Critical care 3

Prevention and care of respiratory failure in obese patients

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With the increase in the global prevalence of obesity, there is a parallel rise in the proportion of obese patients admitted to intensive care units, referred for major surgery or requiring long-term non-invasive ventilation (NIV) at home for chronic respiratory failure. We describe the physiological effect of obesity on the respiratory system mainly in terms of respiratory mechanics, respiratory drive, and patency of the upper airways. Particular attention is given to the prevention and the clinical management of respiratory failure in obese patients with a main focus on invasive and NIV in intensive care during the perioperative period and long-term use of NIV on return home. We also address other aspects of care of obese patients, including antibiotic dosing and catheter-related infections.

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Introduction

Obesity is defined as a body-mass index (BMI) of ≥30 kg/m². The substantial increase in the prevalence of obesity constitutes a global health challenge, particularly as it is a major underlying cause of chronic diseases, multimorbidity,[1] and cancer.[2] The prevalence of morbid obesity, defined as a BMI ≥40 kg/m², is rising even more than other classes of obesity. At a BMI of 40–45 kg/m², life expectancy is reduced by 8–10 years.[3] However, obesity is a heterogeneous disorder with the so-called obesity paradox representing an unexpected inverse association between obesity and mortality. The potential reasons for this paradox include high levels of cardiorespiratory fitness that modify cardiometabolic risk and negate adverse effects of a high BMI, which might explain the good prognosis in this subgroup of patients.[4]

Up to 20% of patients admitted to intensive care units (ICU) are obese. Morbid obesity is the most common reason for initiation of long-term mechanical ventilation at home.[5] Obesity has a strong effect on iatrogenic events, risk of infection, the physiology of respiratory mechanics, respiratory drive, and upper airway functions. These changes, in association with a high prevalence of sleep apnoea in morbidly obese patients, strongly affect clinical management in the perioperative period.[6]

Obesity-related adjustments during sleep

Sleep-related breathing disorders in obesity

Surplus adipose tissue in the abdomen and surrounding the chest wall reduces functional residual capacity with a significant decrease in the expiratory reserve volume.[7] Obese patients breathe at low lung volumes with limited expiratory flow, particularly when supine and during sleep.[6] Fat deposits have direct mechanical effects leading to a reduction in respiratory system compliance associated with greater airway resistance, both of which contribute to an increase in total work of breathing (figure 1). Gas trapping due to premature airway closure generates intrinsic positive end-expiratory pressure (PEEPi) and favours ventilation-perfusion mismatch[6] with the development of atelectasis without adjustment of hypoxic pulmonary vasoconstriction.[7] The alveolar-to-arterial oxygen partial pressure difference ($AaDO_2$) is frequently widened in morbidly obese patients in association with a low PaO_2 (figure 1).

The high prevalence of obstructive sleep apnoea in obese people, up to 60%,[8] is explained by several underlying mechanisms. Surplus fat deposits surrounding the upper airway and reduced lung volume are key features by which obesity synergistically decreases pharyngeal size. Fluid overload, which is common in obese people (especially in acute conditions), develops with a nocturnal rostral fluid shift from the legs to the neck (owing to the recumbent position), and contributes to narrowed upper airways and obstructive events during sleep.[9] This mechanism is amplified in obese people with comorbidities and might contribute to an overestimation of sleep apnoea severity when sleep studies are done in an acute context.

During rapid eye movement (REM) sleep there is generalised postural muscle atonia and the persistence of ventilation is primarily dependent on diaphragm activity. In obesity, faced with an abnormal respiratory workload, most patients develop increased respiratory drive to compensate and allow them to remain eucapnic. If this increased respiratory drive cannot be maintained, hypoventilation, initially confined to REM

Key messages

- There is a physiological effect of obesity on the respiratory system mainly in terms of respiratory mechanics, respiratory drive, and patency of the upper airways.
- Obesity is not associated with an increase in intensive care unit (ICU) mortality, although it does lengthen the duration of ICU stay and use of hospital resources.
- Perioperative atelectasis is more frequent in obese patients, and prevention of atelectasis should be done with early positive pressure ventilation during anaesthesia, from the preoperative until the postoperative period.
- The tidal volume setting must be guided by the patient's height and not by their measured weight.
- Randomised trials are needed to compare different positive airway pressure treatments in well-defined obesity hypoventilation syndrome (OHS) phenotypes, with the goal of offering tailored ventilator support to patients with OHS.

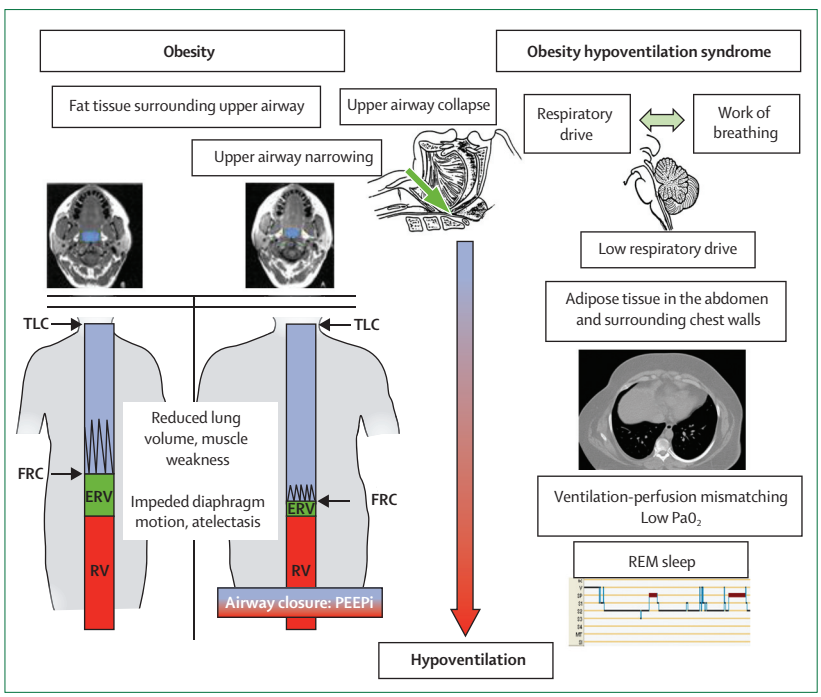

Figure 1: **Obesity-related changes in the respiratory system, respiratory drive, and in breathing during sleep**
REM=rapid eye movements. PEEPi=intrinsic positive end-expiratory pressure. TLC=total lung capacity. ERV=expiratory reserve volume. RV=residual volume.

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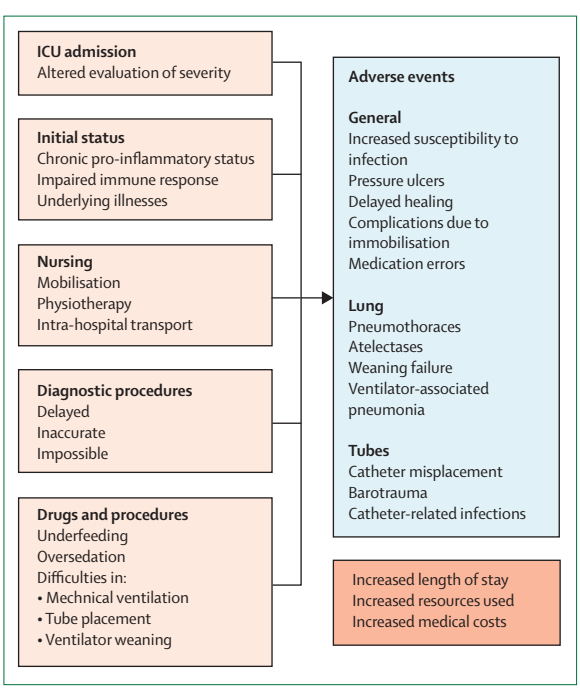


Figure 2: **Morbid obesity in the intensive care unit (ICU): effect for management and prognosis**

sleep, will develop. The repetitive occurrence of REM sleep hypoventilation induces a secondary depression of respiratory drive with daytime hypercapnia, leading to obesity hypoventilation syndrome.

Obesity hypoventilation syndrome: a distinct obesity phenotype with poor prognosis

Obesity hypoventilation syndrome is defined as a combination of obesity (BMI ≥30 kg/m²), daytime hypercapnia ($PaCO_2$ >45 mm Hg), and disordered breathing during sleep (after ruling out other disorders that might cause alveolar hypoventilation).[10] Patients with obesity hypoventilation syndrome show an additional burden of comorbidities and increased mortality compared with obese eucapnic individuals.[11,12] People with obesity hypoventilation syndrome have impairments in respiratory mechanics including slight weakness in their respiratory muscles. 85% of patients with obesity hypoventilation syndrome have obstructive sleep apnoea with long-lasting apnoea and hypopnoea and insufficient post-event ventilatory compensation, which contribute to diurnal hypoventilation. Central hypoventilation during REM sleep is prevalent in 15% of people with obesity hypoventilation syndrome. In patients with obesity hypoventilation syndrome, circulating leptin concentrations are elevated, but patients have central resistance to leptin.[13] Leptin acts as a powerful stimulant of ventilation and controls metabolism and cardiovascular regulation.[13] In obesity hypoventilation syndrome, the central resistance to leptin has cardiometabolic effects and leads to a deterioration of respiratory control.

These obesity-related physiological changes are heightened in the supine position, as is usually the case in a perioperative setting, and will affect management in the intensive care unit (ICU) and outcomes. These physiological changes could adversely affect pulmonary gas exchange with early-onset oxygen desaturation in combination with upper airway obstruction and hypoventilation. This physiopathological context justifies specific mechanical ventilation and oxygenation strategies in obese patients, both to address chronic respiratory failure and to reduce risk and optimise care in the perioperative period.

Morbid obesity in the ICU

Mortality in the ICU

In ICUs, the proportion of obese patients can reach 20%. Health-care providers usually consider that obese, and particularly extremely obese, patients have higher morbidity and mortality due to the presumed difficulties of caring for such patients, including positioning, transport, skin care, intravascular access, diagnostic imaging, and ventilator weaning (figure 2). However, some studies have reported that obesity is not associated with an increase in ICU mortality,[14,15] although it does lengthen the duration of ICU stay[14,16–18] and resource use by the hospital.

Martino and collleagues[19] explored mortality and length of ICU stay of mechanically ventilated patients, after careful adjustment for severity at admission, case mix, and geographical region. Overweight and obese patients had a lower 60-day mortality, and in survivors, length of

ICU stay was extended, especially for extremely obese patients with BMI ≥60 kg/m².

In the ICU, there is a paradox about mortality from acute respiratory distress syndrome for both obesity and diabetes. These underlying pro-inflammatory conditions that show increased levels of cytokines could be (directly or indirectly) involved in making obese patients less prone to developing exaggerated inflammatory responses.[20] Obese patients also have a greater capacity to tolerate the extensive weight loss associated with critical illness than do patients of healthy weight. Another important factor possibly explaining the unexpected decreased mortality is that, especially for extremely obese patients, the thresholds for ICU admission are probably lower than for patients of healthy weight. In the HRS-Medicare cohort,[21] a study involving 1524 patients admitted to hospital for severe sepsis, the 1-year mortality was 40% lower in obese and severely obese patients compared with healthy weight patients. However, obese patients who survived acute lung injury[18] or severe sepsis[21] used more health-care resources and required more Medicare spending in the year after hospital discharge.

Increased risk of iatrogenic events in mechanically ventilated obese patients

Obesity is associated with an increased risk of infections such as ventilator-associated pneumonia and catheter-related bloodstream infections, and increased risk of iatrogenic events such as catheter-related pneumothorax, decubitus ulcers, and thrombo-embolic diseases.[22] In a case-control study in mechanically ventilated patients, obesity was associated with a greater risk of difficult tracheal intubation (15% *vs* 6%) and post-extubation stridor (15% *vs* 3%) compared with non-obese patients, although with no effect on ICU mortality (24% *vs* 25%, respectively).[23]

Risk of treatment errors and inadequate antimicrobial therapy

The usual treatment of critically ill patients requires adequate nutrition and adequate dosing of drugs.[24] Unfortunately, the initiation of nutritional support is often delayed in mechanically ventilated obese patients (probably because of a belief that obese patients do not need to be fed early because they have a great reserve of energy), which might have a deleterious effect on prognosis.[14] Overall, obesity increases the risk of initial under-dosage of drugs and inadequate initial treatment with subsequent overdosing during maintenance treatment. The elimination half-life of benzodiazepines, such as midazolam, is four times higher than for people of healthy weight leading to unnecessarily extended sedation in obese patients.[25] Although propofol is a valuable alternative, its use should not exceed 6 days to avoid propofol infusion syndrome. Despite the absence of pharmacokinetic data, dexmedetomidine is attractive because it is not associated with respiratory depression or obstructive breathing during sedation; its sympatholytic effects should help to stabilise blood pressure and heart rate.[26]

In a multicentre cohort study,[27] obese patients with septic shock less frequently received adequate resuscitation fluids and adequate initial dosages of antimicrobials. These patients were at higher risk of receiving complex antibiotic treatment often inadequately dosed, but for longer courses.[28] Indeed, weight-adjusted dosing is often missing. The volume of distribution and renal clearance is increased in obese individuals along with changes in serum protein levels and hepatic metabolism.

Increased risk of infections

Prolonged immobility and difficult intravenous access requiring the use of central lines are among the reasons for the increased risk of infections in obese patients. Obese patients need more days on ventilation because of their respiratory and intra-abdominal pathophysiology, a factor that increases the risk of pneumonia. Metabolic factors, such as hyperglycaemia and pro-inflammatory status, characteristic of many obese patients, might also alter the immune response with reduced natural killer (NK), B, and T cell and neutrophil counts.

Obese patients have a five-times higher risk of surgical site infection than do non-obese patients.[29] Unselected obese trauma patients had an adjusted odds ratio (OR) of nosocomial infections of 4·7 for BMI 30–40 kg/m² and OR 5·91 for BMI ≥40 kg/m² compared with patients of healthy weight.[30] In a prospective database of 2037 patients, Dossett and colleagues[31] found that severely obese patients (OR 3·2, 95% CI 1·9–5·3) were at very high risk of catheter-related bloodstream infections in the ICU. The authors postulated that this was due to difficulties in achieving both peripheral and central access in obese patients because of the loss of physical landmarks. Difficulty, or reluctance, of providers to replace catheters in case of suspicion of infection might also have contributed towards this result.

In all critically ill obese patients, the subclavian route is associated with a high risk of mechanical complication. A femoral route is more frequently used than internal jugular access. In two studies,[32] the risk of infection and mechanical complications was similar between internal jugular and femoral routes, but significantly lower when a subclavian catheter was used. Catheter tunnelling,[33] chlorhexidine dressings,[34] and antiseptic-impregnated catheters[35] should be used in these patients, especially if a femoral route is the only accessible insertion site.

Obese patients have a theoretically higher risk of nosocomial pneumonia and especially of ventilator-associated pneumonia mainly due to the increased length of mechanical ventilation. Other major risk factors of nosocomial pneumonia include impaired bronchial drainage favouring atelectasis, the high percentage of extubation failures, and difficulties in starting proper respiratory physiotherapy. To obtain high quality chest radiographs of obese patients is difficult and complicates

accurate diagnosis of pneumonia. A CT scan might provide a better visualisation of the parenchyma, but its use is limited by difficulties transporting these patients to the radiology unit and by the weight and aperture limitations of the available equipment.

Perioperative mechanical ventilation of the obese patient

Effect of obesity on perioperative risk of respiratory failure

Perioperative atelectasis, which is more frequent in the obese patient, contributes to increasing the intrapulmonary shunt and is one of the main causes of intraoperative and postoperative hypoxaemia and pulmonary infections.[36] Atelectasis persists for longer postoperatively in obese patients in comparison with full resolution in non-obese patients.[37] The onset of atelectasis is probably multifactorial; the reduced functional residual capacity of the obese patient is exacerbated by the supine position imposed after a surgical procedure. Moreover, obese patients might be bedbound for longer in the postsurgical period and faster mobilisation could certainly contribute to a quicker resolution of atelectasis. Furthermore, obese patients often present respiratory comorbidities such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea or obesity hypoventilation syndrome. Many perioperative complications are directly related to obstructive sleep apnoea, including difficulties in airway management, mask ventilation, intubation, and postoperative obstruction of the upper airway.

Mechanical ventilation strategies in the preoperative, intra-operative and postoperative periods

Obesity and obstructive sleep apnoea are risk factors for difficult mask ventilation,[38] along with being older than 55 years, snoring, having a beard, and having no teeth. Also, tracheal intubation is more difficult in obese people with severe obstructive sleep apnoea (prevalence of 15–20%) than in the general population (prevalence of 2–5%).[39,40] A high Mallampati score, reduced cervical mobility, and obstructive sleep apnoea were associated with difficult intubation in obese patients.[41] In morbidly obese patients, adequate preparation with a specific procedure for difficult intubation should be anticipated.

In obese patients with obstructive sleep apnoea, continuous positive pressure ventilation (CPAP) or non-invasive ventilation (NIV) should be initiated before surgery, especially if the apnoea and hypopnoea index (AHI) is more than 30 events per h or if there are severe cardiovascular comorbidities,[42] and should be maintained throughout the perioperative period.

Before anaesthesia induction, preoxygenation of obese patients should be optimised. In morbidly obese patients, the non-hypoxic apnoea time (length of apnoea after the induction of anaesthesia when the patient has no oxygen desaturation) decreases from 3 min to 1 min.[43] In the supine position, end expiratory lung volume is reduced by 69% after induction of anaesthesia.[44] A positive end expiratory pressure (PEEP) of 10 cm H_2O (1·0 cm=0·39 inches) during preoxygenation and after endotracheal intubation increased the length of apnoea without hypoxaemia by 1 min on average [45] and reduced the atelectasis surface. Preoxygenation for 5 min with pressure support and PEEP (6 cm H_20) resulted in rapid attainment of an exhaled oxygen fraction (FEO_2) above 90%.[46] NIV, especially when applied in a head-up position, restricted the decrease in pulmonary volume and improved oxygenation compared with conventional preoxygenation with a face mask.[47] Consistently, the atelectasis recorded in CT scans decreased after preoxygenation when positive pressure was maintained through mask ventilation and intubation. The use of high-flow nasal cannula oxygen also appears to be interesting for preoxygenation of obese patients in operating rooms, with results being similar to standard facial mask or CPAP.[48]

After preoxygenation and intubation, perioperative positive pressure ventilation should be continued during the surgical procedure. In patients with acute respiratory distress syndrome, ventilation with a low tidal volume (6 mL/kg) has been beneficial.[49] However, if the tidal volume is too low, atelectasis could occur[32] and alveolar recruitment manoeuvres would be necessary to fully reopen the lung after the induction of anaesthesia and PEEP (levels >5 cm H_2O) must be applied to prevent progressive reclosure leading to further atelectasis. High tidal volume of 10 mL/kg predicted bodyweight or greater has been associated with organ failure and extended ICU stays. In the setting of abdominal surgery the IMPROVE study,[50] a multicentre, randomised, double-blinded trial, compared an optimised strategy of ventilation called protective ventilation (tidal volume 6–8 mL/kg predicted bodyweight and PEEP 6–8 cm H_2O with systematic alveolar recruitment manoeuvres every 30 min) with a traditional strategy called non-protective ventilation (tidal volume 10–12 mL/kg predicted bodyweight, without PEEP or recruitment manoeuvres). Protective ventilation decreased the overall rate of a composite criterion including onset of pulmonary complications (pneumonia or need for either non-invasive or invasive ventilation) or extrapulmonary complication (sepsis, septic shock, and death) from 27·5% to 10·5% and reduced the length of hospital stay by 2 days.[50] In the European study, PROVHILO,[51] which specifically included patients at risk of postoperative pulmonary complications after abdominal surgery, all patients received a tidal volume of 8 mL/kg predicted bodyweight and were randomly assigned to either low PEEP (≤2 cm H_2O without recruitment manoeuvres) or high PEEP (12 cm H_2O with recruitment manoeuvres). There was no significant difference between the two groups for a composite criterion of postoperative pulmonary complications in the 5 first days after surgery, but at the expense of more haemodynamic failures in the group with high PEEP.[51]

These two large randomised studies in non-obese populations provided the rationale for protective ventilation

to decrease postoperative pulmonary and extrapulmonary complications, but cautioned against the haemodynamic dangers of excessively high levels of PEEP, especially when not associated with low tidal volume. A multicentre observational study[52] showed that obese patients are still ventilated with overly high tidal volume in the perioperative period, and this is the subject of an ongoing study (NCT02148692). Given their decreased functional residual capacity, obese patients are particularly sensitive to atelectasis and absence of PEEP. For obese people, the optimal tidal volume is therefore between 6 mL/kg and 8 mL/kg of predicted bodyweight associated with PEEP so as to avoid atelectasis by alveolar closing (derecruitment). The tidal volume setting should be guided by the patient's height and not by their measured weight. The easiest predicted bodyweight formula to remember is the following: predicted bodyweight (kg)=height (cm)−100 for men and predicted bodyweight (kg)=height (cm)−110 for women (figure 3). It is preferable to implement PEEP at 10 cm H_2O associated with a tidal volume of 6–8 mL/kg predicted bodyweight from the start of mechanical ventilation and during the whole period of ventilation to both prevent derecruitment and allow alveolar reopening once they have collapsed.[47,53] The potential haemodynamic side-effects of high PEEP should be monitored to avoid a risk of decreased oxygenation due to the effect on cardiac output and of arterial hypotension due to compromised venous return.[54] In cases of auto-PEEP, an extrinsic PEEP of two-thirds the intrinsic PEEP should be used.

To open alveoli once they are closed, recruitment manoeuvres transitorily increasing the trans-pulmonary pressure improve arterial oxygenation and increase available lung volume.[47] The method of reference is a 40 s expiratory pause with a PEEP level of 40 cm H_2O, but alternatives exist, including a progressive increase in PEEP to 20 cm H_2O with constant tidal volume within 35 cm H_2O of plateau pressure, or a progressive increase in the tidal volume.[55] Again, recruitment manoeuvres should be done only when haemodynamically tolerated,[56] but their ideal frequency is debated.

Because respiratory drive is decreased especially in obesity hypoventilation syndrome,[11,12] the respiratory rate should be set at 15–21 breaths per min in morbidly obese patients (BMI >40kg/m²), whereas it generally ranges from 10 to 12 breaths in non-obese patients.[11,57,58]

Which intra-operative ventilatory mode should be recommended in obese patients?

The pressure mode delivers a constant pressure in the airway, decreasing the risk of barotrauma. With the decrease in compliance of the respiratory system that typically occurs with obesity and atelectasis, the delivered tidal volume can decrease, leading to hypercapnic acidosis that should be prevented by monitoring minute ventilation and capnography. Use of the volume mode poses a risk of barotrauma by an increase in the inspiratory pressure delivered to the target volume and requires monitoring the end of inspiration alveolar pressure (ie, the plateau pressure).

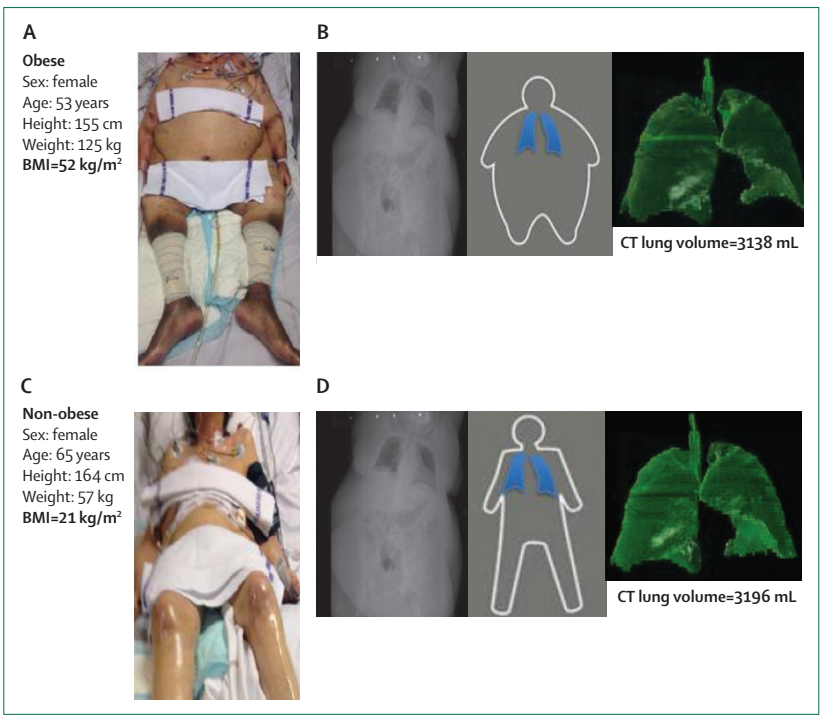


Figure 3: **Assessment of lung volume in an obese and a non-obese patient in the intensive care unit**
Lung size for the obese and non-obese patients is quite similar because the two patients have similar height, but different body-mass index (BMI). Physicians should choose tidal volumes on the basis of predicted bodyweight rather than actual bodyweight. Optimal tidal volume for both invasive and non-invasive ventilation in obese patients is between 6 and 8 mL/kg of predicted bodyweight and should not be calculated from the true bodyweight. Obese (A, B) and non-obese (C, D) patients admitted to the intensive care unit. (C, D) Imaging techniques (chest x-ray and CT scans) showing that even with different body mass indexes, lung volumes are actually the same.

In obese patients, studies comparing pressure support with a controlled mode report contradictory data,[59] though pressure support has the additional benefit of a reduction in ventilator-induced diaphragm dysfunction.[60–62] Further studies are necessary to compare pressure support to more recent ventilatory modes (neurally adjusted ventilatory assisted, adaptive support ventilation, proportional assisted ventilation, and pressure-controlled volume guaranteed ventilation).

Obese patients should be extubated in a lateral or semi-sitting position and only when they are completely awake. The complete disappearance of the neuromuscular block must be checked before extubation, using reversal of the block in the absence of a contraindication. The prophylactic use of NIV after extubation in obese hypercapnic patients decreased the risk of acute respiratory failure, prolonged ICU stay,[63,64] and mortality.[65] Postoperative interventions that could decrease the risk of respiratory failure include postoperative analgesia strategies avoiding opioids, CPAP or NIV use, careful positioning of patients,[66] and monitoring. Compliance to CPAP or NIV will be better if patients bring their own equipment to the hospital. High-flow nasal cannula

oxygen permits the delivery of an adjustable fraction of continuously humidified and warmed inspired oxygen (F_IO_2) and can be used between sessions of NIV or CPAP; however, this has never been assessed in obese patients. The flow given can reach 60 L/min with 100% F_IO_2.[67] This device is able to maintain a moderate level of PEEP when the patient breathes with their mouth closed.[67] Respiratory physiotherapy and exercises such as incentive spirometry or high volume respiration also restrict the reduction in lung volume induced by surgery.

Mechanical ventilation of obese patients in intensive care

Discrepancies in ventilator settings of mechanically ventilated obese patients have been reported between patients with healthy lungs and those with acute respiratory distress syndrome at ICU admission.[68–70] Tidal volumes in obese patients were low (5–6 mL/kg) based on actual bodyweight, but high (10–11 mL/kg) based on predicted bodyweight, along with higher levels of PEEP,[68] suggesting that ICU physicians overestimate lung size for obese patients and choose tidal volumes on the basis of actual bodyweight rather than predicted bodyweight. There is an association between high tidal volumes in patients who are mechanically ventilated for an extra-pulmonary disorder and an increased risk of developing an acute ventilator-associated lung injury.[71,72] Gong and colleagues[70] reported that BMI was associated with an increased risk of acute respiratory distress syndrome in a weight-dependent manner and increased length of ICU stay, but not mortality.

Similar to in the operating room, in the ICU, with the increased pleural pressures that obese patients experience, high PEEP levels might be necessary in both healthy and non-healthy lungs. These high PEEP values (10–15 cm H_2O) are necessary to overcome the collapse of alveoli as a result of obesity and could affect and prevent derecruitment. A strategy of protective lung ventilation, combining low tidal volume, PEEP, and recruitment manoeuvres, is recommended, with the limited tidal volume (6–8 mL/kg) being based on predicted bodyweight.

Long-term mechanical ventilation in obesity hypoventilation syndrome

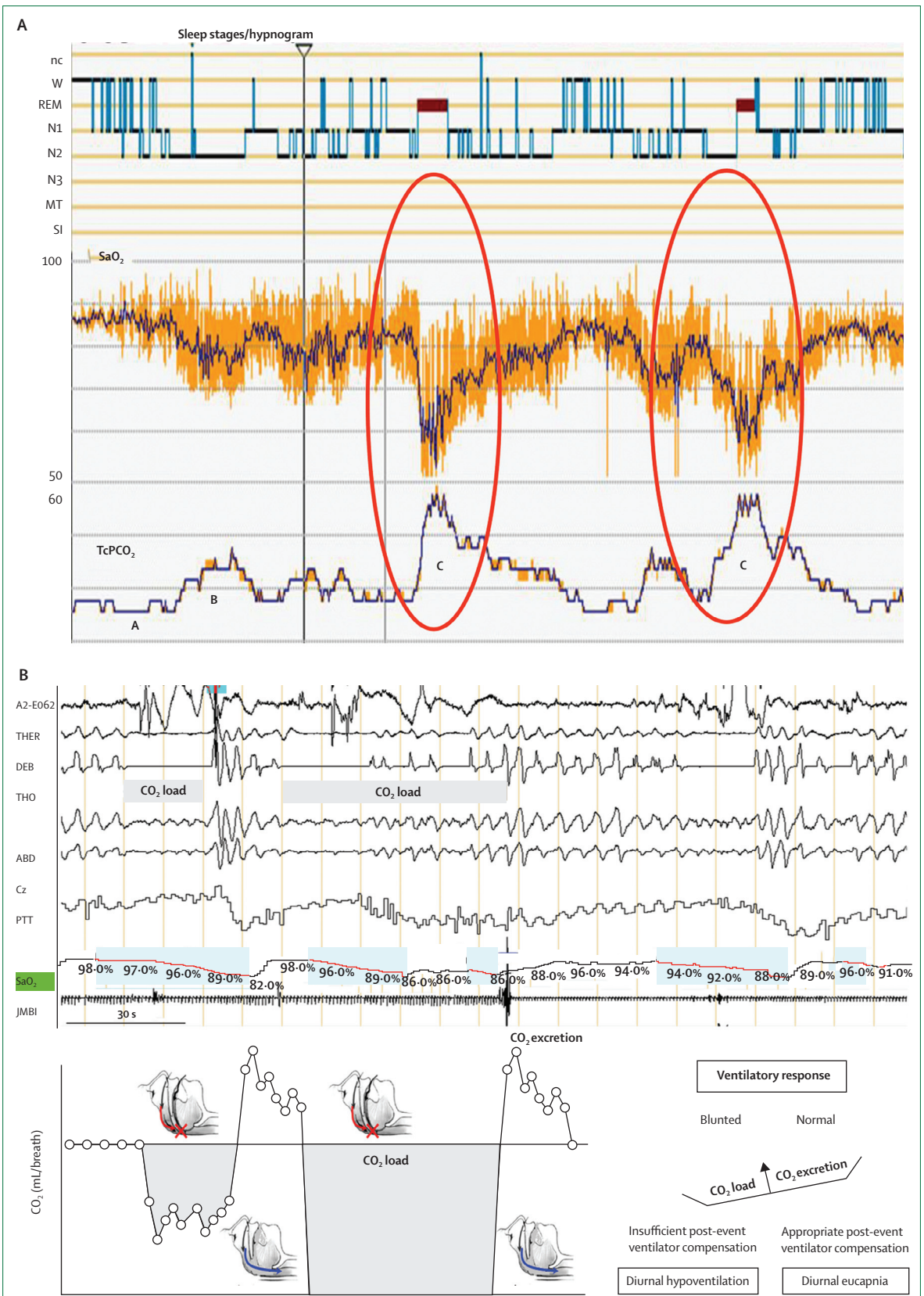
Obesity hypoventilation syndrome is a particular subgroup of obese patients showing respiratory and cardiometabolic impairments leading to a reduction in doing everyday activities and social involvement, increased health-related costs, and higher risks of admission to hospital and death.[10,73,74]

There is a clinical heterogeneity in patients with obesity hypoventilation syndrome that has therapeutic implications (figure 4).[75] One obesity hypoventilation syndrome phenotype is defined as morbid obesity with significant impairment in respiratory mechanics, severe hypercapnia and typical REM sleep hypoventilation (figure 4A). Another obesity hypoventilation syndrome phenotype corresponding to less severely obese patients without respiratory muscle impairment showing long-lasting apnoeas and hypopnoeas, but free of REM sleep hypoventilation (figure 4B) is more likely to exhibit a positive response to CPAP. These patients are typically referred to a sleep laboratory with mild daytime hypercapnia, with upper airway obstruction being the primary reason underlying the development of chronic respiratory failure. In a population of extremely obese subjects (BMI >50 kg/m²) with moderate-to-severe obstructive sleep apnoea plus REM sleep hypoventilation, more than 60% had CPAP failure with persistent sustained desaturation despite the control of upper airway patency.[76] However, the failure of CPAP to improve gas exchange during a single night (titration night) does not preclude improvements in the long term.[74] A significant percentage of acute non-responders to CPAP are efficiently treated after one month.[77] Several weeks of CPAP restores the activity of respiratory centres, reduces intrinsic PEEP and micro-atelectasis, and contributes to $PaCO_2$ normalisation. Thus an initial CPAP trial done for a minimal duration of 2 weeks is recommended in a fixed CPAP pressure mode. Auto-titrating CPAP devices have not been designed to detect hypoventilation, and the download of residual events from auto-CPAP devices might be falsely reassuring, whereas hypoventilation and oxygen desaturation continue to occur during REM sleep. An assessment of CPAP efficacy should at least include nocturnal oximetry, ideally completed by transcutaneous $PtCO_2$ and respiratory polygraphy or polysomnography.[78] In case of uncovered central hypoventilation persisting despite adequate CPAP therapy, there is a justification to shift to NIV.

A limitation of personalised positive airway pressure treatment in patients with obesity hypoventilation syndrome is that available studies have rarely clearly reported the proportions of the different phenotypes included. Future studies need to be done on well delineated subgroups to better apply the evidence to clinical practice. A randomised controlled trial (RCT) of small sample size did a direct comparison between NIV and lifestyle counselling over 1 month.[79] NIV treatment, although substantially improving sleep respiratory disturbances and blood gas measurements, did not change inflammatory, metabolic, and cardiovascular markers. In obesity hypoventilation syndrome, only two RCTs have directly compared CPAP with NIV.[80,81] Neither

Figure 4: **Clinical heterogeneity in patients with obesity hypoventilation syndrome**

(A) Evolution of nocturnal transcutaneous $PtCO_2$ in a typical patient with obesity hypoventilation syndrome. Letter A shows wakefulness reference $PtCO_2$. Letter B shows increase in $PtCO_2$ owing to long-lasting apnoeas and hypopneas (see details in figure 4B). Letter C shows increase in $PtCO_2$ corresponding to REM sleep hypoventilation (red circles). (B) Polysomnographic pattern of obesity hypoventilation syndrome phenotype with long-lasting apnoeas as the main contributor to daytime hypercapnia. The insufficient post-event ventilatory compensation leads to a progressive CO_2 overload across the night contributing to the pathogenesis of diurnal hypoventilation via alteration of ventilatory drive. ABD=abdominal movements. SaO_2=oxygen blood saturation. THER=bucconasal thermistor. THO=thoracic movements. DEB=flow. Cz=electroencephalography. PTT=pulse transit time. SAT=SpO_2. JMB1=leg movements.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CO2 load
Ventilatory response
Blunted
Normal
CO2 load
CO2 excretion
Insufficient post-event ventilator compensation
Appropriate post-event ventilator compensation
Diurnal hypoventilation
Diurnal eucapnia

***Panel:* Research agenda in obesity hypoventilation syndrome**

- Undertake large-scale randomised controlled trials (RCTs) assessing hard outcomes (cardiorespiratory morbidity, admission to hospital, and mortality).[12,82] The Pickwick project (NCT01405976) is ongoing with a 36-month follow-up and days of treatment in hospital as the primary outcome.
- Design RCTs comparing different forms of positive pressure ventilation in well-defined obesity hypoventilation syndrome phenotypes with the goal of offering tailored ventilator support to patients with obesity hypoventilation syndrome.
- Implement RCTs addressing the efficacy of combinations of treatment modalities, including weight loss, physical activity, and NIV.
- Undertake an RCT addressing the interest for patients with obesity hypoventilation syndrome initially treated with NIV of shifting to CPAP after normalisation of blood gases. A register of most ongoing trials can be seen at clinicaltrials.gov.

For more on **ongoing trials** see http://clinicaltrials.gov

study showed CPAP or NIV to be superior in terms of the $PaCO_2$ primary outcome. However, in both trials, a selection bias favoured inclusion of the obesity hypoventilation syndrome phenotype with obstructive sleep apnoea as the prominent underlying factor for hypercapnia, and who were not necessarily the best responders to NIV (ie, persistent desaturation on CPAP and REM hypoventilation). The largest RCT so far (the Pickwick project, n=221)[81,82] compared the effectiveness of lifestyle modification alone versus treatment with CPAP or NIV (target volume mode) combined with lifestyle modification. NIV significantly improved health-related quality-of-life parameters, spirometry, and 6 min-walking distance compared with CPAP. However, the scarce clinical relevance of these improvements does not counterbalance the higher cost and complexity of NIV.

There are no RCTs and very few cohort studies that are well adjusted for confounders addressing the question of efficacy of NIV on hard outcomes (ie, morbidity and mortality). Available studies are essentially retrospective and include small numbers of patients.[83,84] Nevertheless, much higher survival rates (1-year survival >90%) have been reported for patients with obesity hypoventilation syndrome treated by NIV compared with untreated patients. In obesity hypoventilation syndrome, comorbidities are of major importance because they have a significant effect on health-care use and represent the best predictors of mortality in NIV-treated patients with obesity hypoventilation syndrome (panel).[84,85]

Acute ventilatory failure complicating obesity hypoventilation syndrome

A third of patients with obesity hypoventilation syndrome are initially diagnosed via acute-on-chronic ventilatory failure.[83] This highlights the underdiagnosis and undertreatment of obesity hypoventilation syndrome.[12,86] Improved screening for hypercapnia in obese patients needs to be established, and in the primary care setting, venous serum bicarbonate is a suitable candidate. Serum concentrations of 27 mmol/L or more suggest chronic hypercapnia and obesity hypoventilation syndrome, and should lead to referral to a respiratory physician.[87]

All the mechanisms involved in acute hypercapnic respiratory failure[88] in obese patients (ie, increased work breathing, hypoventilation, and upper airway closure) can be successfully addressed by NIV. Expiratory positive airway pressure levels are arbitrarily adjusted to maintain upper airway patency and to abolish obstructive events during sleep. In this population, typical expiratory positive airway pressure pressures range from 8 cm H_2O to 12 cm H_2O,[89] with minimal pressure support at 8–10 cm H_2O to overcome hypoventilation. Obviously, oxygen alone does not resolve and can even aggravate hypoventilation or upper airway obstruction.[90,91] Most patients with obesity hypoventilation syndrome and with acute hypercapnic respiratory failure require supplemental oxygen during the acute phase; most of them becoming free of oxygen supplementation during long-term NIV.

By far the largest prospective study was done by Carrillo and colleagues,[86] assessing 716 consecutive patients with acute hypercapnic respiratory failure, including 173 with obesity hypoventilation syndrome and 543 with COPD. Compared with COPD, for which NIV represents the standard care in the event of acute hypercapnic respiratory failure, patients with obesity hypoventilation syndrome showed significantly better outcomes with less late NIV failure (7% *vs* 13%), fewer re-admissions to the ICU, and lower hospital and ICU mortality (6% *vs* 18%).[86] Another study confirmed that NIV is nearly always effective in this population, except in cases of multiple organ failure and pneumonia.[92]

Switching from one type of ventilator support to another in long-term obesity hypoventilation syndrome

Only half of patients with obesity hypoventilation syndrome referred for acute hypercapnic respiratory failure are continued on positive airway pressure therapies at home.[86] ICU and respiratory physicians should favour the implementation of routine clinical pathways facilitating the transition from ICU to home NIV. After an acute episode or for NIV initiated in chronic conditions, the interest of switching to CPAP therapy once daytime $PaCO_2$ and ventilator responses to CO_2 are normalised is still debated.[74]

NIV initiation, titration, and monitoring

Home NIV is applied with three main ventilatory modes: an "S" (spontaneous) mode in which each pressurisation

by the ventilator is triggered and cycled by the patient (used in Piper and colleagues' RCT[80]); an "S/T" (spontaneous/timed) mode in which, if the patient fails to initiate a pressurisation within a given timeframe based on a back-up respiratory rate, then the ventilator is triggered; and a "T" (timed) mode in which the NIV device delivers pressurisations at a pre-set respiratory rate, during a pre-set inspiratory time. Automatic NIV modes target a set volume by automatic adjustment of the pressure support or back-up rate. In theory, these automated modes have the capability to provide appropriate ventilation during the different phases of sleep, body position, and in particular in morbidly obese patients who exhibit profound REM sleep hypoventilation. These patients have clearly different needs in terms of pressure support during non-REM and REM sleep (figure 4A). However, too much pressure support or respiratory rate per se could reduce respiratory motor output and induce central apnoeas, especially during sleep. For this reason it is important to stress that the target tidal volume should be fixed at 6–8 mL of predicted bodyweight and not as a function of the patient's actual weight (figure 3).

Recent RCTs have mainly compared a fixed pressure S/T mode with volume targeted pressure support.[74,93] Two studies[94,95] reported greater improvements in nocturnal hypoventilation, assessed by transcutaneous $PtCO_2$, using volume-targeted ventilation than without. However, repetitive changes in pressure to adjust tidal volume were suggested as having the detrimental effect of inducing poor sleep quality.[95,96] The most convincing RCT prospectively compared volume-assured pressure support ventilation and the classical pressure support mode with a back-up rate over a 3 month period.[89] No difference was found between the two modes in terms of correction of $PaCO_2$ or health-related quality of life. Furthermore, the new intelligent hybrid modes have not been superior in terms of hard clinical outcomes.[74,93] In clinical practice, it is important to titrate classical fixed-pressure support with a strict setup procedure.[89] First, sufficient expiratory positive airway pressure should be set to prevent upper airway obstruction. This can be achieved at home by auto-CPAP titration or in the laboratory by manual titration. Second, central events can occur in the spontaneous mode,[97] but the use of the S/T mode in some patients might favour patient–ventilator synchrony. Third, after an initial pressure support set at 10–12 cm H_2O, inspiratory positive airway pressure should be increased until hypoventilation is eliminated. Fourth, a higher proportion of pressure-controlled breaths delivered by the ventilator (decrease in percentage of cycles triggered by the patient) is associated with better control of nocturnal $PtCO_2$, larger falls in daytime CO_2, and higher health-related quality of life.[74,89] This can be achieved by setting a high back-up rate.[97] Fifth, targeted volume ventilation should be restricted to selected cases with residual periods of nocturnal hypoventilation after having optimised conventional settings.

NIV per se might also induce de-novo undesirable respiratory events.[78] Ventilation-induced hyperventilation might promote periodic breathing and glottic

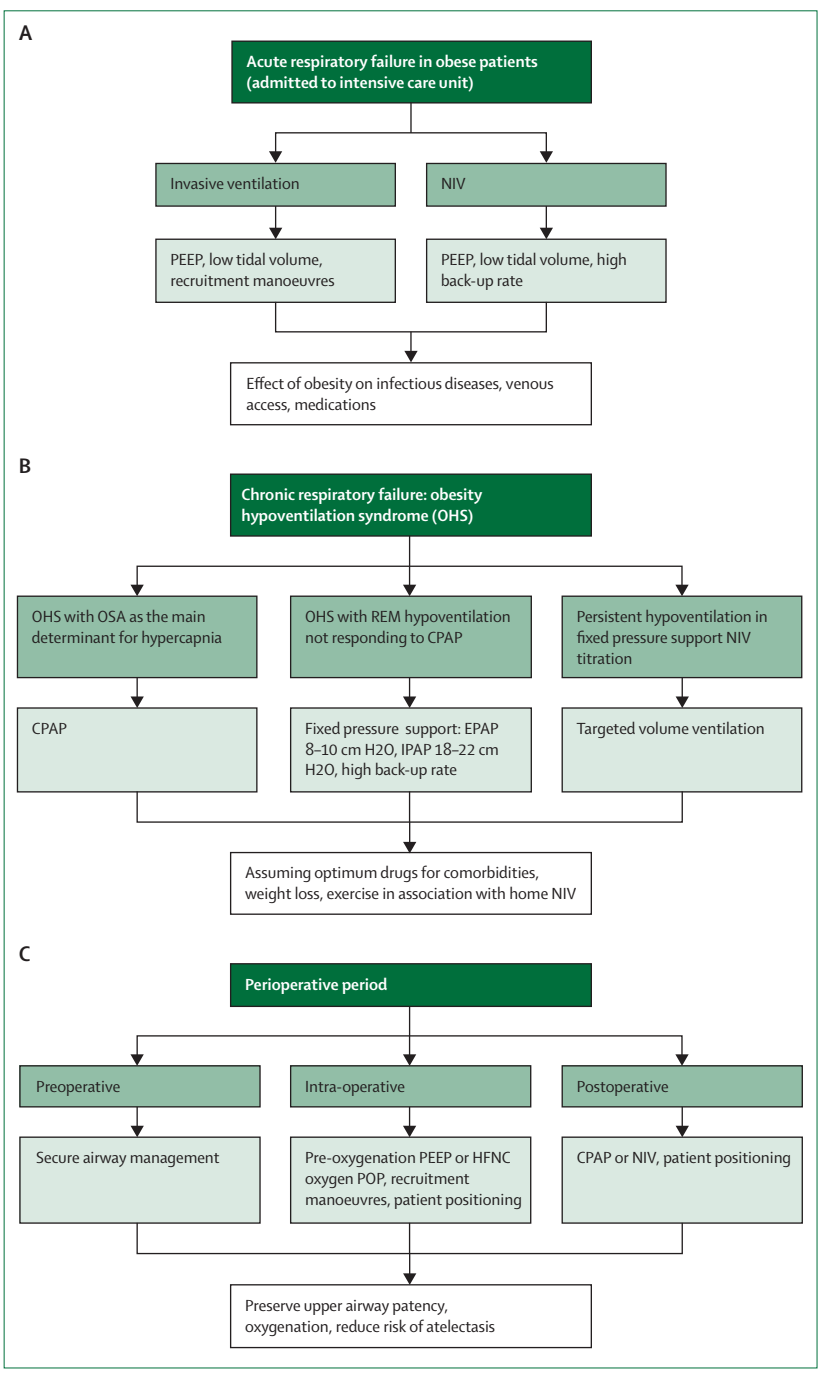

Figure 5: **Summary of mechanical ventilation in obese patients[98]**
POP=perioperative positive protective ventilation. OSA=obstructive sleep apnoea. PEEP=positive end-expiratory pressure. NIV=non-invasive ventilation. REM=rapid eye movement. HFNC=high-flow nasal cannula oxygen. CPAP=continuous positive airway pressure. EPAP=expiratory positive airway pressure. IPAP=Inspiratory positive airway pressure.

Search strategy and selection criteria

We searched PubMed for publications between Jan 1, 2010, and Sept 31, 2015, that related to respiratory failure in obese patients published in English or French. We used the search terms "obesity", "mechanical ventilation", "respiratory failure", "acute respiratory failure", "chronic hypoventilation", "obesity hypoventilation syndrome", "sleep apnoea/apnea", "intermittent hypoxia", "sleep", and "sleep disordered breathing". Selection for inclusion was based on our expertise and our perception of the studies' relevance and effect on the field. We also cite older articles to provide background information and context.

closures. NIV is also inevitably associated with unintentional leaks, which have been shown to alter not only efficacy of ventilation, but also quality of sleep. Simple instruments such as oximetry, transcutaneous $PtCO_2$, and software are available to assess NIV efficacy.[78] Whether a systematic polysomnography is necessary for titrating NIV, as suggested by the American Academy of Sleep Medicine,[98] remains a subject of debate. A realistic and efficient approach is to combine respiratory polygraphy with the concomitant measurement of transcutaneous $PtCO_2$.

Financial constraints and insufficient inpatient facilities have driven the development of ambulatory initiation and adaptation of NIV on an outpatient basis.[99] This outpatient approach must be balanced against the loss in optimisation of NIV titration, which could negatively affect long-term outcomes. A small number of studies suggest that this procedure is not inferior in terms of efficacy and is safe and cost-effective compared with classical inpatient adaptation,[100] but this warrants further investigation.[99]

Conclusions

The optimum management of mechanical ventilation in the obese patient in different key areas (figure 5) is crucial to minimise the risk of perioperative complications, decreasing lung injury in the ICU, preventing re-admissions, and reducing mortality of patients with obesity hypoventilation syndrome. An elective clinical pathway for such complex patients must be implemented between ICU physicians, respiratory physicians, and anaesthetists.

Contributors

All authors contributed to the literature search, article analysis, figures, and writing of the manuscript and approved the submitted version.

Declaration of interests

JLP reports personal fees from Vivatech, Resmed, Perimetre, Philips, Fisher and Paykel, AstraZeneca, Agiradom, Teva and grants from Resmed, Philips, GlaxoSmithKline, Fondation de la Recherche Medicale (France), Direction de la Recherche Clinique du Centre Hospitalier Universitaire de Grenoble (France), and Agir Pour les Maladies Chroniques (France), outside of the submitted work. JFT reports grants from Merck and Pfizer and personal fees from Merck and Bayer, outside of the submitted work. RT reports grants from Resmed Foundation, Philips Healthcare, and Resmed, travel grants from Agiradom and Chiesi, and lecture fees from Novartis, outside of the submitted work. JCB reports grants and personal fees from Philips Healthcare, congress invitation from RESMED, and employment with AGIR à dom Association (a non-profit home care provider), outside of the submitted work. SJ reports personal fees for consulting from Maquet, Draeger, Hamilton Medical and Fisher Paykel. PL declares no competing interests.

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