confine this discussion 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. If this is the case, more detailed information on the nature of their exercise limitation may be obtained from formal cardiopulmonary exercise testing, already used for integrated assessment prior to high-risk surgery.[36] It has also been suggested that dobutamine stress echocardiography (DSE) plays a role in overcoming exercise limitations in this patient population. 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 centres.[37] The role of DSE is not without controversy. A study in 611 patients referred for DSE prior to obesity surgery found that only 1.7% of the patients tested had a positive DSE, and only one in seven of these patients 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. There are complex decisions in patients with demonstrable ischemia concerning whether to proceed to coronary angiography as well as the risks and benefits of coronary artery bypass graft for lesions that cannot be treated at angiography. These decisions require a balanced discussion with the patient and the patient's cardiologist, including input from cardiac surgery.

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 (NT-proBNP), are available to help identify obese patients with systolic or diastolic cardiac dysfunction. Systolic dysfunction may not be clinically evident because of 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. Diastolic dysfunction is associated with an increased risk of postoperative congestive cardiac failure, prolonged hospital stay, and complications in major surgery (especially vascular and cardiac in nature).[39] Elevated BNP or NT-proBNP 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. Based on this, there have been suggestions that the threshold for abnormality in diagnosing heart failure should be lower in the obese.[40] Although BNP rises in diastolic and systolic heart failure, it is also elevated in obese patients with LAD who do not (yet) have echocardiographic evidence of LV diastolic or systolic dysfunction.[41]

Obviously, coexisting cardiac conditions, such as hypertension, ischemia, and heart failure should be medically optimized prior to surgery, and a cardiology consult may be required if this has not been achieved by the family physician. Although statins are a relatively uncontroversial therapy in patients with metabolic syndrome, the role of beta-blockade raises some issues. Perioperative beta-blockade (starting one to two 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.[42] It also seems likely that individual response to these agents is variable and may be significantly influenced by beta-receptor polymorphisms.[43] Beta-blockade in the severely obese, particularly those with MetS, 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 that have much less of a metabolic impact (e.g., carvedilol)[44] 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. Indeed, they may be useful prior to the development of symptomatic heart failure in patients with hypertension and/or MetS who have diastolic dysfunction.[25,45] 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 nonsteroidal anti-inflammatory drugs 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 which showed 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,[46] perhaps in combination with angiotensin receptor blockers.

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 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.[47,48]

The impact of intraoperative body position on the respiratory system must be anticipated and dealt with effectively (see below).

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,[49] 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-related breathing disorders

Much of the focus on obesity-related respiratory dysfunction in the anesthesia literature has centred on the detection and management of OSA. Although OSA is both important

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 of volume and small airway closure
Gas flow & resistance	Fall in FEV_1 & FVC in morbid obesity	This is a variable finding
	Normal FEV_1/FVC ratio	
	Increased airway resistance	Small airway collapse, lower volumes, and potential airway remodelling 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 anerobic 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	

FEV_1 = forced expiratory volumes in one second; FVC = forced vital capacity; A-aDO_2 = alveolar arterial oxygen gradient

and relatively common, we must not forget the existence of obesity hypoventilation syndrome (OHS) and the significant risk of morbidity and mortality attributed to this condition.

Obstructive sleep apnea – definitions, detection, and severity assessment Obstructive sleep apnea refers to a period of partial or complete upper airway obstruction occurring during sleep. Not surprisingly, such episodes may result in hypoxemia and hypercapnia with associated hemodynamic changes, such as hypertension, that occur through the night and commonly lead to daytime somnolence. Long-term untreated OSA results in cardiovascular complications, such as hypertension and right-heart strain. Obstructive sleep apnea occurs in more than 70% of patients with a BMI > 35, and this is combined with OHS in about 10-20% of OSA patients.[50,51] Practice guidelines have been issued on perioperative management of OSA patients,[52] and we refer readers to this document for more detailed information.

The key point is that anesthesiologists must select and utilize appropriate tools to assess the risk and establish the severity of this condition in obese patients. This then allows for appropriate perioperative planning. In some centres, the use of in-hospital sleep studies (polysomnography) is an option to evaluate patients formally. Some experts advocate universal investigation for patients who are morbidly obese or higher. However, many centres do not offer this investigation, and a number of screening questionnaires suited to the preoperative clinic have been developed. These screening tools have been the subject of a recent systematic review.[53] A good example is the STOP-BANG questionnaire developed by Chung *et al.*,[54] which has been shown to have consistently high sensitivity for detecting OSA at different severity levels (84% in mild OSA 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, and high blood Pressure and is combined with BMI > 35, Age > 50, Neck circumference > 40 cm, and male Gender. In keeping with many screening tools, it should be pointed out that 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., if the negative predictive value is good. This may come at the cost of categorizing some patients at higher risk levels than would indicate on further investigation.

Preoperative detection of OSA allows for planning for the pre- and postoperative provision of CPAP or noninvasive 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 NIV is planned postoperatively in patients who do not already use the technique, they must be familiarized with the equipment and conditioned to it 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 without other causes of hypoventilation, such as chronic obstructive pulmonary disease or neuromuscular disorders. This occurs against a background of nocturnal hypoventilation but notably does not require the presence of OSA, although it 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.[55] Obesity hypoventilation syndrome 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. First, it is clear that alterations in lung mechanics and lung volumes seen in obesity are more severe in OHS patients than in BMI-matched patients without OHS. This is partly a result of higher central fat deposits in OHS patients, which disproportionately affect lung volumes and diaphragmatic excursion. Therefore, OHS patients have lower respiratory system compliance, higher airway resistance, greater expiratory gas trapping, and work harder to breathe than eucapnic obese patients. While this is evident in the sitting position, it worsens further when supine. Second, OHS patients suffer from nocturnal hypercapnia with or without OSA, and this leads to secondary bicarbonate retention during the night. The hypercapnia improves during the daytime and is accompanied by a hangover of elevated bicarbonate concentration that produces a metabolic alkalosis and leads to secondary hypoventilation. Third, eucapnic BMI-matched obese controls display an increased respiratory drive that is absent in 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 the degree of elevation of leptin levels.[56]

Obesity hypoventilation syndrome is often absent from discussions around perioperative management of obesity, and this oversight may be clinically very significant. Patients with OHS have worse outcomes than BMI-matched patients without sleep-disordered breathing or patients with "simple" OSA. This impact on prognosis extends to a

higher risk of cardiac disease (including cardiac failure), episodes of acute or chronic respiratory failure, need for critical care, and post-discharge mortality.[57,58] Many severely obese patients do not have an arterial blood gas analysis taken at preoperative 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. A level $\geq$ 27 mmol·L^{-1} 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%).[59] This basic test should be carried out preoperatively for all severely obese patients undergoing major surgery or for less major procedures where parenteral opioids will be used or where patients are anticipated to experience reductions in respiratory function (e.g., laparoscopic surgery, interscalene brachial plexus block). Patients identified on this basis as high risk for OHS should be referred to a respirologist for review and consideration for positive airway pressure therapy. Therapy generally starts as CPAP, but over 20% of cases require up-titration to NIV/bilevel ventilation to eliminate hypercapnia. Oxygen therapy may also be required.

Patients with unidentified OHS are at a high risk for respiratory complications in the postoperative period and are more likely to suffer opioid-related side effects. Patients with OHS should receive anesthesia techniques that minimize the duration and dose of opioids. If these patients are missed at preoperative assessment and identified on the day of surgery, the anesthesiologist and surgeon should discuss the benefits and risks of proceeding with the surgery. If surgery is to proceed, urgent arrangements should be made for postoperative monitoring and respiratory support. In addition to continuous saturation monitoring, carbon dioxide levels should be monitored by blood gas analysis or by transcutaneous CO_2 measurement.

Nutrition status in obesity

Despite macronutrient excess, obese patients remain at risk for 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 the ability to mobilize.

A particularly underappreciated area of critical importance in the severely obese is micronutrient deficiency. Preoperative deficiencies are common, certainly in bariatric surgery candidates.[60] Iron deficiency occurs in 6-29% of these patients, with 3-18% being vitamin B_{12} deficient.[61,62] 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. In an observational study of 54 patients attending for laparoscopic sleeve gastrectomy, 51% of patients were found to have at least one deficiency preoperatively. The most common deficiencies were vitamin D, iron, thiamine, and vitamin B_{12}.[63]

Patients who have undergone previous weight loss surgery 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 as well as accounts of 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.

This vulnerability demands that both surgeons and anesthesiologists attend to nutritional preparation before elective surgical procedures. This will involve appropriate testing for the deficiencies outlined above along with referral to a dietitian or nutritionalist for preoperative dietary optimization and education. Ideally, this optimization would occur over a period of four to six weeks, but if this is not possible, dietary changes over a shorter period can be topped up with targeted enteral or parenteral vitamin and trace element supplementation.

PART 2

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.[64,65] The increase in LBW is counterintuitive. 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 sex 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 and work across a wider range of BMI.[66] 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). In Fig. 2, the relationship between TBW, BMI, and LBW is shown graphically. 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).[64,65,67-74] In Table 4, there is an outline of the calculation methods for the various dosing weights.

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

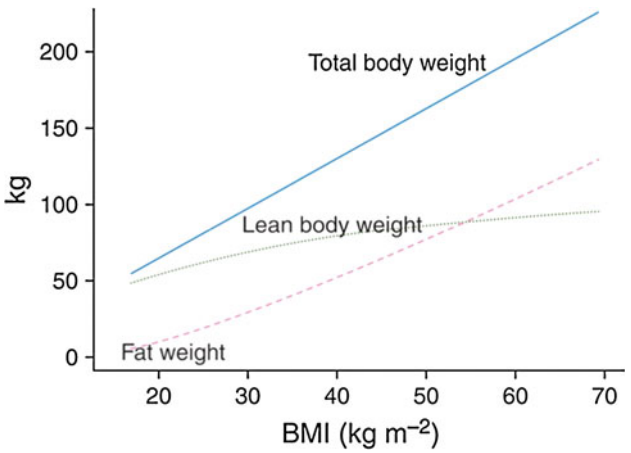

Fig. 2 Relationship of total body weight, fat weight, and lean body weight to body mass index in a standard height male. BMI = body mass index. Reproduced with permission from: *Ingrande J, Lemmens HJ*. Br J Anaesth 2010; 105: i16-i23. Oxford University Press on behalf of the British Journal of Anaesthesia

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 $mg \cdot kg^{-1}$

VTE = venous thromboembolism

Table 4 Body weight adjustment equations

Dosing Weight	Calculation method (weights in kg)
Ideal Body Weight (IBW)	45.4 + 0.89 × (height in cm - 152.4) for females
	49.9 + 0.89 × (height in cm - 152.4) for males
Lean Body Weight (LBW)	*Classical equation:*
	(1.07 × TBW) - (0.0148 × BMI × TBW) for females
	(1.10 × TBW) - (0.0128 × BMI × TBW) for males
	Alternative ("modern") equation:
	(9,720 × TBW)/(8,780 + (244 × BMI)) for females
	(9,270 × TBW)/(6,680 + (216 × BMI)) for males
Predicted Normal Weight	(1.57 × TBW) - (0.0183 × BMI × TBW) - 10.5 for females
	(1.75 × TBW) - (0.0242 × BMI × TBW) - 12.6 for males

BMI = body mass index; TBW = total body weight

agents and opioids should be dosed on the basis of lean body weight.

Vascular access

Poorly defined anatomical landmarks in the obese patient can make vascular access a challenge. Peripheral access may well be achievable even in the severely obese provided that conditions are optimized (e.g., proper lighting, encouraging venodilation through gentle tapping, a patient clinician) and remembering sites, e.g., the anterior forearm. 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. In obese patients, it has been shown that the internal jugular vein overlaps the carotid artery to a greater extent than in non-obese patients, and this may increase the risk of inadvertent arterial puncture if landmark techniques are used. Importantly, the degree of overlap in obese patients is already significant with the head in a neutral position, but the overlap is increased further as the patient's head is rotated to 60° (as it does in the non-obese patient, although to a lesser extent).

The use of ultrasound guidance for central venous catheter insertion may overcome vein location issues, lower the risk of arterial puncture, and reduce the time it takes for insertion as expertise increases. Ultrasound has been shown to aid in the safe placement of internal jugular lines,[75] and it may also be used to guide peripheral venous access[76] and arterial access. Not surprisingly, compared with non-obese patients, obesity can hinder the ultrasound view of the subclavian vein,[77] and novices should not attempt unsupervised ultrasound-guided subclavian line insertion in this patient group.

Regardless of the technique used, anesthesiologists should resist the temptation to embark on a procedure in these high-risk patients with tenuous venous access. Additional time spent on this basic requirement will minimize the risk of loss of access and subsequent failure to rescue the patient from cardiovascular or other compromise.

Blood pressure monitoring

Severe obesity makes the use of noninvasive blood pressure monitoring more difficult, and it is imperative that an appropriately sized cuff be used. Even with the correct cuff in place, recording times can be prolonged, and rapid changes in blood pressure will be missed. Elective placement of an arterial cannula facilitates rapid recognition and response to hemodynamic changes and also allows for relevant blood sampling.

Upper gastrointestinal function and risk of aspiration of gastric contents

Elevated BMI is consistently associated with higher rates of gastroesophageal reflux disease (GERD), particularly in females where estrogen exposure is considered a factor.[78] 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 is not a primary player in aspiration risk.[79] The increase in GERD occurs particularly in patients with elevated abdominal fat mass, and obesity is also associated with greater risk of hiatal hernia.[80]

The function of the esophageal sphincters under anesthesia has been investigated in a study of obese and non-obese patients.[81] 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 shown that the application of positive end-expiratory pressure (PEEP) during anesthesia increases the pressure in the esophagus, which may act as a barrier against regurgitation.[82] 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 airway devices in similar patients, this cannot be extrapolated to patients 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 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 it is often performed with the patient ramped or sitting.

Airway management

Patients with obesity are more likely to suffer serious airway problems during anesthesia than non-obese patients,

and this risk may be up to four times higher in patients with severe obesity.[83] Airway management, particularly bag-mask ventilation and intubation, is challenging in this population, and experienced staff should always be involved. Tools for predicting a difficult airway have recently been compared in a clinical study and reported elsewhere.[84] 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. All of the studies referred to in this section relate to patients with obesity.

Video and optical laryngoscopes Intubation using the Pentax AWS® (Pentax Medical Company, Montvale, NJ, USA) has been compared with intubation using a conventional MAC 4 blade,[85] and success was similar. More data are available on the Glidescope® (Verathon Medical Inc., Bothell, WA, USA), including intubation times and success comparable with oral fibreoptic intubation under anesthesia,[86] better views and reduced difficulty with intubation compared with the MAC 4 blade,[87] and success in the awake intubation scenario – although the success rate on first attempt was only 54%, 12% required three attempts, and 4% were failures.[88] Studies suggest that intubation times with these devices are longer than with conventional laryngoscopy in terms of statistical significance, although it is questionable whether the increase is clinically relevant. The Airtraq® (VYGON, Écouen, France) is an optical laryngoscope (the anesthesiologist places his eye to the viewfinder) with an optional video system. It has shown shorter intubation times and lower intubation difficulty scores compared with a Macintosh laryngoscope.[89] The authors commented on a non-significant increase in soft-tissue trauma with the Airtraq device. In another study the Airtraq device was compared with the CTrach® intubating laryngeal mask airway (see below) and the conventional Macintosh laryngoscope. Intubation times were shortest with the Airtraq, followed by the Macintosh, and the CTrach.[90] In addition, more patients in the Airtraq and CTrach groups maintained oxygen saturation $> 92\%$, and fewer patients in these groups desaturated to $< 88\%$.

Intubation via a laryngeal mask airway (LMA™) There are a number of LMAs designed as conduits for endotracheal intubation, and it certainly is likely that tracheal intubation with such devices will take longer in the obese patient than in the non-obese patient.[91] In a recent randomized study the Intubating LMA airway (ILMA™) was compared with the LMA CTrach™, a modification allowing real-time visualization of the glottic opening during intubation (both LMA North America, San Diego, CA, USA), and the total intubation time was shorter in the ILMA group than in the LMA CTrach group.[92] In this study, the LMA CTrach also required more manipulation to achieve a glottic view and ventilation. Taken together, the ILMA performed better in this evaluation. Even if ILMAs are not used for primary techniques, they are valuable in the setting of failed or difficult conventional intubation.

Conventional laryngeal mask airway devices 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 i-gel® supraglottic airway (Intersurgical Inc., Liverpool, NY, USA), provides for easier insertion and a better seal in lean individuals. In a recent comparison of the i-gel with the LMA Unique™ (LMA North America, San Diego, CA, USA) (a classic LMA with inflatable cuff) in obese patients with a BMI up to 35, the mean insertion time was found to be significantly shorter with the i-gel.[93] In addition, the mean pressures at which leakage occurred were higher in the i-gel group than in the LMA Unique group, indicating a better seal.

Oxygenation and ventilation

Preoxygenation The deleterious impact of obesity on lung volumes, compliance, and airway resistance are amplified under anesthesia. The fall in expiratory reserve volume 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 (potentially precipitous) 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 preoxygenation. Preoxygenation should occur with the patient positioned as upright as possible, e.g., in the sitting position, 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. It is prudent to optimize the process by avoiding sedation prior to preoxygenation and encouraging increased patient effort to achieve deep breaths. 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, USA), the Oxford Head Elevated Laryngoscopy Position (HELP) Pillow (ALMA Medical, Oxford, UK), and the Troop Elevation Pillow® (Sharn Anesthesia, Tampa, FL, USA).

The goal with these devices is to achieve a position that is sufficiently elevated so that the sternum and external auditory meatus are level. In addition, these elevated positions may place greater strain on the patient's arms and the brachial plexus; consequently, careful attention to limb support and padding is needed. The positioning devices may be sold with arm-boards etc. as accessories. 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 preoxygenation, the FRC may be further augmented with the application of 5-10 cm H_2O CPAP[94] or with the use of NIV, e.g., an inspiratory pressure of 7-10 cm H_2O above PEEP of 7 cm H_2O. The addition of NIV is effective in reducing atelectasis formation, and a recent study again showed that both CPAP and NIV improve arterial oxygenation compared with conventional preoxygenation.[95] In the same study, end-expiratory lung volumes may be further enhanced in some patients in the NIV group with the application of a recruitment maneuver following tracheal intubation, although the benefit was only seen in 12 of the 24 patients.

Positive end-expiratory pressure and lung recruitment maneuvers It is important to ensure that the gains in end-expiratory lung volume achieved during preoxygenation with CPAP/NIV are not lost intraoperatively. Common sense would suggest the application of PEEP, and the addition of periodic recruitment maneuvers (repeated sustained lung inflation with peak pressures of 40 cm H_2O have been used) or vital capacity maneuvers has been shown to improve oxygenation beyond the application of PEEP alone.[96,97] These maneuvers should be followed by the application of PEEP to maintain recruitment. Positive end-expiratory pressure values of 10 cm H_2O applied after recruitment/vital capacity maneuvers produce a lower A-a gradient than the application of zero PEEP (known as ZEEP) or 5 cm H_2O PEEP in obese patients undergoing laparoscopic surgery.[98] The degree of obesity, intraoperative positioning, and the nature of the surgery (laparoscopic surgery *vs* open) will dictate the frequency of these maneuvers, but repeated application is more effective than a single post-induction recruitment.[99] There is no benefit to the use of high tidal volumes in an attempt to maintain FRC. It is important to bear in mind the impact that recruitment maneuvers and moderate to high levels of PEEP can have on hemodynamics by way of reducing venous return (right ventricular preload) and increasing right ventricular afterload and ultimately risking systemic hypotension.

Modes of ventilation There is no convincing evidence to indicate 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.[100] With 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, in another study of 36 obese patients undergoing the same surgical procedure, results showed that, despite similar tidal volumes, minute volumes, and plateau pressures, the PCV group had lower $PaCO_2$ [mean 39 (3.0) mmHg *vs* 40.5 (2.25) mmHg; $P = 0.014$], lower expired-arterial CO_2 gradients [0.67 (0.27) *vs* 0.93 (0.27); $P < 0.01$], and better oxygenation [PaO_2/F_IO_2 ratio 281 (107) mmHg *vs* 199 (74) mmHg; $P = 0.011$].[101] There were no significant differences postoperatively in either study.

Patient positioning issues

There are three important aspects to patient positioning. First, appropriate positioning facilitates practical procedures, such as endotracheal intubation, RA, and central venous catheter insertion, in a way that optimizes the procedure and overcomes, or at least mitigates, associated physiological deterioration. Second, appropriate positioning reduces the risk of perioperative nerve, joint, and soft-tissue injury. Third, 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 favourable from the respiratory viewpoint,[102] 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 In the severely obese, this position is associated with significant reductions in lung volumes and increases in the work of breathing, which 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. In 1979, this was reported by Tsueda *et al*. as "obesity supine death syndrome".[103] 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.[104] The impact on severely obese patients who are subject to prolonged surgery in this position is unknown.

Prone position The critical care literature has shown 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 ten consecutive patients with BMI 30-40 but showed an improvement in FRC, lung compliance, and oxygenation in the prone position compared with the supine position.[105] Of importance, emphasis was placed on obtaining free abdominal movement, with weight taken on the chest wall and pelvis. The tidal volume used in the study would be considered high by today's standards, i.e., 12 $mL \cdot kg^{-1}$, and PEEP was not mentioned. It is critical to ensure that the abdomen is free in the obese patient. Failure to do so not only will embarrass the respiratory system but also will 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 handled carefully. If anesthesia with spontaneous breathing is used, pressure support ventilation with PEEP will likely 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 decreases in lung volume and compliance. This position should be avoided in awake morbidly obese patients for all but the shortest time, although NIV 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 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 the patient is required to adopt for the procedure.

Obesity is an independent risk factor for a failed RA procedure, with epidural, paravertebral, continuous supraclavicular, and superficial cervical blocks having the highest failure rates.[106] 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 RA. 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. This will come at the expense of image resolution. It takes time and experience to position the patient for block insertion so as to optimize anatomical landmarks and needle pathways while avoiding respiratory distress. Monitoring and skilled assistance is mandatory during block insertion in these patients. The clinical trial literature on RA 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, and they compared the data with 1,565 blocks in non-obese patients.[107] They reported a 94.3% success rate in the obese group *vs* a 97.3% success rate in the non-obese group, with accidental paresthesia being more common in morbidly obese patients than in non-obese patients (9.6% *vs* 2.2%, respectively). When ultrasound guidance is used in expert hands, severe obesity does not markedly increase the time it takes to perform blocks (e.g., interscalene), and ultrasound guidance may help to improve block success.[108]

Nerve stimulator-guided blocks have the same impact on success rate. Hanouz *et al.* studied nerve stimulator-guided multiple injection axillary brachial plexus blocks and showed a 91% success rate in the obese group *vs* a 98% success rate in the non-obese group.[109] Complications, such as inadvertent vascular puncture, were more common in the obese group than in the non-obese group (27% *vs* 9%, respectively).

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. If ISB is required in a morbidly obese patient, it has been suggested that 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.[110] Schwemmer *et al.* studied ultrasound-guided ISB in 70 patients who were a mix of obese and normal weight individuals.[108] A high-frequency probe was used, and the authors found that nerve visualization in the obese group took 5 (1) min *vs* 4 (2) min in the normal weight group, unlikely to be clinically significant. 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.* looked at retrospective data from 528 ultrasound-guided ISBs to determine if there was a relationship between obesity and block performance.[111] They confirmed that increased BMI was associated with increased time for block placement as well as with pain scores and opioid consumption in the postanesthesia care unit (PACU). There is little doubt that brachial plexus block can be successful in morbidly obese patients, but these successes require expertise and experience that training programs must ensure 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.[112] 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 and patients 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 to perform spinal anesthesia.[113] The ultrasound estimated depth to the epidural space appears to correlate well with the actual needle distance, at least in obese parturients.[114] Description of the ultrasound technique is beyond the scope of this article, and we refer readers to existing reviews on the topic.

Longer epidural and spinal needles will be required for some of these patients, and needle-through-needle techniques may assist to maintain needle trajectory when performing spinal anesthesia. 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 the lateral to the supine position or vice versa. With the insertion technique, a balance must be maintained between allowing additional catheter length to cope with space distance changes *vs* avoiding the risks of catheter malposition. Epidural catheter markings in some kits are provided in centimeters only up to 15 cm with the next marking at 20 cm. This may make recording an accurate insertion distance difficult in patients at extremes of obesity.

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.[115] Unfortunately, only 16 patients in the study had a BMI > 30, and it appears the comparison group received methadone as required on a background of regular intravenous paracetamol. Consequently, this study 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 reduce pain and opioid consumption significantly. There is no doubt that these 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

Prior to tracheal extubation, patients should have full return of neuromuscular function, and they should be cooperative and alert with adequate spontaneous tidal volumes, especially if elective NIV is not planned following tracheal extubation. Careful attention must be paid to ensure adequate doses of reversal agent are used as postoperative 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^{-1} corrected body weight or neostigmine 50 μg corrected body weight in 70 morbidly obese patients.[116] They showed that the time to achieve 90% train-of-four (TOF) ratio was significantly shorter in the sugammadex group than the neostigmine group at 2.7 *vs* 9.6 min, respectively ($P < 0.05$), and the TOF ratio in the PACU was 109.8% in the sugammadex group *vs* 85.5% in the neostigmine group ($P < 0.05$). Care should be taken to understand the dosing weight used when reading studies in this area. Van Lecker *et al.* studied 100 morbidly obese patients assigned randomly to one of four groups administered sugammadex: 2 mg·kg^{-1} ideal body weight, ideal body weight + 20%, ideal body weight + 40%, and actual body weight (69). The time from administration of sugammadex to TOF ratio > 90% was shortest in the IBW + 40% group at 112.5 sec, followed by actual body weight at 128.8 sec, which was not significantly different from the IBW + 40% group. The reversal time for IBW and IBW + 20% were significantly prolonged compared with 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 *vs* 236.5 mg; unfortunately, this outcome was not explained. There were no significant differences in tracheal extubation times or times to eye opening, and reversal was successful in all patients, with the authors recommending dosing based on IBW + 40%.

A number of case reports have shown that the use of sugammadex does not guarantee absence of the risk of recurarization. For example, Le Corre *et al*. reported a case of a 115-kg female who received a dose of sugammadex 1.74 mg·kg^{-1} actual body weight when she had return of two twitches. She subsequently achieved TOF ratio > 90% and required reintubation ten minutes later with loss of neuromuscular function necessitating a further dose of sugammadex.[117]

Careful attention should be paid to the correct use of neuromuscular monitoring equipment. This includes consideration of alternate monitoring locations (e.g., facial) in patients with very high levels of adipose at the wrist. A wrist circumference > 18 cm is associated with ulnar nerve supramaximal stimulation currents of over 70 mA, which monitoring devices may be unable to achieve.[118]

The obese patient should be positioned at least in the reverse Trendelenburg position and preferably in the semi-recumbent or sitting position as soon as is practical after the end of surgery. Tracheal 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 min in duration, and it is important to note that these episodes are not eliminated by the use of supplemental oxygen alone.[119,120] The need for postoperative oxygen supplementation remains one of the main barriers to day-case surgery for patients with obesity.[121]

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 tracheal extubation to CPAP or NIV has been shown to improve postoperative oxygenation and offers flexibility where extubation to conventional facemask oxygen would not succeed.[122] This technique can be utilized in the 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 preoperatively is tenuous, but this approach is logical given the additional physiological insults of surgery. Other options include intermittent NIV 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 to baseline. There remains a need to train surgical floor staff 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 guided by clinical progress and monitoring results should be provided for at least the first 48-72 hr after major surgery. It should be remembered that these patients are at high risk until their normal sleep pattern is fully re-established, which may take three to four days or more. Patients with OHS require particularly careful management to balance their analgesic needs against their respiratory risks and to monitor their arterial blood gases for progress. Higher than necessary concentrations of inspired oxygen that achieve significantly supraphysiological PaO_2 may result in increases in $PaCO_2$ and reduced ventilatory drive in some OHS patients.[123]

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 (F_IO_2) should be avoided without addressing underlying lung pathophysiology. 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 on lung function in 60 patients with BMI 30-40 undergoing minor peripheral surgery.[124] The intervention was carried out in the PACU following tracheal extubation and consisted of repeated sets of incentive spirometry exercises every 15 min for the first two hours after surgery. The intervention group displayed better oxygen saturation in the PACU and at six and 24 hr postoperatively. There were also significant differences in favour of the intervention group in terms of forced expiratory volumes in one second, forced vital capacity, and peak expiratory flow lasting up to 24 hr. 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 and results in reducing the risk of pulmonary infections and venous thromboembolism. An opioid-sparing multimodal analgesia approach is used most often. This incorporates oral (or intravenous where available) paracetamol, nonsteroidal 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 opioids are required, they 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 (e.g., clonidine and dexmedetomidine), pregabalin and gabapentin, and combined clonidine and S-ketamine.[125-128] If opioid-based patient-controlled analgesia is to be used, background infusions should be avoided, and the lockout period should be adjusted to minimize sedation and respiratory depression.

Infection risk

Obesity is an independent risk factor for postoperative infectious complications.[129] 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.[130] 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 accompanying chronic inflammatory state alter the number and function of dendritic epidermal T cells responsible for skin barrier functions and wound re-epithelialization, which results in less efficient wound healing.[131] These cells also play a part in the regulation of wound site inflammation. Elevated FFA levels suppress T cell function and reduce the effectiveness of T-cell receptor signalling. 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.[132]

How can this increased susceptibility to infection be countered? Aside from scrupulous attention to asepsis, perioperative antimicrobial administration should be timed carefully and drug doses should be considered properly to ensure 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.[133] Intraoperative use of appropriately sized mechanical devices, such as intermittent pneumatic compression devices, will also help to improve venous return as well as lower the risk of deep vein thrombosis. If a patient's risk of bleeding is assessed as being low, pharmacological prophylaxis should be offered to all except those with ruptured cranial/spinal vascular malformations. The optimal prophylactic dose of low-molecular-weight heparin is unclear, although weight-based dosing is recommended in the obese patient over fixed doses.[134] For example, it may be that a dose of enoxaparin up to 0.5 $mg{\cdot}kg^{-1}$ actual body weight (once or twice daily depending on VTE risk) is needed to achieve adequate anti-Xa levels.[70,135] 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 $IU{\cdot}mL^{-1}$ has been recommended.[136] 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 of the presence of motor blockade should be made 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, 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 require critical care, more formal enteral or parenteral nutrition support may be required. High protein content hypocaloric feeding is one strategy that has been used successfully in the critically ill.[137] Micronutrient deficiencies may require individual treatment schedules. The use of supplementation for vitamin and trace element deficiencies around bariatric surgery has recently been reviewed.[138] Of particular importance for anesthesiologists is thiamine deficiency. This may present with neurological symptoms, which may be disregarded as minor side effects of regional or neuraxial anesthesia or may actually divert attention away from what is really a complication of regional or neuraxial anesthesia. In general, thiamine supplementation at 50 - 100 $mg \cdot day^{-1}$ 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 which 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.

Multiple Choice Questions

For each question, select the one best response.
The correct responses appear online as Electronic Supplemental Material.

1) Which of the following statements is correct?

   A BMI is calculated as total body weight (kg) divided by height (meters)
   B BMI > 45 is referred to as morbidly obese
   C BMI is a better predictor of visceral fat excess than subcutaneous fat
   D Body fat content may be elevated at normal BMI
   E Elevated BMI always indicates obesity

2) Which of the following statements about adiponectin is correct?

   A It increases sympathetic nervous system activity
   B It leads to reduced free fatty acid oxidation
   C It is involved in regulation of prostaglandin synthesis
   D It is not linked to changes in nitric oxide concentration
   E Increased levels are associated with increases in aldosterone

3) Which of these statements about cardiovascular disorders in obesity is false?

   A The risk of atrial fibrillation is linked to left atrial size, not BMI
   B Angiotensin receptors are upregulated in the coronary circulation
   C Leptin receptors are preferentially located in the left atrium
   D Aldosterone levels are linked to severity of obstructive sleep apnea
   E Diastolic dysfunction is recognized by changes in mitral valve Doppler

4) Severe obesity is associated with which of the following respiratory changes?

   A A reduction in peak oxygen consumption on cardiopulmonary exercise testing
   B Increased minute volume on exercise mainly due to a rise in breathing rate

C A fall in FEV1 due to lung volume loss that exceeds FVC changes
D A marked fall in total lung capacity
E A fall in FRC due to a fall in residual volume

5) Select the false statement regarding obesity hypoventilation syndrome

A Diagnosis requires evidence of an awake $PaCO_2$ above 45 mmHg
B It is present in 30% of formally diagnosed OSA patients
C Lung mechanics and volumes are worse in OHS patients
D The presence of OSA is not required to diagnose OHS
E OHS can be recognized without blood gas analysis

6) Which drug is correctly matched with the relevant dosing weight?

A Thiopental dosed on the basis of total (actual) body weight
B Midazolam infusion dosed on the basis of lean body weight
C Rocuronium dosed on the basis of total (actual) body weight
D Succinylcholine dosed on the basis of ideal body weight
E Remifentanil dosed on the basis of lean body weight

The authors received no funding from any source in relation to this manuscript.

The authors have no commercial or non-commercial affiliations or any other associations that are or may be perceived to be a conflict of interest with the work.

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