In-hospital management of obesity-related respiratory failure

Neeraj M. Shah[1,2],
Patrick B. Murphy[1,2]

[1] Lane Fox Respiratory Unit, Guy's & St Thomas' NHS Foundation Trust, London, UK
[2] Division of Asthma, Allergy and Lung Biology, King's College London, London, UK

Address for correspondence:
Patrick Murphy
Lane Fox Respiratory Unit
St Thomas' Hospital
Westminster Bridge Road
London, UK, SE1 7EH
Phone: +44 2071887727
Fax: +44 2071886116
E-mail: patrick.murphy@gstt.nhs.uk

Summary

Despite the high prevalence of obesity and its associated respiratory complications, obesity-related respiratory failure remains frequently missed during acute admissions to hospital. Even when respiratory failure is severe and requiring critical care it may be attributed to factors other than obesity. The acute management of such patients involves the identification and treatment of the underlying precipitant of decompensation, such as acute infection, with supportive management of respiratory failure. When possible, this should be delivered non-invasively to reduce the morbidity associated with invasive mechanical ventilation. However, the outcome of patients with obesity in critical care is often above that which may be expected and obesity alone should not preclude escalation to invasive ventilation. Adequate non-invasive ventilation set up is required to ensure adequate maintenance of physiological parameters. Once the acute insult has resolved thought should be given to assessment and management of any chronic respiratory failure with home mechanical ventilation. This should be operated by centres experienced with the use and provision of home mechanical ventilation.

KEY WORDS: acute respiratory failure, non-invasive ventilation, obesity-hypoventilation syndrome.

Introduction

Obesity leads to multi-system morbidity and has particular negative consequences for the respiratory system leading to sleep disordered breathing and respiratory failure (obesity related respiratory failure; ORRF). As rates of obesity rise (1) so the respiratory complications of obesity, which are already prevalent, will rise further. Patients presenting with ORRF, or being admitted for elective procedures with previously established respiratory failure, will become an increasing challenge both to acute physicians and anaesthetists (2). In this review, we aim to summarise the consequences of obesity on respiratory physiology and thus the underlying mechanisms by which non-invasive ventilation is an useful therapeutic tool in the care of these patients. We will then provide some practical guidance of the management of these patients, along with peri-operative considerations that should be made.

Pathophysiology of ORRF

ORRF is a relatively common complication of obesity. In patients undergoing bariatric procedures, the prevalence of respiratory failure was 8-14%, depending upon BMI (3). Although these patients can present with hypoxic respiratory failure (type I), they commonly suffer from ventilatory failure (type II) (4). To understand how to manage obesity-related respiratory failure, it is important to understand the pathophysiological basis of this predisposition for their respiratory system to decompensate.

An useful framework to demonstrate the physiological basis of ORRF is the respiratory muscle load-capacity-drive model (5, 6). Obese individuals tend to breathe at lower volumes (7, 8) due to an increased load on the system. This leads to gas trapping, generating intrinsic positive end-expiratory pressure (PEEPi) and increases the resistance in the airways. In addition, pulmonary compliance reduces due to mass loading in the chest (9), breathing at lower volumes (10) and reduced lung compliance due to increased pulmonary blood volume (11). All of these changes lead to an increase in the work of breathing, which necessitates an increase in

Obesity related respiratory failure is usually due to an increase in the work of breathing without a matched increase in neural drive and muscle recruitment leading to ventilatory failure and hypercapnia.

neural drive, with increased muscle recruitment (7) to match this increased need. Overall there is reduced reserve within the respiratory system to overcome extra requirements occurring during insults such as respiratory infections. Thus, obese individuals are at a higher risk of acute respiratory deterioration than non-obese individuals (12-14). It should be noted that when managing patients with ORRF, it is important to treat the underlying cause of the respiratory failure, as well as the failure itself.

Obese individuals are predisposed to sleep-disordered breathing (15-17). When supine, the upper airways are narrowed due to mechanical pressure of increased adiposity (18-20). Central adiposity projects the diaphragm cranially when lying flat, further increasing the mass load (8). This results in a further reduction in functional residual capacity in the lower airways and a resultant ventilation-perfusion mismatch. The usual physiological changes during sleep such as reduced neural respiratory drive further compromise the respiratory system, which combined with the ventilation-perfusion mismatch can lead to night-time hypercapnia. In patients being assessed for bariatric procedures, up to 75% demonstrated evidence of sleep-disordered breathing (21).

Obesity-hypoventilation syndrome (OHS) is a triad of obesity, sleep disordered breathing and ventilatory failure (daytime hypercapnia) in the absence of another cause of hypoventilation (22). The prevalence of OHS in the general population has not been formally assessed with large datasets, however it has been estimated as 0.15-0.6% in the general population (23) and 10-20% in obese individuals (24). OHS patients have increased oxygen consumption and carbon dioxide production due to increased metabolic activity in the excess adipose tissue (25-28). An increase in minute ventilation is required to match the increased ventilatory demand imposed by obesity. In OHS, there is a failure to increase neural drive to match this increased load (29-32). It is not clear why some obese individuals develop OHS, while others do not; the mechanism leading to daytime hypercapnia remains uncertain. A possible explanation involves the renal retention of bicarbonate in response to night-time hypercapnia (33). With repeated episodes of hypercapnia, further bicarbonate is retained. The effect of elevated bicarbonate in blunting hypercapnic ventilatory response will persist beyond sleep, leading to daytime hypoventilation and hypercapnia. The worsened pulmonary mechanics and reduced chemosensitivity to transient carbon dioxide rises in OHS further increase the risk of respiratory deterioration and decompensated respiratory failure (34).

Acute decompensation

Obesity related respiratory failure may complicate other acute presentations which would not normally be associated with respiratory failure in isolation (35). Clinicians across specialties therefore need to be aware of the risk of obesity related respiratory failure complicating an acute admission secondary to other causes. Common causes of acute decompensation include pneumonia, acute cardiac failure and sepsis (34, 36, 37). An acute decompensation leads to hypoxia and hypercapnia, which causes respiratory muscle fatigue, worsening the clinical picture. High-acuity care of obese patients presents several challenges that can lead to increased risk of poor outcomes (38, 39).

Despite the complications listed in Table 1, several studies have demonstrated that obese patients appear to have a paradoxically lower mortality in intensive care than non-obese individuals when co-morbidity and disease severity are accounted for (40, 48). Examining these data in further detail demonstrates that the survival benefit is conferred only in patients requiring invasive mechanical ventilation (49, 50). Furthermore, as expected the presence of multi-organ failure results in worse clinical outcomes (48).

The reasons for this obesity paradox are not clear. It is postulated that lung-protective ventilation can be more successfully delivered to obese patients, as the driving pressure is moderated by increased muscle load, which results in a reduced transpulmonary pressure. One study demonstrated that their morbidly obese mechanically ventilated cohort were generally younger, with lower comorbidity scores and fewer organ failures (48). On the other hand, the increased physical requirement of care, and high anticipation of complications may result in obese patients being triaged to receive higher level care than their equivalent non-obese counterparts.

Table 1 - Obesity related complications.

Obesity related complications	Reference
Increased risk of acute respiratory distress syndrome (ARDS)	(40, 41)
Higher rates of health care associated infections	(42, 43)
Increased risk of veno-thromboembolism	(44)
More likely to suffer from drug errors e.g. under dosing	(45, 46)
Delayed enteral feeding	(47)

Non-invasive ventilation

Obese individuals can suffer from either hypoxic or hypercapnic respiratory failure, however are more likely to deteriorate due to hypercapnic failure. As a cause of hypercapnia is an increase in the work of breathing, and obese patients have a reduced ability of the respiratory system to match this increased requirement, treatment should involve reducing the work of breathing. Foremost, the underlying cause of the deterioration must be elucidated and treated aggressively. In patients with respiratory failure to support the individual whilst the underlying cause for decompensation is treated, ventilation therapy can be used.

NIV in acute decompensated hypercapnic respiratory failure due to obesity-hypoventilation syndrome is equally effective and a slightly better longer-term outcome than in exacerbated COPD.

The cornerstone treatment for patients with hypercapnic failure not requiring invasive mechanical ventilation is bi-level non-invasive ventilation (NIV). NIV has been demonstrated to be an effective management strategy in patients with acute hypercapnic failure, with improved outcomes including length of stay, requirement for mechanical ventilation and mortality (51-54). Whilst the evidence for NIV in acute decompensated hypercapnic respiratory failure is primarily in patients with chronic obstructive pulmonary disease, in OHS, it is equally effective and may have slightly better longer-term outcomes than COPD (36, 37). In fact, OHS has become the second-most common indication for acute NIV after COPD (55-57) demonstrating the increased importance of knowledge and understanding of the respiratory physiology of this patient group.

Selection of patients who are suitable for treatment with NIV is important. Patients who are severely unwell or have multi-organ failure should be supported with endotracheal intubation and mechanical ventilation, given the poor clinical outcomes associated with obesity and multi-organ failure (37, 48). Careful consideration needs to be given to patients who are unlikely to tolerate NIV. Predicting outcome with NIV is notoriously difficult (58). Markers that may suggest NIV failure are displayed in Table 2. However studies tend to investigate NIV use in patients with COPD. No studies have been performed to investigate prognostic markers with NIV exclusively in OHS patients. In patients already established on domiciliary therapy for ORRF, the best predictor for NIV failure is previous poor tolerance to positive airway pressure therapy (38).

There is no strong evidence to argue for the use of a particular type of NIV interface. Patients in ORRF tend to be mouth-breathers and so there may be a theoretical advantage in using an oro-nasal mask to reduce mouth air leak (34, 65-67). This is consistent with a survey that demonstrated that oro-nasal masks were the first choice interface to use in acute ventilatory failure (68).

In obese patients, one of the functions of NIV is to overcome the upper airway obstruction caused by adipose tissue in the neck and reduced pharyngeal dilator muscle tone; it acts to reduce airways resistance and therefore work of breathing. Thus, high expiratory (EPAP) and inspiratory positive airway pressures (IPAP) are usually required to effectively ventilate patients with OHS (69, 70). EPAP should be started at 5 cmH_2O and be increased to alleviate snoring, repetitive desaturations and apnoeas occurring during sleep. An EPAP as high as 15 cmH_2O may be required during sleep but can be lowered during wakefulness to promote comfort. IPAP should be initially delivered at 16 cmH_2O, and increased to visibly augment chest expansion and reduce excess work of breathing with the aim to keep oxygen saturations between 88 and 92%. Typically IPAP needs to be at least 10 cmH_2O above EPAP, and can be as high as 30 cmH_2O. If saturations are not maintained between 88-92% despite adequate ventilation with appropriate ventilatory pressures, well-controlled supplemental oxygen can be entrained cautiously (71, 72). If tidal volumes are not adequate, due to the high EPAP, volume-controlled or volume-assured modes of ventilation can be considered but should be used with specialist advice (73, 74). The patient's blood gases should be reviewed an hour after set-up onto NIV, to ensure physiological improvement and optimise the settings as required. To reduce the anxiety associated with arterial blood sampling (75), venous samples (76) or transcutaneous carbon dioxide monitoring (77, 78) can be used to assess response of respiratory failure to therapy in these patients.

An EPAP as high as 15 cmH_2O may be required during sleep but can be lowered during wakefulness to promote comfort.

Table 2 - Predictors of poor outcome with NIV.

Predictors of poor outcome with NIV	Reference
Low initial pH	(59-63)
High initial $PaCO_2$	(61)
Consolidation on chest radiograph	(37, 59, 64)
Higher ICU severity score	(37, 64)
Low baseline activity of daily living score	(61, 64)

Fluid retention secondary to right heart failure is common in OHS (79). This may impact on the success of NIV therapy and so forced diuresis should be considered in patients with evidence of fluid overload. Good oral hygiene, hydration and nutrition are important components of care whilst the patient is on NIV. While these low level interventions may improve comfort during the acute episode, more importantly this improved comfort may prevent the patient from refusing NIV in the future. Ensuring adequate patient comfort during acute NIV is important as refusal of therapy following late NIV failure in an acute episode confers a high mortality (37).

Once clinical recovery is demonstrated, NIV therapy can be weaned from 24h/day to night-time only ventilation. Initially this should be supported by continuous cardiorespiratory monitoring; this can be stepped down if clinical stability is maintained. If this was a first presentation of possible ORRF, the diagnosis needs to be confirmed using overnight respiratory polygraphy, lung function testing and imaging as per standard practice. Other causes of hypercapnic respiratory failure, such as COPD and neuromuscular disease, must be excluded at this stage. Although the outcome for patients requiring NIV for ORRF is better than in patients with COPD (36), the outcomes are similar if the ORRF patients are not established on domiciliary NIV treatment upon discharge (36). Thus, home mechanical ventilation (HMV) should be considered in these patients either during admission, or soon after discharge. HMV has been demonstrated to improve daytime hypercapnia (79-82) and apnoea-hypopnoea index (80) compared with lifestyle changes alone. Whether HMV alters long-term cardiovascular risk is uncertain but it does not appear to improve the inflammatory cytokine profile associated with such risk (83). Patients receiving HMV for OHS tend to have longer survival compared with those with COPD (84). Interestingly, patients treated with HMV for COPD who were obese had longer survival than those who were non-obese (85). HMV is also associated with a fall in pulmonary artery systolic pressure after six months of therapy (86).

Peri-operative management of ORRF

Patients with established ORRF on treatment with HMV will increasingly be encountered as a part of admissions for elective procedures. Careful preoperative assessment and planning is crucial to reduce the risk of peri-operative complications.

All of the physiological consequences of obesity are exacerbated peri-operatively, as the patient is kept supine (87). The increased abdominal pressure caused by central adiposity reduces diaphragm movement and limits lung expansion. Obesity is a common cause of difficult mask ventilation and endotracheal intubation (88-90). As well as the physical challenge of a narrowed upper airway, the reduced lung volumes that obese individuals breathe at (8, 91) and the consequent V/Q mismatch increase the risk of hypoxic events during the induction and postoperative periods. Pre-oxygenation is a useful tool to reduce the risk of hypoxic events (92); pre-oxygenation combined with low pressure continuous positive airway pressure (5 cmH_2O) resulted in fewer desaturations and apnoeas (93-95). Pre-oxygenation in the sitting position improved the tolerance to apnoea considerably (96). Pre-oxygenation is also an effective protective strategy in the emergency intubation of obese individuals (97).

To reduce the risk of peri-operative complications, pre-oxygenation combined with low pressure continuous positive airway pressure (5 cmH_2O) can result in fewer desaturations and apnoeas.

Postoperatively, opioid analgesia can exacerbate reduced neural drive in obese individuals compromising ventilation. An opioid-sparing analgesia strategy is an important consideration to be made during preoperative assessment (98). Hypoventilation in obesity will exacerbate typical postoperative basal atelectasis; preoperative and postoperative NIV is an useful adjunctive treatment to aid ventilation to overcome this atelectasis. A recent meta-analysis has demonstrated safe and effective use of NIV before and after general anaesthesia (99, 100).

A high index of suspicion for undiagnosed sleep-disordered breathing should be maintained when preoperatively assessing obese patients, and investigations organised before surgery as indicated. There is a high frequency of undiagnosed OSA in surgical patients (101-104) and OHS is frequently underdiagnosed (105). This is particularly important because these conditions are commonly diagnosed in the perioperative period with a presentation of acute respiratory failure (24, 34).

Whilst not within the scope of this review, long-term management of ORRF is crucial to reduce the risk of further deteriorations. Management of obesity with referral to bariatric services, is an important step in these patients' care (12). Whilst long-term CPAP therapy in eucapnic OSA is associated with weight gain, the use of HMV in OHS is associated with weight loss that should be used as part of a multifaceted approach to care of these patients (106).

Conclusion

Obese patients may present to acute hospital services via a number of pathways and suspicion for respiratory complications of obesity should be high with appropriate investigation and onward referral. A high index of suspicion should be maintained in at risk patients and although screening tools are available an arterial blood gas is ultimately required if the diagnosis is considered. Patients with obesity related respiratory failure will usually have a precipitating cause for decompensation and this should be investigated and managed alongside aggressive diuresis for any element of *cor pulmonale*. Non-invasive ventilation should be the mainstay of respiratory support, provided acutely to

maintain adequate gas exchange and long-term to improve sleep quality and daytime functioning.

References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.
2. Dennis DM, Bharat C, Paterson T. Prevalence of obesity and the effect on length of mechanical ventilation and length of stay in intensive care patients: A single site observational study. Aust Crit Care. 2016.
3. Blouw EL, Rudolph AD, Narr BJ, Sarr MG. The frequency of respiratory failure in patients with morbid obesity undergoing gastric bypass. AANA J. 2003;71 (1):45-50.
4. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004;116(1):1-7.
5. Jolley CJ, Moxham J. A physiological model of patient-reported breathlessness during daily activities in COPD. European Respiratory Review. 2009;18 (112):66-79.
6. Shah NM, Murphy PB. Hypercapnic respiratory failure in non-COPD. In: Heunks L, Demoule A, Windisch W. Pulmonary Emergencies. ERS Monograph. 2016; 74: 86-100.
7. Steier J, Jolley CJ, Seymour J, Roughton M, Polkey MI, Moxham J. Neural respiratory drive in obesity. Thorax. 2009;64(8):719-25.
8. Steier J, Lunt A, Hart N, Polkey MI, Moxham J. Observational study of the effect of obesity on lung volumes. Thorax. 2014;69(8):752-9.
9. O'Donnell DE, O'Donnell CD, Webb KA, Guenette JA. Respiratory Consequences of Mild-to-Moderate Obesity: Impact on Exercise Performance in Health and in Chronic Obstructive Pulmonary Disease. Pulm Med. 2012;2012:818925.
10. Behazin N, Jones SB, Cohen RI, Loring SH. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. J Appl Physiol. 1985. 2010;108(1):212-8.
11. Oppenheimer BW, Berger KI, Ali S, Segal LN, Donnino R, Katz S, et al. Pulmonary Vascular Congestion: A Mechanism for Distal Lung Unit Dysfunction in Obesity. PLoS One. 2016;11(4):e0152769.
12. Poulain M, Doucet M, Major GC, Drapeau V, Series F, Boulet LP, et al. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. CMAJ. 2006;174(9):1293-9.
13. McCallister JW, Adkins EJ, O'Brien JM, Jr. Obesity and acute lung injury. Clin Chest Med. 2009;30(3): 495-508, viii.
14. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. Int J Gen Med. 2010;3:335-43.
15. Crummy F, Naughton MT, Elborn JS. Obesity and the respiratory physician. Thorax. 2008;63(7):576-7.
16. Crummy F, Piper AJ, Naughton MT. Obesity and the lung: 2. Obesity and sleep-disordered breathing. Thorax. 2008;63(8):738-46.
17. Leinum CJ, Dopp JM, Morgan BJ. Sleep-disordered breathing and obesity: pathophysiology, complications, and treatment. Nutr Clin Pract. 2009;24(6):675-87.
18. Yildirim N, Fitzpatrick MF, Whyte KF, Jalleh R, Wightman AJ, Douglas NJ. The effect of posture on upper airway dimensions in normal subjects and in patients with the sleep apnea/hypopnea syndrome. Am Rev Respir Dis. 1991;144(4):845-7.
19. Ingman T, Nieminen T, Hurmerinta K. Cephalometric comparison of pharyngeal changes in subjects with upper airway resistance syndrome or obstructive sleep apnoea in upright and supine positions. Eur J Orthod. 2004;26(3):321-6.
20. Owens RL, Eckert DJ, Yeh SY, Malhotra A. Upper airway function in the pathogenesis of obstructive sleep apnea: a review of the current literature. Curr Opin Pulm Med. 2008;14(6):519-24.
21. Reed K, Pengo MF, Steier J. Screening for sleep-disordered breathing in a bariatric population. J Thorac Dis. 2016;8(2):268-75.
22. Hart N, Mandal S, Manuel A, Mokhlesi B, Pepin JL, Piper A, et al. Obesity hypoventilation syndrome: does the current definition need revisiting? Thorax. 2014;69(1):83-4.
23. Balachandran JS, Masa JF, Mokhlesi B. Obesity Hypoventilation Syndrome Epidemiology and Diagnosis. Sleep Med Clin. 2014;9(3):341-7.
24. Chau EH, Lam D, Wong J, Mokhlesi B, Chung F. Obesity hypoventilation syndrome: a review of epidemiology, pathophysiology, and perioperative considerations. Anesthesiology. 2012;117(1):188-205.
25. Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing [VO(2RESP)] at rest. Am J Respir Crit Care Med. 1999;160(3):883-6.
26. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth. 2000;85(1):91-108.
27. deJong AT, Gallagher MJ, Sandberg KR, Lillystone MA, Spring T, Franklin BA, et al. Peak oxygen consumption and the minute ventilation/carbon dioxide production relation slope in morbidly obese men and women: influence of subject effort and body mass index. Prev Cardiol. 2008;11(2):100-5.
28. Pierce AM, Brown LK. Obesity hypoventilation syndrome: current theories of pathogenesis. Curr Opin Pulm Med. 2015;21(6):557-62.
29. Sampson MG, Grassino AE. Load compensation in obese patients during quiet tidal breathing. J Appl Physiol Respir Environ Exerc Physiol. 1983;55(4): 1269-76.
30. Sampson MG, Grassino K. Neuromechanical properties in obese patients during carbon dioxide rebreathing. Am J Med. 1983;75(1):81-90.
31. Leech J, Onal E, Aronson R, Lopata M. Voluntary hyperventilation in obesity hypoventilation. Chest. 1991;100(5):1334-8.

32. Macavei VM, Spurling KJ, Loft J, Makker HK. Diagnostic predictors of obesity-hypoventilation syndrome in patients suspected of having sleep disordered breathing. J Clin Sleep Med. 2013;9(9):879-84.
33. Piper AJ, Grunstein RR. Current perspectives on the obesity hypoventilation syndrome. Curr Opin Pulm Med. 2007;13(6):490-6.
34. BaHammam A. Acute ventilatory failure complicating obesity hypoventilation: update on a 'critical care syndrome'. Curr Opin Pulm Med. 2010;16(6):543-51.
35. Nelson JA, Loredo JS, Acosta JA. The obesity-hypoventilation syndrome and respiratory failure in the acute trauma patient. J Emerg Med. 2011;40(4):e67-9.
36. Carrillo A, Ferrer M, Gonzalez-Diaz G, Lopez-Martinez A, Llamas N, Alcazar M, et al. Noninvasive ventilation in acute hypercapnic respiratory failure caused by obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(12):1279-85.
37. Lemyze M, Taufour P, Duhamel A, Temime J, Nigeon O, Vangrunderbeeck N, et al. Determinants of noninvasive ventilation success or failure in morbidly obese patients in acute respiratory failure. PLoS One. 2014;9(5):e97563.
38. Duarte AG, Justino E, Bigler T, Grady J. Outcomes of morbidly obese patients requiring mechanical ventilation for acute respiratory failure. Crit Care Med. 2007;35(3):732-7.
39. Marik PE, Desai H. Characteristics of patients with the "malignant obesity hypoventilation syndrome" admitted to an ICU. J Intensive Care Med. 2013;28 (2):124-30.
40. Anzueto A, Frutos-Vivar F, Esteban A, Bensalami N, Marks D, Raymondos K, et al. Influence of body mass index on outcome of the mechanically ventilated patients. Thorax. 2011;66(1):66-73.
41. Zhi G, Xin W, Ying W, Guohong X, Shuying L. "Obesity Paradox" in Acute Respiratory Distress Syndrome: Asystematic Review and Meta-Analysis. PLoS One. 2016;11(9):e0163677.
42. Dossett LA, Dageforde LA, Swenson BR, Metzger R, Bonatti H, Sawyer RG, et al. Obesity and site-specific nosocomial infection risk in the intensive care unit. Surg Infect (Larchmt). 2009;10(2):137-42.
43. Timsit JF, Bouadma L, Mimoz O, Parienti JJ, Garrouste-Orgeas M, Alfandari S, et al. Jugular versus femoral short-term catheterization and risk of infection in intensive care unit patients. Causal analysis of two randomized trials. Am J Respir Crit Care Med. 2013;188(10):1232-9.
44. Minet C, Lugosi M, Savoye PY, Menez C, Ruckly S, Bonadona A, et al. Pulmonary embolism in mechanically ventilated patients requiring computed tomography: Prevalence, risk factors, and outcome. Crit Care Med. 2012;40(12):3202-8.
45. Arabi YM, Dara SI, Tamim HM, Rishu AH, Bouchama A, Khedr MK, et al. Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. Crit Care. 2013;17(2):R72.
46. Charani E, Gharbi M, Frost G, Drumright L, Holmes A. Antimicrobial therapy in obesity: a multicentre cross-sectional study. J Antimicrob Chemother. 2015;70(10):2906-12.
47. Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. Intensive Care Med. 2004;30(1):18-32.
48. Kumar G, Majumdar T, Jacobs ER, Danesh V, Dagar G, Deshmukh A, et al. Outcomes of morbidly obese patients receiving invasive mechanical ventilation: a nationwide analysis. Chest. 2013;144(1):48-54.
49. Sasabuchi Y, Yasunaga H, Matsui H, Lefor AT, Horiguchi H, Fushimi K, et al. The Dose-Response Relationship Between Body Mass Index and Mortality in Subjects Admitted to the ICU With and Without Mechanical Ventilation. Respir Care. 2015;60(7):983-91.
50. Tafelski S, Yi H, Ismaeel F, Krannich A, Spies C, Nachtigall I. Obesity in critically ill patients is associated with increased need of mechanical ventilation but not with mortality. J Infect Public Health. 2016; 9(5):577-85.
51. Peter JV, Moran JL, Phillips-Hughes J, Warn D. Noninvasive ventilation in acute respiratory failure-a meta-analysis update. Crit Care Med. 2002;30(3):555-62.
52. Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. Am J Respir Crit Care Med. 2012;185 (2):152-9.
53. Dwarakanath A, Elliott MW. Noninvasive ventilation in the management of acute hypercapnic respiratory failure. Breathe. 2013;9(5):338-48.
54. Masa JF, Utrabo I, Gomez de Terreros J, Aburto M, Esteban C, Prats E, et al. Noninvasive ventilation for severely acidotic patients in respiratory intermediate care units : Precision medicine in intermediate care units. BMC Pulm Med. 2016;16(1):97.
55. Confalonieri M, Gorini M, Ambrosino N, Mollica C, Corrado A, Scientific Group on Respiratory Intensive Care of the Italian Association of Hospital P. Respiratory intensive care units in Italy: a national census and prospective cohort study. Thorax. 2001;56(5): 373-8.
56. Chiner E, Llombart M, Martinez-Garcia MA, Fernandez-Fabrellas E, Navarro R, Cervera A, et al. Noninvasive mechanical ventilation in Valencia, Spain: from theory to practice]. Arch Bronconeumol. 2009; 45(3):118-22.
57. Ciledag A, Kaya A, Akdogan BB, Kabalak PA, Onen ZP, Sen E, et al. Early use of noninvasive mechanical ventilation in patients with acute hypercapnic respiratory failure in a respiratory ward: a prospective study. Arch Bronconeumol. 2010;46(10):538-42.
58. Lightowler JV, Elliott MW. Predicting the outcome from NIV for acute exacerbations of COPD. Thorax. 2000;55(10):815-6.
59. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, Vitacca M. Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax. 1995;50(7):755-7.

60. Brochard L, Mancebo J, Wysocki M, Lofaso F, Conti G, Rauss A, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med. 1995;333(13):817-22.
61. Bhattacharyya D, Prasad B, Tampi PSR, Ramprasad R. Early predictors of success of non-invasive positive pressure ventilation in hypercapnic respiratory failure. Med J Armed Forces India. 2011;67(4):315-9.
62. Bott J, Carroll MP, Conway JH, Keilty SE, Ward EM, Brown AM, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet. 1993;341(8860): 1555-7.
63. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto Meduri G. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1585-91.
64. Pacilli AM, Valentini I, Carbonara P, Marchetti A, Nava S. Determinants of noninvasive ventilation outcomes during an episode of acute hypercapnic respiratory failure in chronic obstructive pulmonary disease: the effects of comorbidities and causes of respiratory failure. Biomed Res Int. 2014;2014:976783.
65. Navalesi P, Fanfulla F, Frigerio P, Gregoretti C, Nava S. Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with chronic hypercapnic respiratory failure. Crit Care Med. 2000;28(6):1785-90.
66. Kwok H, McCormack J, Cece R, Houtchens J, Hill NS. Controlled trial of oronasal versus nasal mask ventilation in the treatment of acute respiratory failure. Crit Care Med. 2003;31(2):468-73.
67. Girault C, Briel A, Benichou J, Hellot MF, Dachraoui F, Tamion F, et al. Interface strategy during noninvasive positive pressure ventilation for hypercapnic acute respiratory failure. Crit Care Med. 2009;37(1): 124-31.
68. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36(2):362-9.
69. Gursel G, Aydogdu M, Gulbas G, Ozkaya S, Tasyurek S, Yildirim F. The influence of severe obesity on noninvasive ventilation (NIV) strategies and responses in patients with acute hypercapnic respiratory failure attacks in the ICU. Minerva Anestesiol. 2011;77(1):17-25.
70. Fischer AJ, Kaese S, Lebiedz P. Management of obese patients with respiratory failure - A practical approach to a health care issue of increasing significance. Respir Med. 2016;117:174-8.
71. Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. Proc Am Thorac Soc. 2008;5(2): 218-25.
72. Davidson C, Banham S, Elliott M, Kennedy D, Gelder C, Glossop A, et al. British Thoracic Society/Intensive Care Society Guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. BMJ Open Respir Res. 2016;3(1):e000133.
73. Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012;67 (8):727-34.
74. Briones Claudett KH, Briones Claudett M, Chung Sang Wong M, Nuques Martinez A, Soto Espinoza R, Montalvo M, et al. Noninvasive mechanical ventilation with average volume assured pressure support (AVAPS) in patients with chronic obstructive pulmonary disease and hypercapnic encephalopathy. BMC Pulm Med. 2013;13:12.
75. Patout M, Lamia B, Lhuillier E, Molano LC, Viacroze C, Benhamou D, et al. A Randomized Controlled Trial on the Effect of Needle Gauge on the Pain and Anxiety Experienced during Radial Arterial Puncture. PLoS One. 2015;10(9):e0139432.
76. McKeever TM, Hearson G, Housley G, Reynolds C, Kinnear W, Harrison TW, et al. Using venous blood gas analysis in the assessment of COPD exacerbations: a prospective cohort study. Thorax. 2016;71(3): 210-5.
77. Delerme S, Montout V, Goulet H, Arhan A, Le Sache F, Devilliers C, et al. Concordance between transcutaneous and arterial measurements of carbon dioxide in an ED. Am J Emerg Med. 2012;30(9):1872-6.
78. Bobbia X, Claret PG, Palmier L, Robert M, Grandpierre RG, Roger C, et al. Concordance and limits between transcutaneous and arterial carbon dioxide pressure in emergency department patients with acute respiratory failure: a single-center prospective observational study. Scand J Trauma Resusc Emerg Med. 2015;23:40.
79. Masa JF, Corral J, Caballero C, Barrot E, Teran-Santos J, Alonso-Alvarez ML, et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016;71 (10):899-906.
80. Borel JC, Tamisier R, Gonzalez-Bermejo J, Baguet JP, Monneret D, Arnol N, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. Chest. 2012;141(3):692-702.
81. Piesiak P, Brzecka A, Kosacka M, Jankowska R. Efficacy of noninvasive mechanical ventilation in obese patients with chronic respiratory failure. Adv Exp Med Biol. 2013;788:167-73.
82. Masa JF, Corral J, Alonso ML, Ordax E, Troncoso MF, Gonzalez M, et al. Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. Am J Respir Crit Care Med. 2015; 192(1):86-95.
83. Borel JC, Burel B, Tamisier R, Dias-Domingos S, Baguet JP, Levy P, et al. Comorbidities and mortality in hypercapnic obese under domiciliary noninvasive ventilation. PLoS One. 2013;8(1):e52006.
84. Berrube L, Declerq P, Lamia B, Muir J-F, Cuvelier A. P2461. Long-term adherence to domiciliary NIV and its relation to survival in patients with chronic respiratory failure. European Respiratory Journal. 2013; 42(Suppl57):P2461.
85. Borel JC, Pepin JL, Pison C, Vesin A, Gonzalez-Bermejo J, Court-Fortune I, et al. Long-term adher-

ence with non-invasive ventilation improves prognosis in obese COPD patients. Respirology. 2014;19(6): 857-65.
86. Castro-Anon O, Golpe R, Perez-de-Llano LA, Lopez Gonzalez MJ, Escalona Velasquez EJ, Perez Fernandez R, et al. Haemodynamic effects of non-invasive ventilation in patients with obesity-hypoventilation syndrome. Respirology. 2012;17(8):1269-74.
87. Pedoto A. Lung physiology and obesity: anesthetic implications for thoracic procedures. Anesthesiol Res Pract. 2012;2012:154208.
88. Pelosi P, Gregoretti C. Perioperative management of obese patients. Best Pract Res Clin Anaesthesiol. 2010;24(2):211-25.
89. Kheterpal S, Healy D, Aziz MF, Shanks AM, Freundlich RE, Linton F, et al. Incidence, Predictors, and Outcome of Difficult Mask Ventilation Combined with Difficult Laryngoscopy. Anesthesiology. 2013;119 (6):1360-9.
90. Riad W, Vaez MN, Raveendran R, Tam AD, Quereshy FA, Chung F, et al. Neck circumference as a predictor of difficult intubation and difficult mask ventilation in morbidly obese patients: A prospective observational study. Eur J Anaesthesiol. 2016;33(4):244-9.
91. Bahammam AS, Al-Jawder SE. Managing acute respiratory decompensation in the morbidly obese. Respirology. 2012;17(5):759-71.
92. Shah U, Wong J, Wong DT, Chung F. Preoxygenation and intraoperative ventilation strategies in obese patients: a comprehensive review. Curr Opin Anaesthesiol. 2016;29(1):109-18.
93. Georgescu M, Tanoubi I, Fortier LP, Donati F, Drolet P. Efficacy of preoxygenation with non-invasive low positive pressure ventilation in obese patients: crossover physiological study. Ann Fr Anesth Reanim. 2012;31(9):e161-5.
94. Harbut P, Gozdzik W, Stjernfalt E, Marsk R, Hesselvik JF. Continuous positive airway pressure/pressure support pre-oxygenation of morbidly obese patients. Acta Anaesthesiol Scand. 2014;58(6):675-80.
95. Hu XY. Effective Ventilation Strategies for Obese Patients Undergoing Bariatric Surgery: A Literature Review. AANA J. 2016;84(1):35-45.
96. Altermatt FR, Munoz HR, Delfino AE, Cortinez LI. Pre-oxygenation in the obese patient: effects of position on tolerance to apnoea. Br J Anaesth. 2005;95 (5):706-9.
97. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. Ann Emerg Med. 2012;59(3):165-75 e1.
98. Fernandez-Bustamante A, Hashimoto S, Serpa Neto A, Moine P, Vidal Melo MF, Repine JE. Perioperative lung protective ventilation in obese patients. BMC Anesthesiol. 2015;15:56.
99. El-Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. Eur Respir J. 2006;28(3):588-95.
100. Carron M, Zarantonello F, Tellaroli P, Ori C. Perioperative noninvasive ventilation in obese patients: a qualitative review and meta-analysis. Surg Obes Relat Dis. 2016;12(3):681-91.
101. Kaw R, Michota F, Jaffer A, Ghamande S, Auckley D, Golish J. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest. 2006;129(1):198-205.
102. Memtsoudis SG, Stundner O, Rasul R, Sun X, Chiu YL, Fleischut P, et al. Sleep apnea and total joint arthroplasty under various types of anesthesia: a population-based study of perioperative outcomes. Reg Anesth Pain Med. 2013;38(4):274-81.
103. Kaw R, Golish J. Obstructive sleep apnea: what to do in the surgical patient? IMPACT consults. Proceedings of the 2nd Annual Cleveland Clinic Perioperative Medicine Summit. Cleve Clin J Med. 2006;73 Electronic Suppl 1:S15-7.
104. Singh M, Liao P, Kobah S, Wijeysundera DN, Shapiro C, Chung F. Proportion of surgical patients with undiagnosed obstructive sleep apnoea. Br J Anaesth. 2013;110(4):629-36.
105. Pepin JL, Borel JC, Janssens JP. Obesity hypoventilation syndrome: an underdiagnosed and undertreated condition. Am J Respir Crit Care Med. 2012; 186(12):1205-7.
106. Murphy PB, Polkey MI, Hart N. Obesity hypoventilation syndrome: the need for a multifaceted approach to treatment. Chest. 2012;142(2):540-1; author reply 1-2.