

Obesity and COVID-19 infection severity: from pathophysiology to clinical implications

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Abstract

Obesity is a significant public health concern with higher morbidity. Obesity patients are at risk of severe COVID-19 infection and obesity is a higher risk factor for intensive Care Unit admission in COVID-19 infection. Obesity status affects lung volumes, cardiac structure and hemodynamics. Obesity is associated with a low inflammation state, endothelial dysfunction, hyperinsulinaemia and metabolic disorders. The authors review cardio-respiratory pathophysiological aspects involved in obesity and propose clinical management in obese patients infected by COVID-19.

Key Words: COVID-19; Obesity; BMI; heart; lung; severity

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Introduction

Obesity, defined by a body mass index (BMI) ≥ 30 kg/m², is a significant public health problem with higher morbidity and mortality (1). Obesity is also associated with early mortality (2, 3). Obesity affects not only adults but also adolescents with a prevalence estimated at 17% in childhood including adolescents in the USA (4). Moreover, the prevalence of obesity reaches up to 35% in adults (5). Obesity is associated with cardiovascular risk factors and events (6, 7). In parallel, obesity affects the respiratory system with a reduction of lung capacity and compliance (8). Obesity patients with COVID-19 are at higher risk of severe COVID-19 form and obesity is a higher risk factor for intensive care unit (ICU) admission (9, 10). In France, the prevalence of obesity reaches 25% in patients with severe COVID-19 (11), while the prevalence in the global population is estimated about 17% (12). In a study conducted in Michigan concerning 463 COVID-19 patients (39.7% required ICU admission), up to 58% of patients were obese (13). In another study in New York City, 46% of ICU patients with COVID-19 were obese (14). In ICU, severe COVID-19 is associated with higher mortality in obese patients (13, 15). Moreover, a severe obesity defined by a BMI ≥ 35 kg/m², was associated with ICU admission (OR=5.39) in a recent study conducted in the United States (16). Finally, obesity status may affect the renin angiotensin system and obesity is associated with endothelial dysfunction, hyperinsulinaemia and a low inflammation state (17, 18).

We aim to review the cardio-respiratory pathophysiological aspects involved in obesity and to propose clarifications in the clinical management of obese patients suffering from COVID-19 infection.

Heart and obesity

Obesity may induce diabetes mellitus, hypertension, insulin resistance and dyslipidemia, leading to an increased risk of cardiovascular disease (19). In addition, metabolic disorders are frequent in obesity and are associated with coronary microvascular impairment with a reduced coronary flow reserve, particularly in patients with diabetes and lipid profile abnormality (20). Patients with cardiovascular risk factors are at risk of severe COVID-19 infection with myocardial injury, acute coronary syndrome, arrhythmia, heart failure and microvascular thrombosis (21, 22, and 23). In addition, patients with COVID-19 infection may have alteration of the left ventricle and the right ventricle (24). Pulmonary hypertension may also be present in the context of COVID-19 infection (25). Myocardial abnormalities can be present, even after COVID-19 infection recovery, as previously shown (26, 27, and 28). Mechanisms involved in the onset of myocardial injury in the context of COVID-19 infection, are multiple and include hypoxemia, cytokines storm, microvascular thrombi, coronary plaque instability, systemic and vessels inflammation, myocarditis, sepsis related cardiomyopathy, stress-related cardiomyopathy and arrhythmia (29, 30, 31,32).

In the context of COVID-19 outbreak, clinical severity might be partially attributable to the underlying myocardial abnormalities in obese patients. From a mechanical point of view, obesity affects the left ventricular (LV) structure and function with the presence of subclinical myocardial impairments (33, 34). In fact, adaptive mechanisms occur in obese patients with an increase of several cardiac parameters: LV mass, stroke volume, cardiac output, and total and central blood volume (35, 36, 37). This hemodynamic changes may

lead to LV dilation and to the onset of eccentric LV hypertrophy (36, 37) (**figure 1**). In the multiethnic cohort study, obesity was found to be associated with LV concentric remodeling and Turkbey *et al* (34) found a positive association between an index of LV geometry (LV mass-to-LV end diastolic volume) and BMI. In fact, BMI is associated with LV tissue Doppler imaging velocities and global longitudinal strain features (33, 38). Diastolic function is also affected in patients with obesity with abnormal tissue Doppler velocities and decreased longitudinal strain (33, 38, and 39). Prevalence of diastolic dysfunction may reach 19% in obese patients (40). Furthermore, obesity affects left atrial (LA) size, LA reservoir and conduit (41) with a significant correlation between LA size and LV mass (42). In this context, obesity increases the risk of heart failure and the risk of atrial fibrillation (43, 44). In a long-term follow-up study (>20 years), that included 15,402 individuals, obesity was found to be significantly associated with cardiovascular hospital admissions and cardiovascular deaths (45). Right heart hemodynamics may also be impaired in severe obese state with an increased right atrial and pulmonary pressure (46). Obesity is also a risk factor for venous thromboembolism (47). Inversely, weight loss is associated with positive cardiac effects that included improvement of cardiac systolic and diastolic function and reductions of LV mass, of stroke volume, of filling pressures and of resting oxygen consumption (48, 49).

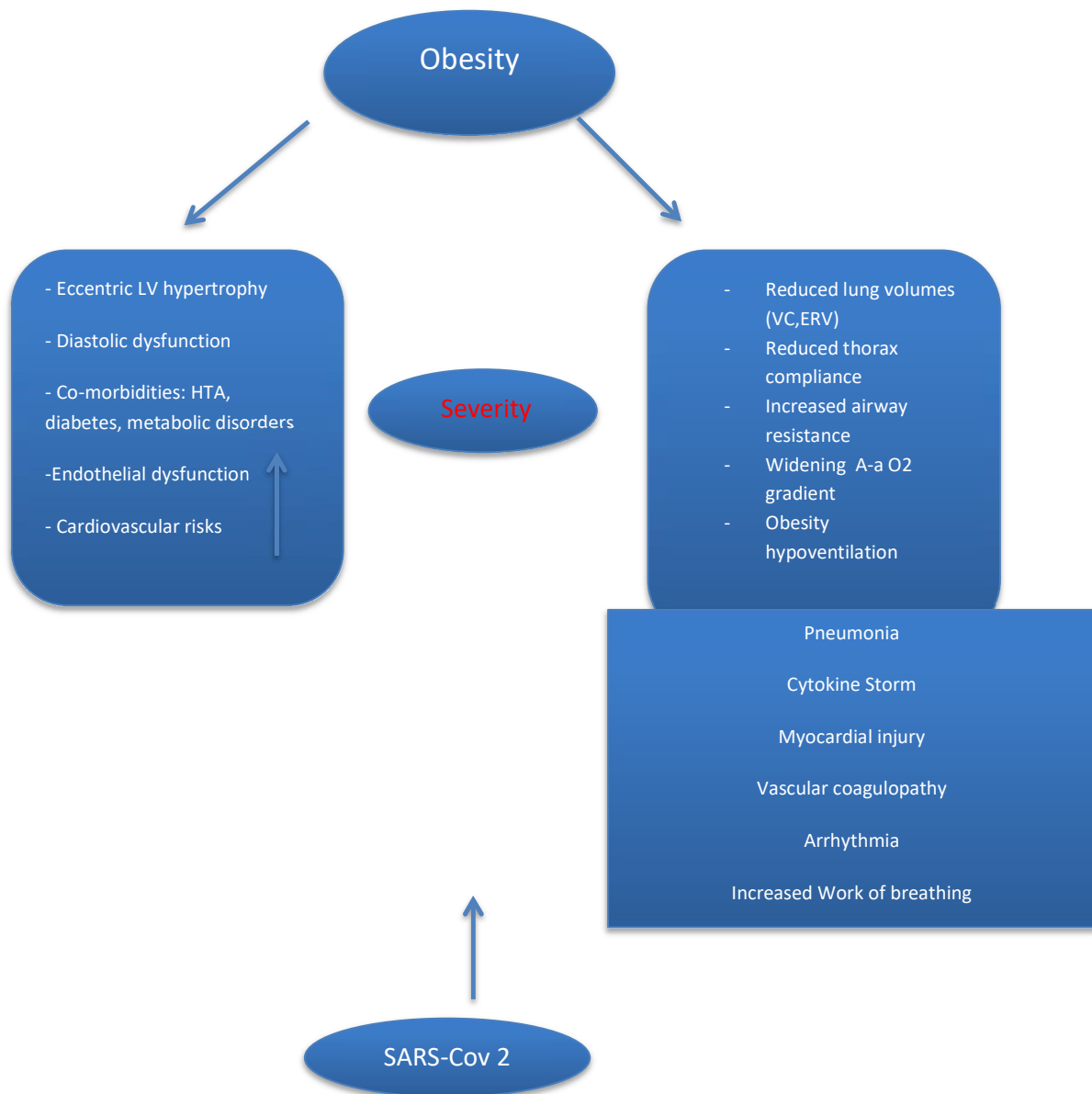


Figure 1: pathophysiological aspects in obese patients

HTA: hypertension; VC: vital capacity; ERV: expiratory reserve volume

Finally, abdominal obesity may have a high accuracy for predicting cardiac features rather than general obesity (50). In fact, an increase of abdominal obesity is associated with LV global longitudinal strain abnormalities and heart failure (39, 51). Abdominal obesity is frequently associated with dyslipidemia, low high-density lipoprotein cholesterol, increased triglycerides, apo lipoproteins B levels, insulin resistance, atherogenic abnormalities and abdominal adiposity is associated with cardiovascular disease (52). The **figure 1** summarizes pathophysiological aspect involved in obesity and covid-19.

Lung function and Obesity

COVID-19 infection affects particularly the lung with severe pneumonia and sometimes onset of acute respiratory distress syndrome (ARDS)(21, 23). The presence of heart failure, diabetes, a BMI>40 kg/m² and aging are factors associates with critical illness severity (15). SARS-CoV-2 has a high affinity for the lung *via* the ACE2 receptor present in respiratory epithelial cells (53). One can assume that the underlying lung function status may worsen clinical status in the context of obesity because of a decrease of lung compliance, a decrease of chest wall compliance (54) and the recumbency position worsen the respiratory compliance (55). In fact, in supine position, the reduction of the expiratory reserve volume (ERV) worsens, due to the ascending of the diaphragm within the thorax and causes a length-tension disadvantage for the diaphragm due to fibre overstretching (56).

Patients with obesity disclosed lower lung volumes that include reductions of forced vital capacity (VC), of forced expiratory volume in one second (FEV1), and of expiratory reserve volume (ERV) (8) (**figure 1**) . This is associated with an increase of airway resistance and an impairment of the upper airway mechanics (56, 57). Obese patients have to overcome this previous airway increase. Inspiratory time is also decreased with an increase of the respiratory rate (56, 58). Abdominal obesity is also associated with lung volume reduction with a negative association between forced vital capacity (FVC) and abdominal adiposity (59, 60).

In obese patients, the work of breathing is increased (57) and the diaphragm motion is impeded by the abdomen adipose tissue. The expiratory flow limitation leads to a dynamic hyperinflation, creating an auto-PEEP, in relation with the incomplete expiration (61, 62). Also, the strength of respiratory muscles is affected in obesity (63, 64). Finally, in the context of obesity, lung bases are under-ventilated but over-perfused, creating a ventilation-perfusion mismatch (65). In addition, obesity may be associated with a mild widening of the A-aO₂ gradient (66, 67). Hypoxemia and A-a O₂ gradient are correlated with ERV (56).

Obesity is also a risk factor for obstructive sleep apnea and obesity hypoventilation syndrome is frequent (68). Obstructive sleep apnea can cause cardiovascular features that include hypertension, endothelial dysfunction, metabolic disorders, arrhythmia and cardiac remodeling (69). Obesity hypoventilation syndrome (OHS) is defined by an increase of daytime PaCO₂>45mmHg, associated with sleep-related breathing disorders in patients with BMI≥30 kg/m², in the absence of known causes of hypoventilation (68). The prevalence of OHS has been reported to range between 8% and 20% in obese patients and the prevalence of hypertension reaches 55% to 88% (70). Other comorbidities associated with OHS are metabolic derangement, coronary artery disease and heart failure (70). One can assume that the presence of these previous comorbidities may worsen clinical status in obese patents in a context of COVID-19 infection.

Obesity, inflammation, Angiotensin 1-7 and COVID-19

Hyperinsulinaemia and endothelial dysfunction, frequent in obese patients, may lead to an activation of the renin angiotensin aldosterone system (RAAS) (17). This RAAS plays a key role in humans, controlling blood pressure, electrolyte balance and cardiac remodeling. The COVID-19 infects the host *via* ACE2 receptors that are membrane-bound amino peptidases receptors, present in many organs that include lung, heart, kidney, endothelial cells, and gut.

Adipose tissue expresses also ACE2 that catalyzes the conversion of angiotensin 2 to angiotensin (1-7), that displays an opposition to pro-inflammatory, vaso-constrictive and pro-atherosclerotic properties of angiotensin-2 (**figure 2**) (71,72). These properties involve the ACE2/ang-(1-7)/MAS axis, MAS being a G protein-coupled receptor for angiotensin (1-7) (**figure 2**). Dysfunction of MAS can lead to endothelial dysfunction, hypertension, thrombosis and metabolic syndrome like state (73). In the context of COVID-19 infection, angiotensin (1-7) production can decrease in patients, contribution to clinical severity (74).

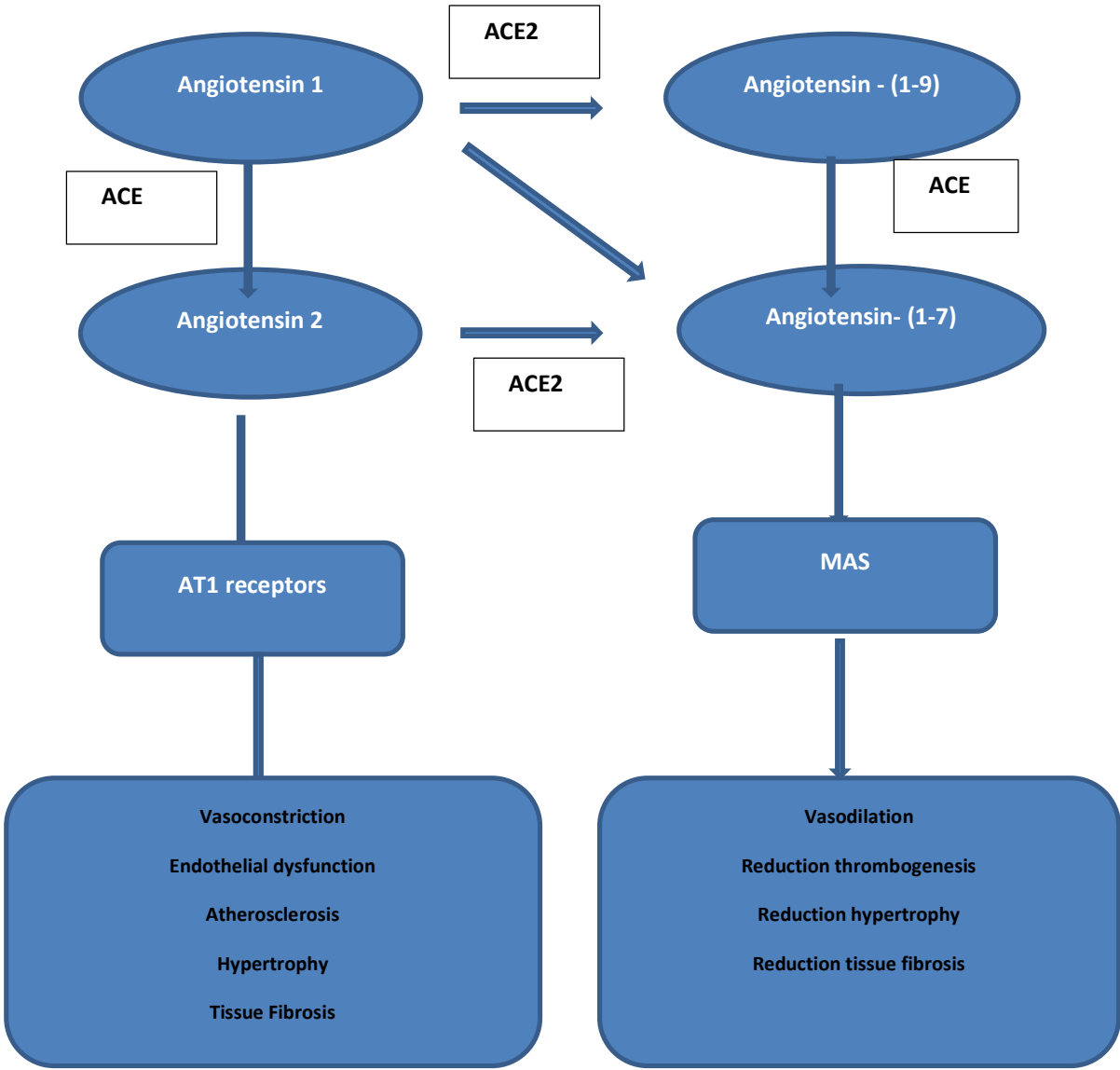


Figure 2: Renin angiotensin system and angiotensin-(1-7)/Mas axis

ACE2: angiotensin converting enzyme type 2

Adipose tissue may play also a role in COVID-19 infection. In fact, adipocytes seem to be significant targets for SARS-CoV-2 entry *via* ACE2 receptors and might play a role as a viral reservoir (75, 76, and 77). In addition, adipokines, secreted by adipocytes, may interplay in the inflammatory pathway and in metabolism in the context of obesity. Adipokine and interleukin 6 (IL6) are increased in obesity (78). Leptin, involved in food intake, is increased in obese patients (79), whereas adiponectin is reduced. Insulin resistance, which can be assessed by the ratio leptin/adiponectin, might be a potential link between COVID-19 infection and clinical severity in obese patients (80). In addition, immunological system is over activated with an inflammatory state and a cytokine release syndrome in COVID-19 patients (18). In fact, patients with COVID 19 display a high level of IL6, significantly associated with disease severity (81). Deceased patients with COVID-19 disclosed higher concentrations of IL6, interleukin 8, interleukin 10 and tumor necrosis factor (TNF) *alpha* (82). Finally, a low-grade chronic inflammation is present in obese patients, in relation with adipose tissue dysfunction (83). In the context of COVID-19 infection, an exaggerated – adipose tissue lipolysis may occur, in response to the production of pro-inflammatory cytokines (83).

Clinical implications in the management of obese COVID- 19 patients

In addition with classical tools used to stratify patients (CURB-69), BMI should be mentioned in the managements of COVID-19 pneumonia patients. Cardiorespiratory monitoring should be mandatory.

Regarding the respiratory system, it may be useful to avoid supine position. In the context of COVID-19 infection, an imbalance between the demand on the respiratory muscles and their capacity to generate tension may worsen respiratory symptoms in obese patients (84). In addition, since the rest gradient A-a O₂ is mild widening and because the gradient A-a O₂ is associated with pneumonia severity (85), one may expect that obese COVID patients experienced severe gradient A-a O₂. Furthermore, the onset of thrombo-embolism events can be higher on obese patients with COVID-19 since obesity state and COVID-19 are two risk factors for thromboembolic events (86, 87). In this context, anticoagulation should be used particularly in obese patients to avoid thrombo-embolic events.

Regarding the cardiac system, cardiac comorbidities are often present in obese patients. One should focus on cardiac function, particularly the diastolic function in the context of COVID-19 pneumonia. Global longitudinal strain can be affected in COVID-19 infected patients (**figure 3**). Risk factors associated with diastolic dysfunction are classically age, hypertension, obesity, coronary disease, and arrhythmia and kidney disease (88). Cardiac biomarkers and electrocardiogram should be performed and monitored to stratify patients and to search for eventual cardiovascular complications (32, 89,90), since these parameters affects prognosis (21,22). Echocardiography that must be performed with health worker protection's measures can help to stratify patients focusing on LV geometric, LV function, diastolic function, RV function and pulmonary pressures.

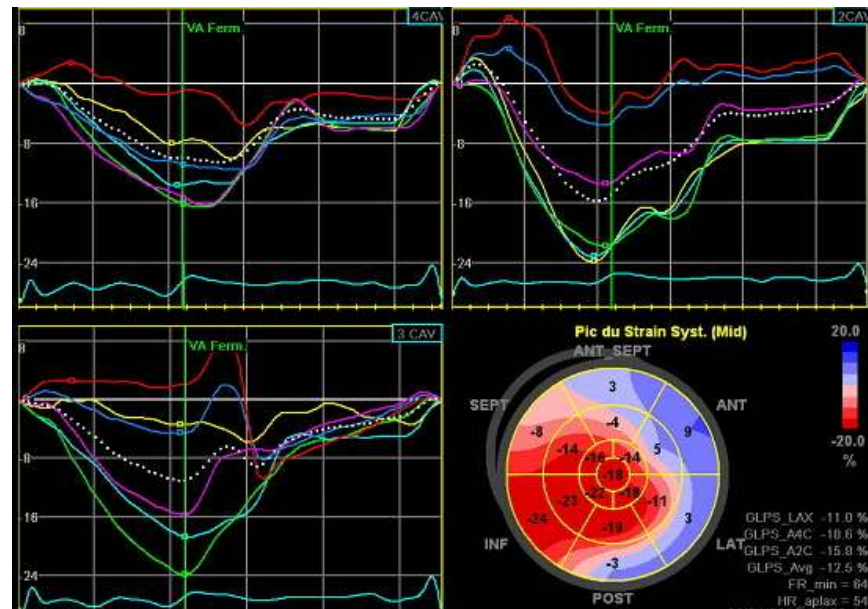


Figure 3: 2D strain echocardiography in a COVID-19 patient

Note the reduced left ventricular global longitudinal strain

In critically ill obese patients, difficulties in the airway management during the induction-intubation phase must be anticipated. Regarding ventilation setting, tidal volume should be adapted using the predicted body weight (91). These patients are at high risk of atelectasis during anesthesia in supine position (92). In fact, during anesthesia, in supine position, the large abdominal adipose tissue leads to a cranial displacement of the diaphragm that can contribute to the onset of atelectasis (92). Positive end expiratory pressure (PEEP), that prevents atelectasis and that is also used in patients on ARDS, should be adapted, since PEEP can cause hemodynamic impairment, right ventricle dysfunction (**figure 4**) and can impede venous return (93).

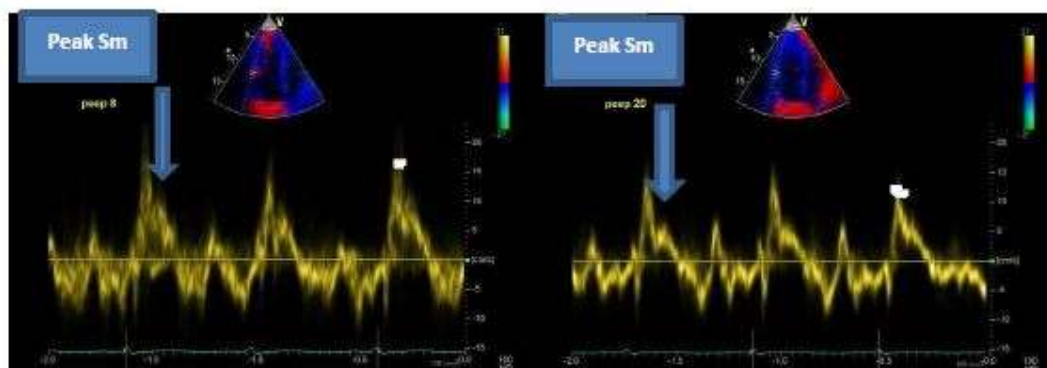


Figure 4: Right ventricular function analysis using Tissue Doppler imaging (Doppler-Echocardiography) in a COVID-19 ARDS patient on mechanical ventilation

Note the significant reduction of the peak right ventricle peak Sm velocity, depending on PEEP level (from PEEP 8 cmH2O to PEEP 20 cmH2O); ARDS: Acute respiratory distress syndrome; PEEP: positive end expiratory pressure

Monitoring plateau pressure and driving pressure is crucial, in addition with the search for the presence of intrinsic PEEP in patients on mechanical ventilation (91). In fact, during mechanical ventilation, monitoring trans-pulmonary pressure, that is the difference between alveolar pressure and pleural pressure, can be useful to adapt ventilation setting and to avoid lung collapse (92).

Patients with severe ARDS experienced long ICU length of stay. This parameter is known to affect diaphragm function and mass (94). Since respiratory muscles inspiratory strength may be affected in obese patients, one may expect to have severe diaphragm function dysfunction in obese COVID-19 and a longer ICU length of stay. Diaphragm ultrasound can be used to assess and follow diaphragm function in this context (**figure 5**). Diaphragm dysfunction is a classical cause of respiratory related weaning failure. This diaphragm dysfunction can be evaluated using ultrasound by measuring diaphragm thickening and/or diaphragm motion during a spontaneous breathing trial (**figure**) (95, 96).

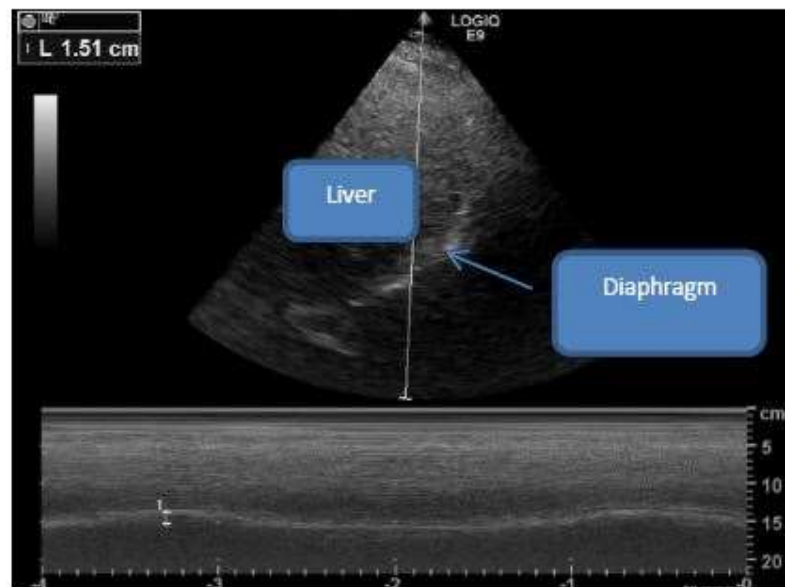


Figure 5: Right diaphragmatic motion using ultrasound in COVID - 19 patient with obesity

Physicians must be vigilant in this population during weaning process. In fact, weaning failure is associated with an increase of morbidity, nosocomial pneumonia, severity outcomes and mortality (97, 98). Weaning failure may be due to heart failure, respiratory muscle weakness, and sepsis. Echocardiography should be done, searching for left ventricular impairment, left ventricular diastolic dysfunction, combined to diaphragm ultrasound (99, 100).

Diastolic dysfunction is relatively frequent in critically ill patients, in the context of sepsis and myocardial ischemia (101, 102). Diastolic dysfunction is a classical cause of weaning failure in ICU patients (103, 104). Liu *et al* (105) reported an incidence of weaning failure reaching 45% (among them, 59% of weaning-induced pulmonary edema). Risk factors of weaning - induced pulmonary edema are obesity, previous cardiopathy and COPD (105).

In fact, during the weaning process, the shift from mechanical ventilation to spontaneous breathing induces a negative intra thoracic pressure that can affect cardiac function (95, 106). This negative intra-thoracic pressure caused by the transition from mechanical ventilation to spontaneous breathing, increases venous return, left ventricular afterload and may cause ischemia, as reported initially by Lemaire *et al* (107). In addition, adrenergic tone increases during spontaneous breathing trial (107) and myocardial oxygen demand increases (108). Physicians should be careful in the context of COVID, since myocardial ischemia and myocardial injury are frequent in critically ill COVID-19 patients (109) and myocardial ischemia can occur during weaning process in ICU patients (110). Plasma BNP level and plasma BNP variation during a spontaneous breathing trial can be used to predict weaning failure (111). Finally, COPD can be associated with obesity (112). COPD patients are at risk of weaning failure. In fact, in COPD, a high negative intra-thoracic pressure is necessary to generate tidal volume, since COPD is associated with airway obstruction. During weaning trial, this phenomenon increases the work of breathing, the venous return, the LV afterload and can induce RV dilation by an increase of RV afterload (112). All these previous pathophysiological aspects may explain the relative higher critically illness in ICU obese patients.

Conclusion

Obesity is acknowledged to be a factor of severe COVID-19 presentation, which requires attention by physicians in case of respiratory presentation. ICU physicians must be wary of the necessity of surveillance in the weaning process after intubation, because of a reduced muscle functionality and capacity. Cardiologists must be vigilant about the potential diastolic and systolic left ventricular dysfunction particularly in patients with cardiovascular risk factors and co morbidities.

Compliance with Ethical Standards:

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AF declares that he has no conflict of interest

MCDC declares that he has no conflict of interest

NM declares that he has no conflict of interest

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BD declares that he has no conflict of interest

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

Informed consent : not applicable

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