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ORIGINAL ARTICLE

COVID-19 SECTION

Application of average volume assured pressure support (AVAPS) and ultrasound assessment in COVID-19 infection: real-life observation

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ABSTRACT

BACKGROUND: ARDS in COVID-19 patients admitted to Emergency Departments (ED) is characterized by reduced diaphragm motility and increased work of breathing (WOB) by accessory respiratory muscles. Reduced perfusion of compliant lungs as consequence of vascular abnormalities has been highlighted as possible explanation of typical hypoxemia. Non-invasive mechanical ventilation (NIMV) has been proposed to treat ARDS. AVAPS is a hybrid modality of NIMV combining features of pressure and volume ventilation.

METHODS: we enrolled 38 patients with COVID-19 ARDS to whom we applied NIMV with AVAPS modality. We assessed Tidal Volume (TV), diaphragm excursion (DE) and PaO_2/FiO_2 before starting NIMV and after three (T3) and six hours (T6) of ventilation.

RESULTS: Admissions to ICU were avoided in 68% of our patients. TV (627±147.6 *vs.* 747.1±226 mL, P<0.00005) and DE (21.8±5.4 *vs.* 17.9±6.1 mm, P<0.00005) already improved after three hours of AVAPS. TV (521.5±120 mL, P<0.00005), DE (25.8±6.9 mm, P<0.00005) and PaO_2/FiO_2 (197.3±75.3 *vs.* 158±67.7, P<0.005) significantly improved in our cohort of patients after six hours.

CONCLUSIONS: NIMV with AVAPS modality can be confidently used in the clinical management of COVID-19 patients with ARDS, since AVAPS has positive effects on ventilation-perfusion matching and WOB. We recommend low PEEP value and ultrasound assessment of diaphragm motility and lung characteristics, although further studies are needed to individuate clinical features of NIMV best-responder patients.

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Patients with SARS-CoV-2 infection can develop coronavirus disease 2019 (COVID-19). Up to 8-15% of patients might develop severe illness including respiratory failure, acute respiratory distress syndrome (ARDS), multiple organ failure, and potentially death. Need for ventilatory support management requires hospitalization and Intensive Care Unit (ICU) admis-

sion.[1] Among those admitted to the ICU, mortality ranged from <14% to >66%, depending on patient-specific factors such as age, comorbidities and smoking habits.[2] Information about the clinical characteristics of infected patients who require intensive care is limited[3] and also guidance on the management of COVID-19 patients, including ventilatory support protocols, is lacking.[4] When respiratory distress and/or hypoxemia cannot be relieved after standard oxygen therapy, non-invasive mechanical ventilation (NIMV) treatment should be considered.

Another aspect of COVID-19 ARDS is proclivity to spontaneous efforts to breathe and development of severe diaphragm myopathy.[5] Activity of diaphragm is directly and negatively influenced by increasing driving pressure and controlled ventilator settings. Increase in diaphragm excursion (DE) has been associated with a decrease in arterial partial pressure of carbon dioxide ($PaCO_2$).[6]

Ultrasound is the method of choice in the investigation of suspected diaphragmatic movement abnormality[7] and can be excellently used to assess patient-ventilator interaction and weaning failure in critically ill patients.[8] In patients with *de-novo* ARDS under NIMV, large expiratory tidal volumes (ETV) may be generated in assisted pressure-controlled modes by the ventilator pressure and the one generated by the respiratory muscles.[9]

To our knowledge, in acute settings, the Average Volume Assured Pressure Support (AVAPS) has been successfully used in adults with Chronic Obstructive Pulmonary Disease (COPD) and severe hypercapnic encephalopathy, COPD and type II respiratory failure[10] as a result of either internal or surgical reasons.[11] AVAPS provides inspiratory positive airway pressure (IPAP) between maximum (Pmax) and minimum (Pmin) set values, according to the patient's inspiratory effort and TV. AVAPS mode showed more rapid and steady improvement of clinical parameters and less duration on NIMV,[12] facilitating rapid recovery in pH and $PaCO_2$ values compared to conventional BIPAP-ST mode[10] and showing positive effects also on patient comfort and need for sedation.[11] Based on this body of evidence and need to control both pressure and volume ventilation, we applied NIMV with AVAPS modality to a selected cohort of COVID-19 patients with the aim of minimizing ventilator-induced lung injury (VILI), ameliorating patient compliance to NIMV and improving ventilation of poor perfused but compliant lung regions.

TABLE I.—*Clinical features of patients enrolled in the study.*

Total	38
Male (%)	27 (71)
Female (%)	11 (29)
Age (y), mean±SD	69±13
Symptoms at ED admission (% of total)	
Fever only	7 (18)
Dyspnea with or without fever	31 (82)
Discharge areas (% of total)	
Infectious disease wards	7 (18)
Pneumological semi-intensive care unit	19 (50)
ICU	12 (32)

Materials and methods

Patient characteristics are detailed in Table I. Thirty-eight patients (27 men, 11 women, mean age 69±13 years) with ARDS as result of COVID-19 pneumonia were included in the study. Patients with a good response (*e.g.* increased in arterial oxygen saturation ($SatO_2$) and partial pressure of oxygen (PaO_2) and reduced dyspnea) to oxygen therapy with face-mask or nasal catheter and, on the other hand, those who presented severe ARDS needing endotracheal intubation (EI) were excluded from the study. All patients were evaluated (see below) at three different time points: baseline, three hours (T3) and six hours (T6) after starting NIMV.

SARS-CoV-2 and ARDS assessment

SARS-CoV-2 infection was confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs (Thermofisher [Waltham, MA, USA], Bosch [Gerlingen, Germany] and Seegene Kits [Seegene Technologies, Inc., Seoul, Korea]).

ARDS[13] was detected evaluating partial pressure of oxygen/oxygen concentration ratio (PaO2/FiO2) ≤300 on room air at rest state and respiratory distress was defined for respiratory rate (RR) ≥30 breaths/min, anomalies in blood gas analysis and in particular SatO2 <90%.

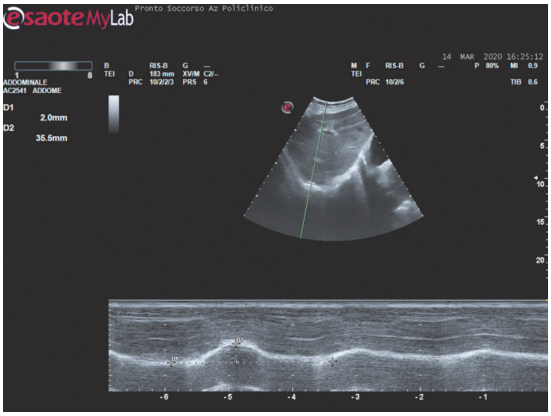

Figure 1—Ultrasound M-mode assessment of diaphragmatic excursion (D2 measurement).

Critical ultrasound

Critical ultrasound was used to detect lung interstitial changes, consolidation and DE. DE was measured with an abdominal probe (2-5 MHz) directed cranially and a small dorsal tilt, just below the right costal arch on the midclavicular line. Excursion was quantified in M-mode, with the M-line perpendicular to the direction of motion.[8] Value of excursion of 18±3 mm in men and 16±3 mm in women is considered normal during voluntary sniffing[14] and diaphragm weakness was diagnosed by an excursion <15 mm (Figure 1).

NIMV settings and parameters evaluation

Philips V60 Ventilator (Philips, Amsterdam, the Netherlands) was used with BIPAP - AVAPS mode setting. The ventilator parameters were adjusted with low levels of pressure as follows: positive end-expiratory pressure (PEEP) from 4 to 8 cmH_2O, Pmin from 8 to 12 cmH_2O and Pmax from 12 to 18 cmH_2O and Tidal Volume (TV): 4 to 6 mL/kg of predicted body weight. A total face mask was chosen for its easy fitting and application. If possible, according to patient's compliance, prone position ventilation was performed. If necessary, dexmedetomidine (0.2-1.4 mcg/kg/h) was used as sedative agent.

Basal DE and PaO_2/FiO_2 were measured before starting NIMV and basal TV after the first ten breaths after NIMV was started. Visualization of flow and pressure waveforms on ventilator display gave us useful information to evaluate if the settings chosen were right for each patient. Hemodynamic parameters and state of consciousness by Glasgow Coma Scale (GCS) were assessed and arterial blood gases were performed each hour. Worsening of overall reassessments and signs of NIMV failure represented an indication to modify NIMV parameters or to perform intubation.

Outcome

We evaluated clinical outcome of patients by assignment to areas of care at the discharge from Emergency Department (ED), distinguishing among infectious disease wards (low intensity of care, not needing for NIMV), pneumological sub-intensive unit (middle intensity of care, needing for NIMV) and ICU (needing for EI or NIMV with instable vital signs).

Statistical analysis

Analysis of the data and statistical significance was performed using Graph pad/Prism software. Student's *t*-test was performed and P value <0.05 were considered statistically significant.

For all the patients written and oral consent for the NIMV and the study was acquired and recorded in the patient's clinical file.

Results

After six hours of NIMV with AVAPS, 26 (68%) patients showed stable vital parameters. 7 (18%) of them did not require NIMV anymore and were transferred from ED to a low intensity care ward. 19 (50%) patients showed stable improvement in vital status and arterial blood gas analysis, so continued NIMV in pneumological sub-intensive unit. One patient was intubated after the first three hours of NIMV and other 11 patients were transferred to ICU after six hours of AVAPS since vital signs were not stable or ventilation parameters were not improving, or in consideration of their comorbidities and risk of worsening. Overall, 32% of patients were addressed to ICU (Table I).

In our sample, basal PaO_2/FiO_2 ranged from 68 to 319 (158±67.7). Increase in PaO_2/FiO_2 values was not statistically significative after three hours of NIMV (178.6±87, P>0.05), whereas it was at T6 (197.3±75.3, P<0.005) (Figure 2A).

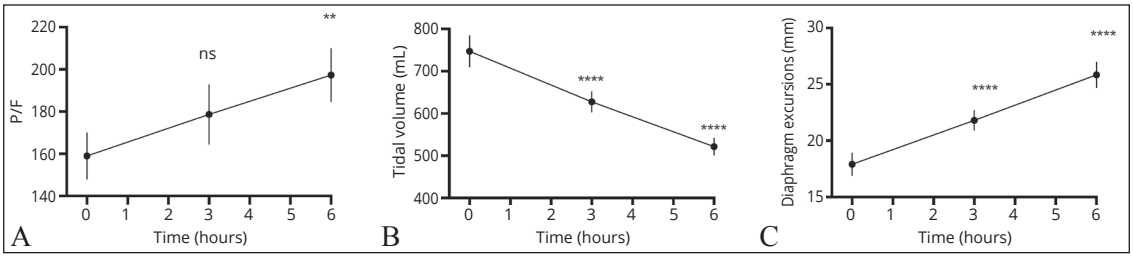

Figure 2.—PaO2/FiO2 (A), tidal Volume (B) and diaphragm excursion (C) measurement at the different time points. Error bars represent standard error of the mean (SEM).
Ns: non-significant.
**P<0.005, ****P<0.00005.

Mean basal TV was 747.1±226 mL. A significant reduction of TV was found both at T3 (627±147.6 mL, P<0.00005) and T6 (521.5±120 mL, P<0.00005) (Figure 2B).

All our patients had multifocal infiltration shadows, occasionally consolidation and pleural effusion, usually reduced diaphragm motion before starting NIMV, 50% of values being below 18 mm, and basal mean DE value being 17.9±6.1 mm. After three hours of NIMV, mean DE was 21.8±5.4 mm (P<0.00005) and after six hours was 25.8±6.9 mm (P<0.00005) (Figure 2C).

Discussion

COVID-19 clinical and biological heterogeneity contributes to the complexity of managing this syndrome. There are three levels that might influence NIMV success: the patient characteristics, the physician expertise and the device used.[7] SARS-CoV-2 pandemic has challenged physician due to overworking in low-resources settings taking care of patients with not well-known pathologic characteristics. As a consequence, also NIMV settings and its success have been challenging and general clinical practices involving ventilatory support lack uniformity, with limited use of standard protocols.[4]

AVAPS is a hybrid modality combining features of pressure and volume ventilation. It consists of an adaptative targeting scheme to adjust the inspiratory positive airway pressure (IPAP) to deliver a target TV. On the other hand, the warranted TV let us recruit collapsed alveolus, to control hyper-insufflation and to reduce death space. This reduces diaphragm fatigue and accessory respiratory muscles work of breathing (WOB). WOB can be a surrogate marker of compliance of the lungs and may serve as a useful clinical tool to assess failure of non-invasive respiratory support and progression to a typical ARDS lung. WOB is determined by the magnitude of pleural pressure swings and TV.[15] Palpation of the sternomastoid contraction, tracheal tug, inspection of the suprasternal fossa and intercostal spaces for recession and the presence of diaphoresis have been proposed as physical signs of WOB.[16] These are all signs of accessory respiratory muscles overworking and are common in COVID-19 critical patients[15] since the diaphragm, the main inspiratory muscle, compared with peripheral muscles, appears to be more affected by critical illness and mechanical ventilation.[17]

DE was used as indicator of reduced WOB of accessory muscles, since the last decreases when diaphragm motility increases and canonic assessment by esophageal pressure was not possible in our setting. PaO_2/FiO_2 was assessed to study the ventilation-perfusion matching. If PaO_2/FiO_2 significantly increases and RR decreases with a relatively low VT, the non-invasive strategy could be working, and intubation delayed.[9]

According to our results, AVAPS increases ventilation-perfusion matching, measured by PaO_2/FiO_2 values, through the application of warranted PEEP and variable IPAP. Moreover, ventilation with AVAPS modality increases DE and reduces WOB, since also TV is reduced.

Large observational studies suggest that patients with COVID-19-associated ARDS have similar respiratory system mechanics to patients with ARDS from other causes.[18] On the other hand, Gattinoni *et al*.[19] suggested that the loss of

lung perfusion regulation (*e.g.*, loss of pulmonary vasoconstriction or pulmonary emboli or thrombi) of poorly ventilated, but compliant, lung regions might be the main cause of hypoxemia in a subgroup of patients (the so-called L-type patients). For these reasons, L-type patients are more likely to respond to NIMV. Discrepancies between the severity of hypoxemia and relatively preserved respiratory system compliance, also suggest that severely abnormal ventilation-perfusion matching is a prominent feature in ARDS associated with COVID-19. Because the lungs appeared relatively open, they recommended a lower PEEP strategy. Higher PEEP can be harmful in patients with low recruitability, who have hypoxemia due largely to pulmonary vascular pathology. Furthermore, elevated pressures may cause excessive air leakage, asynchrony and patient discomfort[20] which increased risk of NIMV failure. For these reasons and on the base of our results, we recommend application of low PEEP in AVAPS modality to those patients with high compliant and low recruitability lungs. Therefore, individualization is needed because the response to PEEP might differ based on individual respiratory mechanics and lung injury characteristics. Furthermore, PEEP should be targeted to improve oxygen delivery while mitigating the risk of VILI and patient self-inflicted lung injury. Identifying patients who are good candidate to NIMV treatment and selecting the best ventilator settings to avoid EI is an incoming challenge.

We are testing ultrasound to screen patient lung characteristics since it has been proposed to identify patients with different disease severity classes and to choose the correct therapeutic strategies in ED and the subsequent adequate assignment to areas of care at different intensities.[21] Finally, AVAPS utilization not only reduces the need for EI but also the rate of ICU admission.

Conclusions

The AVAPS has positive effects on ventilation-perfusion matching and WOB and can be confidently used in clinical practice of COVID 19 patients and in particular for L-Type ones, in which we suggest lower PEEP value. The appropriate selection of patients, defining criteria to better individuate L-type patients is essential in this direction. Ultrasound might be useful to achieve this goal in ED. These observations provide promising avenues to pursue, since ventilatory support protocols are lacking. The ability of the team and patients to achieve a proper adaptation to the NIMV are crucial for its success, although close monitoring must be provided, since the patient's status might rapidly deteriorate, and EI performed promptly.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Lucilla Crudele has given substantial contribution to the study design and to the manuscript draft; Marcello Albanesi contributed to the data analysis; Paola De Luca gave contributions to the provision of ultrasound image; Vito Procacci has given contributions to the study design and supervision; Lucilla Crudele and Marcello Albanesi equally contributed to the manuscript draft. All authors read and approved the final version of the manuscript.

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