

Review article

Severe Respiratory Complications in Obese Patients with SARS-CoV-2 Virus Infection: Characteristics and Oxygen Treatment

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SUMMARY

Considerable share of patients admitted to the intensive care unit, during the current Covid-19 pandemic, are obese. Obesity is associated with chronic low-grade inflammation, higher endothelial injury, higher levels of angiotensinogen II and increased expression of angiotensin-converting enzyme 2 receptors in the adipose tissue. These alterations along with accompanying comorbidities make the obese patients susceptible for the development of severe respiratory complications, including acute respiratory distress syndrome (ARDS) during SARS-CoV-2 infection. The choice of optimal mode of oxygen delivery rests on both a prior patient's functional status and the progress and severity of Covid-19 in obese patients. Non-invasive ventilation and high-flow nasal cannula, prone position and hyperbaric oxygen therapy are effective in obese patients with mild or moderate ARDS. If mechanical ventilation is unavoidable, lung protective ventilation mode with lower tidal volume and optimal positive end-expiratory pressure is crucial for treatment of SARS-CoV-2-induced ARDS. Extracorporeal membrane oxygenation is reserved only for patients with inadequate response to previous oxygen therapy. Optimal knowledge of physiological changes in obesity and timely treatment with adequate oxygen therapy could improve clinical outcome of these sensitive patient subgroup.

Key words: Covid-19, obesity, ARDS, oxygen therapy, respiratory support

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INTRODUCTION

Large share of the total number of patients admitted to the intensive care unit (ICU), during the current Covid-19 pandemic, are obese. Although the clinical picture of Covid-19 disease may vary from mild to severe forms, obese patients are at higher risk for the development of severe complications, including the acute respiratory distress syndrome (ARDS). In the US health care system, the percentage of obese hospitalized patients with Covid-19 was 41.7% (1), while 47.5% of those admitted to the ICU were obese with predominant BMI ≥ 30 kg/m² (2, 3). An altered response to SARS-CoV-2 infection is the result of the physiological changes in obesity and the accompanying respiratory, cardiovascular and renal comorbidities and coagulation system disturbances (4 - 6). This sensitive population required more invasive mechanical ventilation (IMV) in nearly 90% (2) and had a mortality rate of 62% compared to 36% recorded in lean patients (3). Mortality from Covid-19 in obese patients without comorbidities was 3-fold higher comparing to lean patients and reached up to 6-fold increase when obesity was associated with comorbidities (7).

The current treatment of Covid-19 disease is limited to the supportive care. However, in obese patients, traditional supportive care often fails, necessitating IMV. Once on the ventilator, Covid-19 patients are difficult to wean and the risk of mortality rises sharply. For the reasons given above, authors will discuss the mechanisms responsible for susceptibility to more severe disease development in obese patients. More importantly, the focus of this review will be on various approaches to oxygen delivery in SARS-CoV-2 virus-induced lung injury and ARDS with an emphasis on non-invasive mode of oxygen therapy in obese patients.

PATHOPHYSIOLOGICAL CHANGES AND THE MOST COMMON COMORBIDITIES IN OBESE PATIENTS WITH COVID-19 INFECTION

Obese patients are already at high risk of severe complications of Covid-19 infection due to their coherence with physiological changes such as chronic low-grade inflammation, higher endothelial injury, increased angiotensin-converting enzyme 2

(ACE-2) receptors concentration, and the higher activity of the renin-angiotensin-aldosterone system (RAAS).

The state of chronic low-grade inflammatory condition in obesity is characterized by increased circulating neutrophil levels (8), increased blood levels of adipokines and cytokines such as α -interferon, TNF- α , IL-1 β , IL-8 and IL-6 (9 - 11). Persistence of chronic low-grade inflammation impairs the immune-response (11) and influences the inflammation in the lung parenchyma and bronchi (12), with a consequent increase of susceptibility to infection or bacteremia in obese patients (13). The injury of endothelial microvasculature is a major contributor to increased permeability and development of pulmonary edema during acute lung injury and ARDS in this population. It is often a result of inadequate production of vasoactive agents and activation of innate immune cells (14 - 16). A combination of vasoconstriction and higher vascular inflammation with underlying atherosclerosis and a higher activity of platelets and adhesiveness of leukocytes leads to impairment of hemostasis and thrombosis in obese organisms (17). Angiotensin-converting enzyme 2 receptor on the cell surface is crucial for the penetration of SARS-CoV-2 virus into the human cells. There is a broad distribution of ACE-2 receptor expression on human tissues and organs including the gastrointestinal tract, lung, heart and kidney (18). The adipose tissue also strongly expresses ACE-2 receptor, making these cells an important viral reservoir (19). Adipocytes are also highly active in the production of circulating angiotensinogen and angiotensin II (20, 21). This may partially explain a higher activity of the renin-angiotensin-aldosterone system activity in obese patients (22). The implications of these finding in Covid-19 infection are unfavorable, especially having in mind the data concerning a positive correlation between a higher level of angiotensin II and the severity of lung injury. More precisely, the higher level of angiotensin II induces pulmonary vasoconstriction and disrupts the ventilation/perfusion mismatch, leading to hypoxemia and promoting acute lung injury (18). The abovementioned mechanism is not unique for a high predisposition of the obese patients to develop severe lung injury and exacerbation of Covid-19 infection (23, 24).

The list of comorbidities and physiological changes caused by obesity is long and is beyond the

scope of this review. Further discussion will be focused only to factors considered significant for the development of severe clinical picture during SARS CoV-2 infection.

Due to mechanical effects, obese individuals often develop atelectasis. They also have decreased total lung capacity, lower functional residual capacity and vital capacity. Their airway resistance and closure are increased, respiratory muscle strength is lower and ventilation/perfusion mismatch is more pronounced than in lean individuals (25). Their ventilation of the lung base is impaired and cause decreased oxygen saturation of blood (26). The changes in respiratory physiology might contribute to more frequent admission to ICU and the need for assisted ventilation in SARS-CoV-2 related pneumonia, compared to normal weight population, even in younger age patients (27). These factors could also increase the sensitivity for the development of ventilator-associated lung injury during IMV. Coronary heart disease and hypertension are also more commonly present in obese population, especially in cases with higher level of low-density lipoprotein cholesterol and triglycerides with diabetes mellitus type II, metabolic syndrome and "visceral" obesity (28). Functional changes of nephrons that include glomerular and podocyte dysfunction are often the cause of chronic kidney disease in obese patients. It was found that the central adipose tissue could decrease estimated glomerular filtration rate and effective renal plasma flow with the consequent subnephrotic proteinuria (20). Obese patients are at higher risk of developing venous thromboembolism due to hypercoagulability (29). Obesity-related hypercoagulability is multifactorial. It is associated with higher level of adipocytokines, hyperactivity of coagulation factors, decreased fibrinolysis, increased level of angiotensin II, endothelial dysfunction, venous stasis and impaired venous return (30, 31). Therefore, obese patients with Covid-19 have increased hypercoagulability and thrombosis as a result of both effects, obesity and viral infection.

OXYGEN THERAPY IN OBESE COVID-19 PATIENTS

Acute respiratory failure due to prolonged hypoxemia is the major manifestation in severe Covid-19 disease with the poor outcome in these patients (32). The development of respiratory complications in obese patients is characterized by the

deterioration of pulmonary clinical picture and low partial pressure of arterial oxygen (PaO_2) and oxygen saturation (SaO_2) on admission to the levels requiring higher inspiratory fraction of oxygen and prolonged oxygen delivery in order to improve oxygenation (33). Thresholds for titrating ventilation settings in obese patients with ARDS are: SaO_2 between 88 - 94%, PaO_2 between 55 - 80 mm Hg and carbon dioxide levels leading to drop of $\text{pH} > 7.25$ (34). Other authors have suggested different criteria in Covid-19 positive patients, such as: respiratory rate ≥ 30 breaths per minute, $\text{SaO}_2 \leq 93\%$, partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio < 300 mm Hg, and increase in lung infiltrates $> 50\%$ within 24 - 48 h (35). Whatever criterion is chosen, rational and effective respiratory support is crucial in the management of Covid-19 patients, especially for obese patients. So far, oxygenation in patients with Covid-19 lung disease has been done mostly with non-invasive respiratory support as non-invasive ventilation (NIV), (in 44% of patients in one large patient series), and high-flow nasal cannula (HFNC) (in 11% of cases in the same cohort), as well as with invasive mechanical ventilation (IMV) (in 47% cases), and only in few cases ARDS was treated with extracorporeal membrane oxygenation (ECMO) (36). The use of NIV is optimal for hemodynamically stable patients with mild to moderate ARDS matching levels of $\text{PaO}_2/\text{FiO}_2 > 200$ mm Hg (37). In severely hypoxemic patients with ARDS and $\text{PaO}_2/\text{FiO}_2 < 200$ mm Hg, IMV should be a therapeutic option (38).

Lung deterioration in early phase during Covid-19 infection could be treated using NIV and HFNC, with or without placing a patient in the prone position (38 - 40), or using hyperbaric oxygen therapy (41). These modalities could delay intubation and IMV (42). Non-invasive ventilation and HFNC were used in about one-third and two-thirds of critically ill patients with Covid-19 in China, respectively (39, 43, 44). The use of NIV and HFNC may decrease the need for tracheal intubation without the influence on mortality (42, 44), although some authors have reported increased mortality when HFNC was used in unselected patients (45). Another contradictory report has found that prolonged use of NIV or HFNC in Covid-19 patients is associated with higher risk of emergency intubation and prolonged desaturation after intubation (46).

The NIV method of oxygenation with continuous positive airway pressure (CPAP) could efficiently recruit alveolar units, improve hypoxemia

and reduce the work of breathing. The clinical goal of NIV method is to maintain at least minimal respiratory capacity. These benefits are possible if only careful titration and close monitoring of obese patients are performed (47). In case of hypercapnia, NIV with the application of higher positive end-expiratory pressure (PEEP) should be used for prolonged time (48). In case of NIV treatment associated with unsuccessful CPAP and PEEP above 10 cm H₂O, the risk of rapid clinical status worsening within a few hours is high and patients may require IMV (49, 50). Unsuccessful NIV treatment could be expected in comatose patients with sufficient breathing and in anxious patients with increased respiratory drive because of hypercapnic encephalopathy. For these conditions, NIV is considered inappropriate (37). Tolerance of NIV could be achieved with remifentanyl that could make a balance between the reduction of respiratory drive and maintenance of breathing capacity (51).

The application of HFNC for oxygen therapy in severe and critically ill Covid-19 patients is summarized in the following experiences. Firstly, it is important to provide the proper size of nasal catheter and maintain the patency of the upper respiratory airway. Secondly, an initial flow of humidified and warmed oxygen (60 L/min) with an adjustable FiO₂ should be given immediately to patients with obvious respiratory distress or weak cough ability; otherwise, low-level support should be given first and the amount should be successively and gradually increased. Thirdly, SpO₂ should be kept above 95% when using HFNC in order to avoid hypoxia or hypoxemia in patients without chronic pulmonary disease. Finally, patients should wear a surgical mask during HFNC treatment in order to reduce the risk of virus transmission through droplets or aerosols (52). Failure of HFNC could be avoided with proper selection of patients, i.e. who do not have extreme hyperventilation, with timely application and with improvement of compliance (50). It should be noted that older patients are vulnerable if HFNC fails (53). Until further data are available, HFNC and NIV alone or with prone position should be reserved for patients with mild or moderate ARDS (54). Minimal data exist to confirm or refute safety concerns regarding the risk of aerosol generation by these devices. Epidemiological sources suggest that NIV was linked with nosocomial transmission of SARS (55) and with generation of the aerosols, which was not in concordance with other report (56). In spite of the lack

of evidence, the use of side room or negative pressure rooms, pre-emptive change of mask and circuit with a viral filter in combination with personal protective equipment should minimize the risk for aerosol generation (57). Also, the use of helmet during the application of CPAP could prevent generations of aerosols (47).

Prone positioning should be applied as an early therapeutic option, given its association with improved oxygen saturation and reduced mortality in Covid-19-related ARDS. Although outcome data on prone positioning in Covid-19 are currently lacking, (prone was used in 12% of patients in one ICU study from Wuhan) (39) the tendency for SARS-CoV-2 to affect the peripheral and dorsal areas of the lungs provides the ideal conditions for a positive oxygenation response to prone positioning. In short, while median SpO₂ at triage was 80%, after the application of supplemental oxygen with room air, it raised to 84%, and after 5 minutes of proning, SpO₂ improved to 94%. However, 24% of patients failed to improve after proning, maintained poor oxygen saturation, requiring endotracheal intubation within 24 hours since the arrival to the emergency department (32). These patients showed intolerance to prone positioning due to anxiety or their impossibility to change position (58).

Hyperbaric oxygen therapy (HBOT) represents another feasible option for the prevention of IMV in Covid-19 patients with tachypnea and low oxygen saturation, especially if high FiO₂ oxygenation is applied. HBOT may reverse hypoxia and pulmonary inflammation with its anti-inflammatory and potentially viricidal properties, although the exact mechanism of action is unclear. A single HBOT treatment could cause the prompt resolution of labored breathing with the rise in SaO₂ values and improved symptoms in Covid-19 patients. A decrease in oxygen requirement below FiO₂ of 50% took between one and six HBOT sessions, with an average of five HBOT treatments per patient (41).

Although the majority of patients with Covid-19-related ARDS received NIV, the strategy of early intubation and IMV showed a better outcome in these patients than NIV. After 2 weeks of receiving IMV, 22% of patients were extubated, 47% underwent IMV and 31% died (50). There are contradictory results where early intubation and IMV could increase the mortality and prolonged extubation time of these patients (42). Until now, there is no precise consensus and the final decision is according to personal

assessment of the anesthesiologist. Clinical experience with in SARS-CoV-2 infection has shown that emergency tracheal intubation was more often necessary in male patients, aged 65 years or more, and those hypoxemic with $\text{SaO}_2 < 90\%$ (59). When hypoxemia is severe, with $\text{PaO}_2/\text{FIO}_2 \leq 200$ mmHg, intubation and IMV is the treatment of choice. The main goal of IMV in ARDS induced by SARS-CoV-2 is the avoidance of ventilator-induced lung injury, while facilitating gas exchange via lung-protective ventilation (60). Lung-protective ventilation might compensate diminished functional residual capacity in obese patients and improve oxygenation (61, 62). Lung-protective ventilation with low tidal volume $V_t \leq 6$ ml/kg, optimal PEEP (> 10 cm H₂O) and inspiratory airway pressure ≤ 30 cmH₂O has become a cornerstone of management in obese patients (39, 45, 63). Another method of lung protective ventilation in obese patients with ARDS might be the use of higher tidal volume (8 ml/kg), although it is still unclear whether tidal volume should be based on estimated or ideal body weight (64). Also, individualized PEEP titration to mean values of 18 cm H₂O, with electrical impedance tomography, could optimize end-expiratory lung volume (65). Higher inspiratory airway pressure could promote ventilator-induced lung injury and increase the risk of barotrauma. Therefore, more research is needed for better implementation of lung-protective ventilation in these patients. In the selected cases, recruitment manoeuvres and prone positioning may be required to counteract the onset of atelectasis in the dependent region of the lungs, but their use remain controversial (61, 66). In cases of severe ARDS with a $\text{PaO}_2/\text{FIO}_2 < 150$ mm Hg, prone positioning of the patients should be consistently done in at least 16 h intervals. From the aspect of ventilation, these patients need high PEEP and responded favourably to recruitment manoeuvres with

the application of inhalational nitro-oxide and muscle relaxants (67). Extracorporeal membrane oxygenation is reserved only for patients with the most severe ARDS, with some evidence that it might improve survival. This approach is considered as a rescue therapy if lung protective ventilation combined with lung recruitment manoeuvre, prone positioning and high-frequency oscillation ventilation shows no improvement (68, 69).

CONCLUSION

Obesity induce chronic low-grade inflammation and endothelial injury, increased expression of ACE2 receptors in adipose tissue and higher level of angiotensinogen II. Along with accompanying comorbidities, these factors make the obese patients vulnerable for the development of Covid-19-related ARDS and unfavourable outcome. The choice of oxygen therapy in obese patients should be based not only on the progress and severity of Covid-19, but also on their prior functional status. Non-invasive respiratory support alone or with prone positioning and hyperbaric oxygen therapy are recommended for cases with mild or moderate ARDS and for preventing or delaying intubation and invasive mechanical ventilation of Covid-19-related ARDS. Covid-19-related ARDS requires increased attention and the use of lung protective mechanical ventilation, with utilization of lower tidal volume and optimal positive end-expiratory pressure. Transition from mechanical ventilation to extracorporeal membrane oxygenation is reserved for patients with resistant ARDS. Optimal knowledge of physiology and comorbidities of obese patients with timely and adequately non-invasive respiratory support could improve the clinical outcome of these high-risk patients with SARS-CoV-2 induced ARDS.

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Teške respiratorne komplikacije kod gojaznih bolesnika sa SARS-CoV-2 virusnom infekcijom: karakteristike i oksigenoterapija

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SAŽETAK

Značajan procenat bolesnika primljenih u Jedinicu intenzivne nege tokom pandemije Covid-19, bili su gojazni bolesnici. Gojaznost je povezana sa hroničnom inflamacijom niskog stepena, većim stepenom endotelnog oštećenja i nivoom angiotenzinogena II, kao i povećanom ekspresijom receptora za angiotenzin konvertujući enzim 2 u masnom tkivu. Ove promene udružene sa komorbiditetima, čine gojazne bolesnike podložnijim za razvoj teških respiratornih komplikacija, uključujući i akutni respiratorni distres sindrom (ARDS), tokom SARS-CoV-2 infekcije. Izbor optimalnog načina isporuke kiseonika kod gojaznih bolesnika zavisi od njihovog funkcionalnog statusa i uznapređovalosti Covid-19 infekcije. Neinvazivna ventilacija i visoki protok kiseonika putem nosne kanile, potbušni položaj bolesnika i hiperbarični kiseonik, predstavljaju efikasne načine oksigenacije gojaznih bolesnika sa blažom ili umerenom formom ARDS. Ukoliko je mehanička ventilacija neophodna, primena protektivne ventilacije pluća sa manjim disajnim volumenom i optimalnim pozitivnim pritiskom na kraju ekspirijuma, od presudnog je značaja za lečenje SARS-CoV-2 uzrokovanog ARDS. Ekstrakorporalna membranska oksigenacija rezervisana je samo za bolesnike sa neadekvatnim odgovorom na prethodni mod ventilacije. Optimalno poznavanje patofizioloških promena gojaznosti i blagovremeno lečenje, uz adekvatnu primenu kiseonične terapije, može poboljšati klinički ishod ove osetljive grupe bolesnika.

Ključne reči: Covid-19, gojaznost, ARDS, oksigenoterapija, respiratorna potpora