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Lung Recruitability of COVID-19 Pneumonia in Patients Undergoing Helmet CPAP

Reclutamiento alveolar en la neumonía por COVID-19 de pacientes tratados con sistema helmet-*CPAP*

Dear Editor,

COVID-19 pneumonia can result in acute hypoxemic respiratory failure (hARF) with the need of positive end-expiratory pressure (PEEP).[1] The application of a continuous positive airway pressure (CPAP) through a helmet improves oxygenation and reduces the risk of intubation compared to oxygen therapy in patients with severe hARF due to pneumonia.[2,3] The identification of the best PEEP for each individual COVID-19 patient undergoing helmet CPAP treatment is helpful to optimize lung recruitment and avoid complications related to over-distention.[4] We designed a feasibility study to evaluate the physiological effect in terms of lung recruitability of the application of different PEEP values in patients with hARF due to COVID-19 pneumonia undergoing helmet CPAP.

Consecutive adults (≥18 years) with hARF and with an indication for helmet CPAP treatment were enrolled in a pilot, feasibility study conducted at the COVID-19 high-dependency unit (HDU) of the Policlinico Hospital in Milan, Italy, between 19th March and 16th April 2020. Indications for helmet CPAP treatment included all the following: a diagnosis of pneumonia as the only cause of hARF and a partial arterial pressure of oxygen to fraction of inspired oxygen (PaO_2:FiO_2) ratio <300. The presence of other causes of hARF were excluded through clinical evaluations. Patients with at least one of the following criteria were excluded: need for immediate intubation, Glasgow Coma Scale <15, respiratory acidosis, and systolic blood pressure (SBP) <90 mmHg despite fluid resuscitation and/or use of vasopressors, swallowing disturbance with increasing risk of aspiration pneumonia, and inability to protect the airway. The Ethical Committees of the Policlinico hospital approved the study (No. 345_2020). All the patients underwent a standardized and non-invasive lung recruitability test (LRT) through the evaluation of vitals and blood gas analysis parameters every 30 minutes at different PEEP values (0–baseline-, 2.5, 5, 7.5, 10, 12.5, and 15 cmH_2O). Flow in the CPAP circuit was at least 80 L/min for each value of PEEP and FiO_2 delivered did not change during the trial. The primary endpoint was the rate of success and partial success of the LRT. Successful LTR was defined as the occurrence of all the following: (1) A decrease of the alveolar-arterial gradient ($A\text{-}aO_2$) of at least 20% compared to baseline; (2) Equal or reduced respiratory rate (RR) compared to baseline; (3) Absence of hemodynamic instability; (4) Equal or increase SpO_2 values compared to baseline; (5) Absence of patient's discomfort. Partial success of LTR was defined by all the criteria mentioned above but decrease of $A\text{-}aO_2$ less than 20%. Failure of LRT was defined as the occurrence of at least one of the following before reaching success criteria: (1) An increase in RR compared to baseline; (2) An increase of $A\text{-}aO_2$ compared to baseline; (3) hemodynamic instability; (4) SpO_2 <90%; (5) Respiratory distress; and (6) Patient's discomfort. No specific computations were carried out.

During the study period 87 patients were treated in COVID-19 HDU. 61 (71%) patients were treated with helmet CPAP, 15 (17%) patients with venturi mask oxygenation and 11 (13%) patients with high flow nasal cannulae oxygenation. Among the 34 patients [71% male; median (IQR) age: 63 (50-72) years] enrolled, the most prevalent comorbidities were systemic hypertension (42%), dyslipidemia (24%) and obesity (18%). All patients had hARF due to COVID-19 pneumonia and underwent helmet CPAP with a median (IQR) PaO_2:FiO_2 ratio of 177 (144–242) and $A\text{-}aO_2$ of 146 (121–234). LRT was successful in 9 (26.5%) patients: 1 at 5 cmH_2O, 1 at 7.5 cmH_2O, 5 at 10 cmH_2O, and 1 at 12.5 cmH_2O. Partial success of LRT occurred in 17 (50%) patients: 6 at 5 cmH_2O, 4 at 7.5 cmH_2O, 4 at 10 cmH_2O, 1 at 12.5 cmH_2O and 2 at 15 cmH_2O. LTR failed in 8 (23.5%) patients because of the occurrence of hemodynamic instability ($n = 5$, 14.7%), respiratory distress ($n = 1$, 2.9%), and increase in RR ($n = 2$, 5.9%). Baseline characteristics of the three groups are summarized in Table 1. There was a statistical significant difference in RR among the 3 groups ($p = 0.018$), in particular patients with a successful LTR showed higher baseline RR compared to LRT failure patients (30 [25–37] *versus* 21 [20–24] breaths per minute, $p = 0.004$). In patients with a successful LTR the median (IQR) decrease of $A\text{-}aO_2$ was 26% (22-35%), while in patients with a partial success LTR the median decrease of $A\text{-}aO_2$ was 10% (8–13%).

Although well-tolerated, only a small proportion of LRTs conducted in COVID-19 patients on helmet CPAP leads to a complete success, while a decrease of the $A\text{-}aO_2$ lead to a partially success in about half of patients. Furthermore, the median level of PEEP was highly variable among patients that fully or partially success. The $A\text{-}aO_2$ gradient was adopted as endpoint because of the COVID-19 pneumonia-related ARF. $A\text{-}aO_2$ gradient can better assess gas exchange dysfunction in comparison with PaO_2:FiO_2 ratio being some of the patients hypocapnic. Notably, 14.7% of the tests failed because of hemodynamic instability. Physicians should be aware of strict monitoring of blood pressure and cava collapse at ultrasound evaluation during LRT, especially in case higher levels of PEEP are adopted. This study has several limitations. First, it was designed as a purely physiologic study, without assessment of the potential impact of tests on clinical outcomes. Further randomized, control trials are needed to evaluate the efficacy LTR on clinically meaningful outcomes such as intubation and mortality. Second, someone could speculate that a 30-minute length of duration of each PEEP application is relatively short to assess improvement in oxygenation as a consequence of a stable reopening of atelectatic lung. Furthermore, the relatively low success rate might be mainly related to the complex pathophysiology of respiratory failure in COVID19 patients, where diffuse alveolar damage and diffuse endothelial damage leading to pulmonary intravascular coagulopathy with evidence of disseminated microthrombosis.

In conclusion, the identification of a positive physiological response to the application of PEEP during helmet CPAP treatment along with optimal levels of PEEP is of paramount importance among patients with hARF due to pneumonia in general and especially due to COVID-19. Our feasibility study paves the way for future clinical studies looking at a possible impact of LRT during helmet CPAP on clinically meaningful outcomes of COVID-19 patients.

Table 1
Baseline characteristics of the study population (data are presented as n [%] or medians [IQR: 25th–75th interquartile range]).

	LRT success ($n=9$)	LRT partially success ($n=17$)	LRT failure ($n=8$)	p value
Male	8 (88.9%)	11 (64.7%)	6 (62.5%)	0.370
Age, years	55 (45–68)	65 (52–70)	70 (53–79)	0.203
Comorbidities				
COPD	0	3 (17.6%)	1 (12.5%)	0.413
History of myocardial infarction	1 (11.1%)	2 (11.8%)	0	0.602
Transient ischemic attack/Stroke	2 (22.2%)	2 (11.8%)	1 (12.5%)	0.758
Systemic hypertension	4 (44.4%)	6 (35.3%)	4 (50%)	0.764
Diabetes	2 (22.2%)	3 (17.6%)	0	0.386
GERD	0	2 (11.8%)	1 (12.5%)	0.552
Dyslipidemia	4 (44.4%)	2 (11.8%)	2 (25%)	0.173
Obesity	0	5 (29.4%)	1 (12.5%)	0.158
Immunodeficiency	1 (11.1%)	1 (5.9%)	1 (12.5%)	0.829
Symptoms				
Fever (BT > 37 °C)	5 (55.6%)	12 (70.6%)	7 (87.5%)	0.353
Dyspnea	7 (77.8%)	11 (64.7%)	6 (75%)	0.747
Cough	6 (66.7%)	9 (52.9%)	5 (62.5%)	0.773
Asthenia	4 (44.4%)	9 (52.9%)	5 (62.5%)	0.758
Time from symptoms onset to LRT, days	12 (10–16)	15 (14–16)	16 (14–21)	0.090
Time from hospitalization to LRT, days	1 (0–6)	7 (4–9)	5 (1–11)	0.080
Radiology				
Normal	1 (11.1%)	0	0	0.239
Consolidation	1 (11.1%)	4 (23.5%)	2 (25%)	0.712
Interstitial	1 (11.1%)	3 (17.6%)	0	0.441
Interstitial and consolidation	6 (66.7%)	10 (58.8%)	6 (75%)	0.725
Vital parameters baseline				
Systolic Blood Pressure, mmHg	124 (120–154)	130 (116–149)	131 (119–155)	0.953
Diastolic Blood Pressure, mmHg	72 (65–78)	75 (66–77)	69 (65–79)	0.922
Heart rate, bpm	72 (71–93)	72 (63–91)	83 (80–88)	0.585
Respiratory rate, bpm	30 (25–37)	25 (20–30)	21 (20–24)	0.018*
SpO_2, %	95 (94–97)	94 (93–96)	94 (93–96)	0.585
Arterial-blood gas test				
pH	7.46 (7.38–7.47)	7.45 (7.44–7.48)	7.46 (7.43–7.51)	0.598
$PaCO_2$, mmHg	39 (33–41)	36 (35–38)	37 (33–42)	0.841
PaO_2, mmHg	79 (67–90)	72 (65–92)	79 (71–90)	0.812
PaO_2:FiO_2 ratio	176 (165–250)	176 (141–228)	218 (145–261)	0.811
A-aO_2	161 (124–205)	146 (129–245)	121 (105–225)	0.344
Lactate, mmol/l	0.9 (0.7–1.4)	1.3 (0.7–1.9)	1.1 (0.8–1.2)	0.458
FiO_2, %	37 (33–48)	40 (35–50)	36 (35–47)	0.317
Laboratory tests				
CRP, mg/dL	9.9 (5.8–20.4)	10.1 (7.6–15.4)	12.5 (10–21.5)	0.582
White blood cells count, 10^9/L	6.48 (5.82–10.07)	4.63 (2.91–6.07)	7.01 (5.87–8.8)	0.013**
Lymphocytes, 10^9/L	1.04 (0.59–1.31)	0.82 (0.62–1.35)	0.79 (0.73–1.06)	0.901
Neutrophils, 10^9/L	4.9 (4.3–8.57)	3.67 (2.19–4.45)	5.49 (4.44–7.55)	0.007***
Platelets, m/mm^3	211(186–348)	188 (131–289)	272 (234–308)	0.304
Hb, g/dL	12.9 (9.3–13.5)	12 (10.6–12.8)	12 (11.3–12.7)	0.317
Therapies				
Antibiotic	6 (66.7%)	14 (82.4%)	5 (62.5%)	0.497
Corticosteroid	4 (44.4%)	12 (70.6%)	2 (25%)	0.087
Hydroxychloroquine	6 (66.7%)	15 (88.2%)	5 (62.5%)	0.265

Abbreviations: COPD: chronic obstructive pulmonary disease, GERD: gastro-esophageal reflux disease, BT: body temperature, LRT: lung recruitment test, $PaCO_2$: partial pressure of arterial carbon dioxide, PaO_2: partial pressure of arterial oxygen, FiO_2: fractional inspired oxygen, A-aO_2: alveolar–arterial gradient of oxygen, CRP: C-reactive protein, Hb: hemoglobin.
Footnotes:
* LRT Success vs. LRT Partially Success $p=0.107$; LRT Success vs. LRT Failure $p=0.004$; LRT partially Success vs. LRT Failure $p=0.124$.
** LRT Success vs. LRT Partially Success $p=0.013$; LRT Success vs. LRT Failure $p=0.963$; LRT partially Success vs. LRT Failure $p=0.016$.
*** LRT Success vs. LRT Partially Success $p=0.004$; LRT Success vs. LRT Failure $p=0.673$; LRT partially Success vs. LRT Failure $p=0.016$.
A p-value <0.05 was defined as statistically significant.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

Prof. Aliberti reports grants and personal fees from Bayer Healthcare, grants and personal fees from Aradigm Corporation, grants and personal fees from Grifols, personal fees from Astra Zeneca, personal fees from Basilea, personal fees from Zambon, personal fees from Novartis, personal fees from Raptor, grants and personal fees from Chiesi, personal fees from Actavis UK Ltd, personal fees from Horizon, grants and personal fees from INSMED, outside the submitted work. Prof. Blasi reports grants and personal fees from astrazeneca, grants from bayer, grants and personal fees from chiesi, grants and personal fees from gsk, personal fees from guidotti, personal fees from grifols, grants and personal fees from insmed, personal fees from menarini, personal fees from mundipharma, personal fees from novartis, grants and personal fees from pfizer, personal fees from zambon, outside the submitted work.

Acknowledgments

We would like to acknowledge the support of all the respiratory fellows and consultants, nurses and respiratory physiotherapists of the COVID-19 high-dependency unit of the Policlinico Hospital in Milan.

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https://doi.org/10.1016/j.arbres.2020.09.017

Lung Ultrasound for Evaluation of COVID-19 in Children

Ecografía torácica para evaluar la COVID-19 en niños

Dear Editor,

Although the evidence is still limited, studies describing the course of SARS-COV-2 infection suggest that the disease is mild in children. Most frequent complication is pneumonia, which occurs between 30 and 80% of cases, eventually requiring hospitalization.[1–3] Pulmonary involvement has been described in children and adults in pauci or even asymptomatic patients, especially when computerized tomography (CT) is used. In fact, the sensitivity of CT has been suggested to be even higher than PCR for COVID-19 diagnosis, but is not justified in children.[4]

In recent years, point-of-care ultrasound (POCUS) is being increasingly used in pediatrics, as it is rapid, portable, repeatable, and non-ionizing. Specific patterns of lung ultrasound (LU) have shown to be useful in the differential diagnosis of pneumonia or acute bronchiolitis, with potential for prognosis.[5–7] First case series describing main ultrasound findings in children with confirmed COVID-19 pneumonia have been published recently, suggesting a pulmonary involvement similar to the one described in other viral infections.[8]

The aim of this study was to address the usefulness of point-of-care LU, performed by pediatricians, to address pulmonary involvement in children with symptoms considered possibly attributable to SARS-CoV-2, during the first pandemic wave in Madrid.

We performed a prospective observational cohort study, including patients that consulted with symptoms attributable to SARS-CoV-2 infection, from April to June 2020 at the Paediatrics Department of a tertiary hospital in Madrid. The study protocol was reviewed and accepted by the local Ethics Committee.

Patients below 18 years of age evaluated for fever and/or respiratory symptoms were eligible for inclusion in the study. Exclusion criteria were: chronic lung disease, congenital heart disease, immunodeficiency, and congenital or anatomical defects of the airway.

A LU was performed at the Emergency Room or within the first 24 h of admission, using an E-Cube I7 (Alpinion Medical Equipment) equipped with a 3–12 Hz lineal probe. Scans were performed by 4 pediatricians with ultrasonography experience, following a common systematic methodology including longitudinal and transversal sections collected on the anterior, lateral, and posterior chest wall, as previously described by Copetti et al.[9] Ultrasound findings included: lung sliding, more than 3 B-lines per intercostal space, confluent B-lines and subpleural consolidations. The presence of A lines and fewer than 3 B lines per intercostal space defined normality.

All patients were managed according to the current treatment protocol. Data were collected from the patients' medical records including all microbiological results, treatment and clinical outcome.

A total of 20 patients were included in this pilot study, with a median age of 5.2 years [IQR: 2.9–11.4], 65% were male. All patients were symptomatic, presenting with fever (80%), cough (55%), short of breathing (40%) and 45% were admitted for a median of 4.5 days [IQR:4–10]. Median duration of symptoms was 5 days [IQR: 2.5–8.5] and 25% of all patients needed oxygen support. SARS-CoV-2 infection was confirmed in 50% of patients either by PCR (42%) or by a positive serology (8%). In two cases, an alternate etiology was found (one mycoplasma, one metapneumovirus). No differences were found in epidemiological and clinical variables between COVID-19 confirmed and unconfirmed cases. Three cases (15%) were transferred to PICU without fatalities.

All but one patient had abnormalities on the chest X-ray, mostly ground glass opacities (35%), perihilar infiltrates (30%) and consolidations (30%), with no differences between the groups (Table 1). Three COVID-19 patients displayed a completely normal LU, vs. one in the comparison group. In all cases presenting with respiratory symptoms, LU revealed signs of lung involvement during COVID-19 infection. Ultrasound abnormalities were bilateral in 75% of cases in both groups. Pleural irregularities (50% anterior, 70% posterior), more than 3 B lines per intercostal space (uni or bilaterally) were present in 70% of cases, and consolidations in 30%, with no differences between groups. In total, six patients presented with consolidation bigger that 2 cm (three in each group). There was no pleural effusion in any. The presence of ultrasound abnormalities did not predict the need of supportive oxygen. Isolated, none of the ultrasound findings showed high sensitivity for COVID-19, and no particular ultrasound pattern characterized the infection.

In this pilot study in children screened with COVID-19 suspicion, ultrasound findings on admission did not show predictive ability for the identification of SARS-CoV-2 infection. The accuracy of point-of-care thorax ultrasound was comparable to chest X-ray in order to detect lung abnormalities in the context of SARS-Co-V infection, but findings were indistinguishable from other respiratory infections.

The accuracy of PCR for the diagnosis of SARS-Co-V infection seems to be lower in children compared to adult patients.[10] Chest X-ray is unspecific in most cases, and point of care ultrasound has been suggested as a promising tool by some pediatric studies.[8] The accuracy of LU in detecting pediatric pneumonia of any etiology has been extensively proven,[5,9,11] and the scarce data in the literature suggest that the accuracy in the context of