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Obesity and Acute Lung Injury

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Synopsis

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common indications for intensive care unit (ICU) admission and mechanical ventilation. ALI/ARDS also consumes significant health care resources and is a common cause of death in ICU patients. Obesity produces changes in respiratory system physiology that could affect outcomes for ALI/ARDS patients and their response to treatment. Additionally, the biochemical alterations seen in obese patients, such as increased inflammation and altered metabolism, could affect the risk of developing ALI/ARDS in patients with another risk factor (e.g. sepsis). The few studies which have examined the influence of obesity on the outcomes from ALI/ARDS are inconclusive. Furthermore, observed results could be biased by disparities in provided care.

Acute lung injury (ALI) is a clinical syndrome defined by the acute onset of hypoxemic respiratory failure and bilateral pulmonary infiltrates not primarily due to left atrial hypertension (1;2). When hypoxemia is more severe, the condition is termed acute respiratory distress syndrome (ARDS). ALI/ARDS is a common cause of respiratory failure with a crude incidence of 78.9 per 100,000 person-years and an age-adjusted incidence of 86.2 per 100,000 person-years (3). In-hospital mortality remains unacceptably high between 38% and 60% (2; 3). It is estimated that there are almost 191,000 cases of ALI annually, accounting for 3.6 million hospital days and almost 75,000 deaths (3).

Because of physiologic and biochemical changes associated with obesity, it is possible that excess weight affects the incidence and/or outcome of ALI. Alterations in thoraco-abdominal compliance and gas exchange might predispose obese patients to respiratory failure and ALI and could affect the response to therapeutic measures. The inflammation of obesity might also incline obese patients to lung injury when they suffer a secondary insult (e.g. sepsis). However, provider bias and disparities in provided care could be as influential in the outcome of obese patients with ALI and require consideration in the assessment of any such association (4;5).

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Pulmonary Physiology in Obesity and Implications for ALI Patients (also see Table 1 and article in this issue by Sood)

The most significant change in pulmonary mechanics seen in obesity is a decrease in pulmonary compliance (6) which has been attributed to one of several factors: fatty infiltration of the chest wall, increased pulmonary blood volume, and extrinsic compression of the thoracic cage by weight from excess soft tissue (6–9). As a result, obese subjects exhibit an increased work of breathing (6;10) and may note a subjective increase in dyspnea (11). In addition, respiratory resistance has been shown to be increased in obese subjects (9;12).

Pelosi and colleagues (12) compared the respiratory mechanics of sedated, paralyzed, morbidly obese (Body Mass Index [BMI] $\geq$ 40) patients to normal subjects and found significant alterations in the obese group. Obesity resulted in a decrease in both lung and chest wall compliance and was associated with a marked increase in both airway and total lung resistance. In a separate study of 24 consecutive sedated, paralyzed patients, BMI was directly related to respiratory compliance and resistance (10). The authors found that respiratory compliance decreased with increasing BMI, primarily as a result of the pulmonary component, while the chest wall compliance was weakly dependent on BMI. Similarly, total respiratory resistance increased with increasing BMI, largely due to an increase in lung resistance. Chest wall resistance was relatively unaffected. Zerah and associates (9) found a similar relationship between total respiratory resistance and BMI in awake, obese patients. In this series, both respiratory resistance and airway resistance correlated with BMI but chest wall resistance did not change significantly with the degree of obesity.

Decreased respiratory muscle function in obese patients may compound the above mentioned changes in respiratory physiology. It has been shown that the maximum voluntary ventilation (MVV) is decreased in obesity (13–16) and is related to increasing BMI (14). It has been suggested that this occurs as a result of upward displacement of the diaphragm within the thoracic cavity rather than as a result of true respiratory muscle weakness (17).

The most predictable abnormalities in pulmonary function tests in obese subjects occur in the static lung volumes, with reductions in expiratory reserve volume (ERV) and functional residual capacity (FRC) most commonly described (13;15;16;18–20). As outlined above, these alterations are most likely attributable to the decreased respiratory compliance which occurs in response to excess soft tissue and weight. A reduction in vital capacity (VC) has been reported over a wide range of BMI by some authors (13;20–22) but others have reported a decrease in VC only with extreme obesity (15). Total lung capacity (TLC) is often preserved in obese subjects (13), but may be reduced with increasing BMI (15).

Many authors have reported that the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) are preserved in obese subjects (20;23;24). Others have suggested that obesity may cause airflow limitation, with reductions in both FEV1 and FVC (13;25). In this case, the FEV1 and FVC are often symmetrically decreased, resulting in a preserved (11) or increased FEV1/FVC ratio (13) consistent with a restrictive pattern. Evidence for mild obstructive abnormalities exists, however. Rubinstein and colleagues found increased airway resistance and reduced FEV1 in obese, nonsmoking men when compared to non-obese controls (25). Pankow and associates described expiratory flow limitation (EFL) and associated intrinsic positive end-expiratory pressure (PEEPi) in obese subjects at tidal respiration that was not present in normal weight controls (26) which worsened in the supine position. In contrast, Ferretti and colleagues showed that EFL was uncommon in obese subjects in the seated position, but noted that it was frequently identified in the same subjects in the supine position (27).

The diffusing capacity of carbon monoxide (DLco) is generally preserved in obesity (13;16; 17;20), supporting the concept that the pulmonary parenchyma is healthy in these individuals, and that alterations in pulmonary function are most likely related to the aforementioned changes in pulmonary mechanics. Interestingly, a few authors have identified an increase in DLco which seems to correspond to BMI (15;19;28). It has been hypothesized (Saydain, 2004 [Ref # 83]) that this increase in DLco results from an increase in capillary blood volume which occurs with the increased total blood volume and cardiac output observed in obese patients (29;30), Despite this, arterial hypoxemia and an elevated alveolar to arterial oxygen gradient (A-a) gradient are often observed in obese subjects (10;12;13;16;17;20). It has been hypothesized that ventilation/ perfusion (V/Q) mismatching is a least partially responsible for this, with obese subjects preferentially ventilating the upper lung zones while preserving perfusion to the lung bases (31;32). It appears that this V/Q mismatching is worsened in the supine position (32). Others have suggested that the tendency of obese individuals to develop atelectasis is greater than normal subjects (33–35) and may be explained by the previously described reduction in FRC (10;12).

The alterations in pulmonary physiology and function have significant implications in the care of obese patients with ALI and ARDS. Alveolar over-distention and barotrauma, which may occur as a result of elevated airway pressures, may be compounded by the reduced lung volumes and increased airway resistance described above (36). Initial tidal volume settings during mechanical ventilation should be based on ideal body weight, with a goal of limiting transpulmonary pressures to 30–35 cm H_2O. The development of PEEPi (26;27) and V/Q mismatching (32) seems to be worsened by the supine position, so patient positioning should be adjusted whenever possible. Accordingly, Burns and associates (37) found that the reverse Trendelenburg position at 45 degrees improved pulmonary mechanics and facilitated weaning in a small series of patients with obesity or ascites and respiratory failure. The addition of positive end-expiratory pressure should help prevent atelectasis and associated abnormalities in gas exchange (38) by improving pulmonary mechanics in obese patients.

Pathophysiology of acute lung injury and the possible role of obesity

A full description of the pathophysiology of ALI/ARDS is beyond the scope of the current review and the reader is directed to recent reviews for further details (2;39). In brief, in ALI/ ARDS imbalances occur between pro- and anti-inflammatory cytokines, oxidants and anti-oxidants, and coagulation factors. Alterations in neutrophil activation, recruitment and clearance and release of proteases also are important. The net result of these changes is alveolar filling with proteinaceous fluid, alveolar and interstitial edema, surfactant inactivation and injury of the pulmonary microvascular bed.

Endothelial injury in the pulmonary microvasculature is a major contributor to the increased permeability pulmonary edema of ALI/ARDS (40). Two mediators thought to play a role in this endothelial dysfunction are endothelin-1 and von Willebrand factor (VWF). Endothelin-1 (ET-1) is released by endothelial cells in response to stress and injury, resulting in vasoconstriction and inflammation (41). ET-1 is elevated in the plasma of patients with ALI/ ARDS, compared to healthy controls (42). VWF is also released in response to endothelial activation and higher levels of VWF have been associated with increased mortality in ALI/ ARDS patients (43).

Plasma levels of ET-1 and VWF are both increased in non-critically ill obese patients. ET-1 is released by subcutaneous adipose tissue and greater levels are secreted in obesity (44). VWF is also increased in obesity (45) and appears to be linked to insulin resistance and endothelial dysfunction (46). Despite this, it is unknown if ET-1 and VWF are increased in obese ALI/

ARDS patients or if alterations in these pro-inflammatory mediators predispose obese patients to the syndrome.

In addition to endothelial injury, ALI/ARDS is characterized by damage to the alveolar epithelium. Characteristic lesions in the alveolar epithelium lead to loss of epithelial integrity and result in pulmonary edema and impaired clearance of lung water. Injury to type II cells leads to impaired surfactant production and lung repair (47). A comparison of the underlying mechanisms of damage to the alveolar epithelium and the degree to which it occurs in obese versus non-obese ALI/ARDS patients is lacking.

Neutrophils play a critical role in the development of ALI/ARDS with increased neutrophils found in the lung and bronchoalveolar lavage fluid of ALI/ARDS patients (47;48). There are a number of putative mechanisms thought to be involved in neutrophil recruitment and activation, which may contribute to the development of ALI/ARDS, including up-regulation of adhesion molecules, induced neutrophil deformation, release of neutrophil-derived proteases and dysregulated neutrophil clearance (39). Alterations in neutrophil recruitment in the obese ALI/ARDS patient may exist, but evidence is inconclusive. There appears to be an increase in multiple adhesion molecule markers in the blood of obese patients, including intracellular adhesion molecule-1 (ICAM-1) and E-selectin, which correlates with the degree of obesity (49). However, other studies find that selected neutrophil adhesion antigens, such as CD62L (L-selectin), are reduced in obese patients, suggesting the possibility of impaired neutrophil recruitment (50). As with endothelial damage, we are unaware of studies directed at differences in recruitment or activation of neutrophils in obese and non-obese ALI/ARDS patients.

The inflammatory condition in ALI/ARDS is promoted and modulated by a complex interplay of cytokines produced by a wide variety of cell types (51). Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF- α) are early response cytokines which promote subsequent inflammation (39). IL-8 is thought to enhance this initial inflammation through recruitment of neutrophils (52). These inflammatory markers are accompanied by anti-inflammatory cytokines, such as IL-10 and IL-11, and inhibitors of pro-inflammatory cytokines, such as soluble TNF receptors, IL-1 receptor antagonist and auto-antibodies against IL-8 (39). In response to inflammatory stimuli, a number of cells release reactive oxygen and nitrogen species which may be responsible for much of the cellular damage occurring in ALI/ARDS (53).

Data linking obesity and ALI/ARDS is, perhaps, most convincing on the basis of chronic excessive inflammation and oxidative stress in obese patients compared to nonobese patients (54). There is a significant increase in abnormal cytokine production and acute-phase reactants and an up-regulation of pro-inflammatory signaling pathways in otherwise-healthy obese patients (55). Additional weight gain stimulates further induction of pro-inflammatory cytokines and mediators, such as TNF-α, IL-6, pre-B-cell-enhancing factor (PBEF), plasminogen activator inhibitor -1 (PAI-1), angiotensinogen, retinol-binding protein-4 (RBP-4), leptin, and IL-1β (54). In fact, adipose cells can contribute up to 30% of circulating IL-6 in obese individuals (56).

Obesity is associated with an increase in oxidative stress and formation of reactive oxygen species (57). Reactive oxygen species cause cellular injury through direct damage to cellular membranes and by cellular adhesion of monocytes and release of chemotactic factors and vasoactive substances (58). Oxidative stress has been associated with diaphragmatic dysfunction (59). Diaphragmatic dysfunction has also been described in obesity (60) but a direct link between oxidative stress, obesity and diaphragm function has not been reported.

Adipocytokines and ALI/ARDS

In addition to classic cytokines, adipose tissue releases adipocytokines which act as mediators of subsequent pro-inflammatory and anti-inflammatory pathways (54). While there are a number of known adipocytokines, of primary importance are leptin and adiponectin (54). Leptin is a polypeptide hormone secreted by adipocytes which is elevated in states of obesity and functions as a mediator of energy balance (61). It is secreted mainly by adipose tissue and meant to signal adequate stores of energy and feelings of satiety. When energy levels diminish, leptin levels fall to stimulate feelings of hunger. Leptin levels are increased in patients with obesity and are thought to play a role in the development and maintenance of obesity and its morbid complications. These increased levels may be a result of leptin-resistance, which is present in more than 90% of patients with type II diabetes and is believed to be due to receptor down-regulation (62).

In addition to its regulation of energy balance, leptin also functions as an adipocytokine to affect inflammatory cells. Leptin can induce the production of TNF-α, IL-1β, IL-1RA, IL-R2, and IL-6 as well as that of reactive oxygen species, and to increase phagocytosis in some antigen presenting cells (63). Leptin has a structural similarity to other cytokines, such as IL-6, which is known to serve a pro-inflammatory role. However, leptin's role in acute inflammatory conditions leading to ALI/ARDS, such as sepsis, is unproven. For example, in normal volunteers, plasma leptin is not increased above baseline after intravenous endotoxin administration at 6 or 24 hours (64). Similarly, studies exploring an association between leptin levels and outcomes from sepsis are conflicting. One showed an association between elevated leptin levels and higher mortality (65), another found no association (66), and others showed higher leptin levels in sepsis survivors (67;68).

One recent study attempted to evaluate the role of leptin and leptin resistance and its potential protective properties in mice with hyperoxia induced acute lung injury (69). With hyperoxia, lung leptin levels were increased in wild-type and leptin-receptor deficient mice. However, leptin resistant mice developed less lung edema and lung injury and had improved survival compared to mice with normally functioning leptin receptors. This suggests that the activation of the leptin receptor plays a role in the development of acute lung injury from hyperoxia and leptin resistance may be protective in preventing acute lung injury and associated morbidity and mortality. The relevance in alternate models of ALI/ARDS and in patients with ALI/ARDS is unknown.

Patients with diabetes mellitus, many of whom have elevated leptin levels, appear to be protected from acute lung injury. Several studies have suggested that diabetic patients are at lower risk for developing ARDS when suffering an acute insult associated with ALI/ARDS (70;71). It is unknown if this apparent protection from ALI/ARDS in diabetic patients at risk is due to an effect of leptin resistance, excess weight or alternate mechanisms.

Adiponectin is another adipocytokine that might play a role in the pathogenesis of ALI/ARDS of obese patients. It stimulates fatty acid oxidation, decreases plasma triglyceride levels, and improves insulin sensitivity (72). Adiponectin levels are generally decreased in obese individuals (73). Adiponectin has anti-inflammatory effects, including suppression of TNF-α, IL-6 and nuclear factor-κB and up-regulation of IL-10 and IL-1RA (74).

Studies using animal models (most commonly transgenic rodents with dysfunctional leptin receptors) have begun to explore a possible interaction between obesity and acute inflammation. In an experimental model of acute pancreatitis, pulmonary levels of TNF-α mRNA were significantly higher in obese than lean rats. However, there were no significant differences in pulmonary mRNA levels of IL-6, IL-10, or pancreatitis-associated protein (75). In a study exploring bronchial hyper-responsiveness seen in obese mice lacking the leptin

receptor, investigators measured bronchoalveolar (BAL) levels of cytokines and adipocytokines (76). There were minimal differences between the wild-type and transgenic mice in regards to BAL inflammatory cytokines. However, BAL leptin levels were higher in obese than lean mice and there was a trend toward lower adiponectin levels in the obese mice. It remains unknown if these differences might also affect the murine response to stimuli causing ALI/ARDS.

Obesity and Outcomes from Acute Lung Injury

While a number of studies explore the association between obesity and outcome for critically ill adults (see article in this issue by Honiden and McArdle), few articles have focused specifically on patients with ALI/ARDS (see Table 2). The first such study (77) reported a secondary analysis of patients enrolled in the National Heart, Lung and Blood Institute's (NHLBI) multicenter, randomized trials of the Acute Respiratory Distress Syndrome Network (78–80). These studies included comparisons of lower and higher tidal volumes (6 ml/kg versus 12 ml/kg predicted body weight, respectively) and ketoconazole or lisofylline versus placebo. Of note, patients with a weight-to-height ratio (kilograms divided by centimeters) of >1.0 were excluded from these studies. BMI calculated from height and weight at the time of study enrollment was used as the measure of excess weight with a variety of variable formats used in the analyses. Risk-adjusting methods incorporated multi-variable logistic regression with survival to 28 days being the primary outcome.

BMI data were missing for 6.1% (n=55) of subjects enrolled in the initial studies. The investigators also excluded subjects with an underweight BMI (<18.5 kg/m^2, 4.7%, n=40). Ultimately, 807 subjects were included in the analysis. Based on NHLBI categories of BMI, 31.5% (n=254) of subjects had an overweight BMI and 27.1% (n=219) had an obese BMI. In unadjusted analyses, there were no significant differences in 28-day or 180-day mortality, achieving unassisted ventilation by day 28 or ventilator-free days between patients with overweight or obese BMIs and those with normal BMIs. After adjusting for the effects of age, severity of illness, PaO_2/FiO_2 ratio, study group assignment, peak airway pressure, primary lung injury category, and gender, there was no significant increase in the adjusted odds of 28 day mortality for subjects with overweight (adjusted odds ratio 1.10 [95% confidence interval 0.71 – 1.69]) or obese BMIs (adjusted odds ratio 1.11 [95% confidence interval 0.69 – 1.78]), compared to subjects with normal BMIs. There was also no significant association in multivariable analysis including BMI as a continuous variable, when severe obesity (BMI ≥ $40kg/m^2$) was considered or when the subject's BMI was adjusted for the fluid balance for the 24 hours preceding study enrollment. The same risk-adjusting model was refit for 180-day mortality, achieving unassisted ventilation by day 28, and ventilator-free days. In no analysis were overweight or obese BMIs associated with outcomes.

A second retrospective study by the same authors used data from Project IMPACT®, a subscription database designed for ICU benchmarking (www.cerner.com/piccm/products_pi.html), to further explore any possible association between obesity and outcomes among ALI patients (81). The investigators analyzed data from 1488 patients admitted from December 1995 to September 2001. Subjects were included if (1) admission data allowed for a BMI calculation, (2) there was an admission diagnosis consistent with ALI and (3) the subject required mechanical ventilation within 24 hours of intensive care unit (ICU) admission. Again, BMI was used as an indicator of excess weight and was calculated from data included in the admitting record. The primary outcome was hospital mortality and multivariable logistic regression was used to account for possible confounding. Underweight patients were included in the analysis.

Of the included subjects, 26.8% (n=399) had an overweight BMI, 21.9% (n=326) had an obese BMI, and 8.8% (n=131) were severely obese, by NHLBI categorization (82). In unadjusted analyses, there was a significant association between BMI and hospital mortality ($p<0.001$). Crude hospital mortality was highest in patients with underweight BMIs (54.6%) and lowest in the severely obese patients (29.0%). Hospital mortality was intermediate in the other BMI categories. ICU and hospital length of stay and discharge destination were not different between the various BMI categories. The best fit of the non-categorized BMI variable with hospital mortality was found to be a quadratic transformation and this was also significantly associated with hospital mortality in unadjusted analyses ($p<0.0001$). After adjustment for an assortment of possible confounders found in preliminary analyses, BMI category remained associated with hospital mortality ($p<0.0001$) when the group with normal BMIs were considered the referent group. The highest adjusted odds for mortality were in the patients with underweight BMIs (adjusted odds ratio 1.94 [95% confidence interval 1.05 – 3.60]) and patients with an obese BMI had significantly lower adjusted odds of death (adjusted odds ratio 0.67 [95% confidence interval 0.46 – 0.97]). A trend toward lower mortality for the overweight and severely obese BMI groups was also suggested in risk-adjusted analyses (adjusted odds ratios, 0.72 and 0.78, respectively) but failed to reach statistical significance. A similar association was observed when the transformed BMI variable was included in the risk-adjusting model with the highest adjusted odds seen at underweight BMI levels and the lowest odds seen at a BMI of 35–40 kg/m^2.

The most recent study examining the association between obesity and acute lung injury used data gathered as part of a population-based, prospective cohort study among 21 hospitals in and around King County, Washington between April 1999 and July 2000 (KCLIP) (3). All patients receiving mechanical ventilation in the participating hospitals were screened for enrollment based on the American-European Consensus Conference definition of ALI (1). In the analysis of this data examining obesity (83), BMI was calculated from height and weight recorded at hospital admission and NHLBI categories were utilized. Outcomes included ICU and hospital mortality, ICU and hospital length of stay, duration of mechanical ventilation and discharge disposition. Multivariable logistic and linear regression models were used for risk-adjusting.

As in the prior studies examining excess weight and ALI, the majority of subjects were either overweight (28.7%, n=237) or obese (28.7%, n=237). Crude mortality was highest in the patients with underweight BMIs (44.0%) and decreased as BMI increased. ICU and hospital lengths of stay and duration of mechanical ventilation were similar among all BMI categories in unadjusted analyses. After adjustment for age, severity of illness and ALI risk factor, there were no statistically significant differences in mortality between the underweight, overweight, obese or severely obese BMI groups and the reference group (patients with normal BMIs). ICU and hospital lengths of stay were markedly increased among the severely obese patients (BMI ≥ 40) compared to patients with normal BMIs. Moreover, compared to survivors with normal BMIs, the risk-adjusted duration of mechanical ventilation among surviving severely obese patients was increased by 4.1 days (95% confidence interval 0.4 to 7.7 days). Finally, severely obese patients were more likely to be discharged to rehabilitation facilities and skilled nursing facilities. These differences in lengths of stay, duration of ventilation and discharge location among the severely obese were not observed among the patients with overweight and obese BMIs compared to those with normal BMIs.

Obesity as a Risk Factor for Acute Lung Injury and Multi-Organ Failure in At-Risk Patients

Because of changes in physiology and inflammation associated with excess weight, it is conceivable that obese patients might be at greater risk for ALI/ARDS when suffering a

predisposing acute event, such as sepsis or trauma. One of the earliest studies exploring an association between obesity and outcome among the critically ill reviewed data from 184 patients admitted to a trauma service over six months (84). In this study, mortality was significantly higher in patients with a BMI>31 kg/m^2 (42.1% versus 5.0% in patients with BMI<27) and this increased mortality remained after adjustment for severity of injury. The authors also noted that the higher BMI group had a significantly higher rate of complications per patient and this "was predominantly accounted for by an increase in pulmonary complications." The details of these pulmonary complications were not provided. However, the authors also presented the cause of death among the 17 patients who died. Seven of eight higher BMI patients had ARDS listed as the primary factor leading to death. No patients in the lower BMI group (BMI <27) had ARDS listed as the primary factor leading to death, although 3 of 6 had multi-organ system failure listed.

A more recent retrospective cohort study re-explored this association among 242 consecutive patients admitted to an intensive care unit following blunt trauma (85). There were no differences in the development of ARDS between subjects with an obese (BMI≥30kg/m^2) or a non-obese BMI (8% vs. 6%, p=0.55) but obese subjects had a higher rate of multi-organ system failure (13% vs. 3%). After adjustment for head injury, pulmonary contusion, injury severity and age, the subjects with obese BMIs had significantly higher mortality (adjusted odds ratio 5.7 [95% confidence interval 1.9 – 19.6]). However, only one death in the study was attributed to respiratory failure. Multi-organ system failure was a more common cause of death among the obese-BMI subjects than the non-obese-BMI subjects (35.0% vs. 17.2%).

A secondary analysis of a prospective cohort study of critically injured adults sought to determine if obese and severely obese patients were at increased risk of pulmonary complications, including ARDS (86). The study cohort included 1219 adults admitted to an ICU following trauma. ARDS occurred in 21% of normal-BMI patients, 32% of obese-BMI patients and 11% of severely obese-BMI patients. After adjustment for age, gender and severity of injury, the patients with severe obesity had a statistically significant decrease in the risk of ARDS (adjusted odds ratio 0.36 [95% confidence interval 0.13 – 0.99]) compared to the normal-BMI group. A similar effect was not seen amongst the overweight- (adjusted odds ratio 0.97) and obese-BMI groups (adjusted odds ratio 1.0). When BMI was explored as a continuous variable, the peak of unadjusted risk for ARDS occurred between a BMI of 20 and 30. Ventilator management practices, including tidal volume, were not reported.

While there are hypothetical reasons that obesity could create a pathologic milieu promoting the development of ALI/ARDS in patients otherwise at risk, definitive data are lacking. Most studies have focused on less specific outcomes such as length of stay and mortality for obese ICU patients. As discussed subsequently, even those studies focusing on the development of ALI/ARDS in obese patients suffer from potential bias due to the definition of ALI/ARDS and lack of standard care practices.

Limitations of Human Studies Exploring an Association between Obesity and Acute Lung Injury

Measures of excess weight and the heterogeneity of obesity

Existing studies of excess weight and ALI have only examined BMI as the measure of excess weight. While this measure is highly reliable and associated with adult body fat in ambulatory patients (87), BMI might not be the best representation of risk (or benefit) for critically ill patients. For example, the distribution of excess weight may have particular relevance for mechanically ventilated patients kept in a supine or semi-supine position (88). In selected epidemiologic studies, waist circumference is a better marker of cardiovascular risk than BMI

(82). Since centripetal obesity is more likely to affect thoraco-abdominal compliance than excess weight distributed elsewhere in the body, it is possible that measures of the *distribution* of excess weight may be more strongly associated with outcome than BMI in mechanically ventilated patients, such as those with ALI. Further research is needed to explore alternate measures of excess weight. Such efforts would be an initial effort to consider the heterogeneity of pathogenesis and pathophysiology in the construct lumped together as "obesity."

Fluid balance

Studies of the association between excess weight and acute lung injury have used height and weight as recorded at ICU (81) or hospital admission (83;86) or at the time of study enrollment (89). However, many of the conditions that lead to ALI (e.g. sepsis, trauma) are accompanied by fluid resuscitation and changes that may alter fluid handling (e.g. "third-spacing", acute renal failure). The administration of fluid or induced diuresis prior to weight measurement might, therefore, affect the calculated BMI. Furthermore, the course of illness leading to ALI (e.g., anorexia due to infection) might alter the patient's weight prior to intervention and may not reflect the patient's true BMI.

The previously discussed study utilizing data from the ARDS Network considered the effects of therapeutic fluid manipulation on measured BMI in the analysis (89). For the 24 hours prior to study enrollment (and weight measurement), fluid balance was determined. There was a wide range in net fluid balance (mean balance, 2591 mL gained [95% confidence interval 5527 mL lost to 10,709 ml gained]). In other words, based on net fluid balance alone, on average, subjects were 2.6 kg (5.7 pounds) heavier on the day of study enrollment compared to the prior day. The adjustment for individual fluid balances resulted in 14.4% of subjects changing BMI category. When BMI was adjusted for this fluid balance, there remained no association with outcome.

Differences in net fluid balance prior to BMI calculation could explain some of the variation in observed results across studies. Early appropriate resuscitation may be important for outcome in patients with ALI and its predisposing conditions (90–92). Patients receiving earlier volume resuscitation will likely gain more fluid (and weight) prior to BMI calculation. They are then more likely to migrate into higher BMI categories and this could bias the results. Additionally, since obese patients are less tolerant of fluid loading than the non-obese (93; 94), similar resuscitation practices might then affect obese and non-obese patients differently. This could also confound the observed association.

Diagnosis of ALI/ARDS in obesity

The current clinical definition of ALI or ARDS is based on the American-European Consensus Conference statement which requires the presence of bilateral pulmonary infiltrates on chest radiograph (1). Obesity often decreases the quality of chest radiographs (95), and may limit the usefulness of this definition in many patients. Typical settings used to obtain chest radiographs may not allow adequate penetration of the X-ray beams in an obese patient, resulting in lower image contrast and increased background scatter (96). In addition, the increased body thickness through which x-ray beams must travel in obese patients requires increased exposure time and may result in excessive motion artifact. Accordingly, the distinction between infiltrates and overlying soft tissue may be difficult, and the presence of mediastinal adipose tissue may produce abnormalities on chest radiograph which mimic other clinical conditions (36). Finally, when a large surface area is imaged, the area of clinical interest may lie outside the field of view (95). A computed tomography scan may provide better visualization of the pulmonary parenchyma, but factors such as the difficulty transporting obese

patients and the weight and aperture limitations of available equipment may limit the usefulness of these studies in many patients (36;96).

Disparities in processes of care

Observational studies rely upon appropriate risk adjusting to reach unbiased conclusions about the measured results. Among patients with ALI, several care practices have high-level evidence supporting their use. If such practices are differentially applied to non-obese and obese patients, this disparity in care might bias the results. The use of lower tidal volume ventilation (e.g. 6ml/kg predicted body weight and plateau airway pressure <30) was associated with an 8.8% absolute risk-reduction in hospital mortality (78) compared to traditional tidal volumes (e.g. 12 ml/kg predicted body weight). In a secondary analysis of the data from this randomized controlled trial, the tidal volumes used just prior to the institution of the study protocol were analyzed by BMI category (77). Patients with obese BMIs had significantly higher tidal volumes (10.76 ml/kg predicted body weight) than patients with normal BMIs (10.05 ml/kg predicted body weight). This study also concluded that there was no significant interaction between patient BMI and the benefit of lower tidal volumes, arguing that lower tidal volumes should be used for ALI patients of all BMIs.

The King Country study also found significantly higher tidal volumes on day 3 of mechanical ventilation among obese and severely obese patients (10.5 and 11.4 ml/kg predicted body weight, respectively) than among patients with normal BMIs (9.9 ml/kg predicted body weight) (83). Noting the possible effect of such disparities in ventilator practices, the authors did not include tidal volume in their risk-adjusting estimates since they could be in the causal pathway to worse outcomes for obese patients. Based on existing data, clinicians should be attentive to tidal volumes based on predicted body weight for *all* ALI patients. Particular attention should be paid to obese ALI patients since they seem most prone to the use of potentially injurious tidal volumes.

In a retrospective cohort study of ALI patients in an observational database, other care practices were observed to be used differently for obese and non-obese patients (97). For example, heparin prophylaxis for thromboembolic disease was utilized more frequently for obese and severely obese patients (46.0% and 57.2% of patients, respectively) than for normal BMI patients (43.8%). Importantly, this increased use of what is considered best-practice for prevention of venous thromboembolism in mechanically ventilated patients (98) mediated approximately 10% of the observed protective effect of severe obesity in this study. Said another way, a significant portion of the apparent “protective” effect of severe obesity in this study was due to an increased use of appropriate thromboembolism prophylaxis in the severely obese patients. Whether this is a causal effect of thromboembolism prophylaxis or if this observation is merely a marker for other unmeasured disparities in provided care is unknown. However, it emphasizes the need to consider differences in clinical care in observational studies determining an association between obesity and outcome.

Increasing evidence points to excessive use of sedatives and/or analgesics to be major causes of poorer outcomes, including prolonged time requiring mechanical ventilation, increased rates of delirium and higher mortality among mechanically ventilated patients (99–101). Because many of these medications are extremely fat soluble, their volume of distribution is altered in obese patients (102). While most data on the pharmacokinetic and pharmacodynamic properties of these agents in obese patients are based on their use in elective surgery or healthy volunteers, rather than in critically ill mechanically ventilated patients, differences in response to these medications could confound any observed association between obesity and outcome for ALI patients.

Benzodiazepines are highly lipophilic drugs that are commonly used in mechanically ventilated patients. Among obese patients, there is a significant increase in volume of distribution and elimination half-life for benzodiazepines (103). The increase in volume of distribution into excess fat appears to be directly associated with the lipid solubility of the drug. For example, after a single 5 mg intravenous bolus, midazolam has a total volume of distribution more than three times larger in obese than non-obese subjects (104). The elimination half-life was also almost four times longer (8.4 hours vs. 2.7 hours) in the obese subjects. This was due to the dramatic increase in volume of distribution, rather than changes in clearance of drug. Therefore, while single doses of midazolam should be based upon total body weight, continuous infusions should be adjusted based on ideal body weight However, in the intensive care unit, infusions are usually titrated to effect (e.g. level of sedation), rather than dose. If bolus doses of midazolam are not based on actual body weight, there may be a delay in the desired level of sedation. This could leave a patient at risk for complications from under-sedation. Furthermore, we have anecdotally noted an increased reliance on higher infusion rates in these instances to mitigate the apparent resistance to the inadequately dosed bolus. This might then produce an overshoot in the depth of sedation and a subsequent delay in drug washout.

Obesity's effects on distribution and elimination of synthetic opioids and alternative sedatives are less consistent than those observed for benzodiazepines. Sufenatil and alfentanil have increased volumes of distribution in obese subjects and prolonged elimination half-lives when compared with non-obese patients (105;106). However, the pharmacokinetics of fentanyl do not appear to be appreciably altered by obesity while the volume of distribution is increased (106). Propofol is a highly lipophilic drug commonly used for mechanically ventilated adults. While there is an increase in the volume of distribution of propofol in obese patients, it is paralleled by an increase in drug clearance. Therefore, the elimination half-life of propofol is similar in non-obese and obese patients (107). We are unaware of a published study which compares various strategies of sedation and analgesia among obese versus non-obese patients. Known alterations in pharmacokinetics of these commonly used drugs could affect outcomes by producing prolonged sedation and increased incidence of delirium, even if identical practices are employed for obese and non-obese patients.

Conclusions

ALI/ARDS is a common cause of acute respiratory failure with a high mortality rate. While current data are premature, obesity and ALI/ARDS appear to share alterations in inflammation, endothelial dysfunction, and oxidative stress. This raises the possibility that obese patients may be at higher risk of developing ALI/ARDS and have poorer outcomes from ALI/ARDS. However, data supporting such an association are inconclusive. Additionally, obese ALI/ARDS patients may receive different care than nonobese patients. These disparities in provided care might worsen (e.g. tidal volumes influenced by total body weight) or improve (e.g. greater use of appropriate thromboembolism prophylaxis) outcomes in obese ALI/ARDS and bias observed results. With the epidemic of obesity, a greater number of ALI/ARDS patients will be obese and greater understanding of the mechanisms underlying lung injury in these patients is needed to better characterize the syndrome and improve treatment.

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Table 1

Changes in respiratory mechanics and pulmonary function tests in obesity

RESPIRATORY MECHANICS		
Total respiratory compliance		Decreased
	Pulmonary (lung) compliance	Decreased
	Chest wall compliance	Decreased
Total respiratory resistance		Increased
	Airway resistance	Increased
	Additional pulmonary (lung) resistance	Increased
	Chest wall resistance	Increased or unchanged
PULMONARY FUNCTION TESTS		
	FVC	Decreased or unchanged
	FEV1	Decreased or unchanged
	FEV1/FVC	Decreased or unchanged
	VC	Decreased or unchanged
	FRC	Decreased
	ERV	Decreased
	TLC	Decreased or unchanged
	D_LCO	Increased or unchanged

FVC = forced vital capacity; FEV1 = forced expiratory volume in one second; VC = vital capacity; FRC = functional residual capacity; ERV = expiratory reserve volume; TLC = total lung capacity; D_LCO = diffusion capacity for carbon monoxide

Table 2

Studies examining the association between outcome and obesity in ALI/ARDS patients

	O'Brien(89)	**O'Brien(97)**	**Morris(83)**
Setting	Retrospective analysis of randomized clinical trial	Retrospective cohort study of subscription database	Prospective cohort study of ICU patients in King County, WA
Definition of ALI/ARDS	AECC	Diagnostic codes	AECC
Years of study	1996 – 1999	1995 – 20001	1999 – 2000
Sample size	807	1488	825
Measure(s) of excess weight	BMI, fluid-adjusted BMI by NHLBI categories, continuous	BMI by NHLBI categories, continuous and quadratic transformation	BMI by NHLBI categories
Percentage of obese subjects	27.1%	30.7%	28.7%
Primary outcome	28 day mortality	Hospital mortality	Hospital mortality
Crude association with primary outcome	Not statistically significant	Highest mortality in underweight (54.6%) and lowest in severely obese (29.0%)	Highest mortality in underweight (44.0%) with lowest in severely obese (25.9%)
Risk-adjusted association with primary outcome	Not statistically significant	Statistically significant with highest adjusted odds of hospital mortality in underweight and lowest adjusted odds ratio in obese BMI groups, relative to normal BMI	Not statistically significant
Secondary outcome(s)	180-day mortality, achieving unassisted ventilation, ventilator-free days	None	Hospital length of stay, ICU length of stay, duration of mechanical ventilation
Risk-adjusted association with secondary outcome(s)	Not statistically significant	N/A	Statistically significantly longer length of stay in severely obese relative to normal BMI patients; statistically significantly longer ICU length of stay and duration of ventilation among severely obese hospital survivors relative to normal BMI survivors
Miscellaneous findings	Lower tidal volume ventilation appeared to have similar benefit for all BMI groups; 14% of subjects changed BMI category when adjusted for fluid balance; higher pre-enrollment tidal volumes in higher BMI groups	Higher BMI patients more likely to receive heparin prophylaxis and this mediated some of "benefit" of higher BMI	Day 3 tidal volumes were higher with higher BMIs; severely obese patients more likely to be discharged to a higher level of care on hospital discharge

ALI/ARDS = Acute lung injury/Acute respiratory distress syndrome; AECC = American-European Consensus Conference; BMI = Body mass index; NHLBI = National Heart, Lung and Blood Institute;