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modified. Post-market modification of valves from AMBU bags (AMBU Inc, Columbia, MD, USA) may be more susceptible to failure during use compared with our use of commercial pressure regulators (produced under ISO standards).

Our data do not cover the full range of clinical parameters. For our studies, inspiratory times were kept fixed, although in actual patients, inspiratory times may be intermittently adjusted. Furthermore, this scheme is not intended as a permanent solution for ventilating multiple patients, and should be used only with hospital administration approval and acknowledgement of the unique ethical considerations during a crisis (such as the COVID-19 pandemic).^{11,12} Although the COVID-19 pandemic inspired our designs, it may have utility in other mass casualty scenarios such as natural disasters, terrorist attacks, and battlefield medicine. Future versions should aim to extend to more than two patients per ventilator.

Declarations of interest

GWF is a consultant for and on the speaker's bureau of Edwards LifeSciences. All other authors have no conflicts to declare.

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Noninvasive ventilation for COVID-19-associated acute hypoxaemic respiratory failure: experience from a single centre

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Keywords: COVID-19; intensive care; mechanical ventilation; noninvasive ventilation; respiratory failure

Editor—In a minority of coronavirus disease 2019 (COVID-19) patients, severe acute hypoxaemic respiratory failure (AHRF) necessitates admission to an ICU for invasive mechanical ventilation with an associated mortality of >50%.^{1–3} Published cohorts suggest that noninvasive ventilation is a commonly used intervention in COVID-19-related AHRF^{4,5} although no formal evaluation has been reported in the setting of a clinical trial. It is uncertain whether noninvasive ventilation is beneficial or harmful for patients with COVID-19. Here, we report a single centre experience of the role of noninvasive ventilation in patients with respiratory failure associated with COVID-19.

We report an evaluation of the use of ventilatory support in a single academic medical centre (University Hospital Southampton NHS Foundation Trust) during the early phases of the COVID-19 pandemic within the UK. Ethical approval was obtained as part of the REACT observational study of COVID-19 (a longitudinal cohort study to facilitate better understanding and management of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] from admission to discharge across all levels of care): REC Reference; 17/NW/0632, SRB Reference Number; SRB0025. Informed consent was waived because of the study design. Consecutive patients diagnosed with COVID-19 based on laboratory reverse transcriptase polymerase chain reaction (RT-PCR) tests and with associated AHRF were assessed from hospital admission to establish suitability for invasive mechanical ventilation, noninvasive ventilation, or both in the event of severe respiratory failure. Indications for escalation of care to noninvasive ventilation/invasive mechanical ventilation were based on respiratory distress, gas exchange, other organ dysfunction, and the rate of change in their clinical condition. Patients who were candidates for escalation to invasive mechanical ventilation were admitted to the general ICU (Cohort 1). Patients in whom noninvasive ventilation was defined as the ceiling of ventilation care were admitted to a Level 2 area (Cohort 2). Data were collected from existing electronic hospital records, from the index patient (March 6, 2020) until 16.00 on May 14, 2020. For descriptive statistics, data were presented as median (25th–75th centiles) as variables were found to be non-normally distributed when assessed by the Kolmogorov–Smirnov test. A comparison of proportions was performed using the χ^2 test. Unadjusted univariate logistic regression was performed to obtain non-adjusted odds ratios and 95% confidence intervals for important variables.

A total of 586 confirmed COVID-19-positive patients were hospitalised during the study period, of whom 103 (17.6%) required noninvasive ventilation or invasive mechanical ventilation. Of these, 79 were admitted to the ICU to receive noninvasive ventilation or invasive mechanical ventilation (Cohort 1), and 24 were admitted to a separate Level 2 area for noninvasive ventilation support as a ceiling of ventilatory care (Cohort 2). Cohort 2 patients were older (median age 67 yr), more frail (median Rockwood clinical frailty scale of 6),⁶ had more comorbidities (median Charlson comorbidity index of

4),⁷ and were more hypoxic when care was escalated to noninvasive ventilation ([Table 1](#)).

Among Cohort 1 patients, 58/79 (73%) had an initial trial of noninvasive ventilation whilst 21/79 (27%) underwent immediate tracheal intubation (Group IMV alone). Among those patients who had an initial trial of noninvasive ventilation, 27/58 progressed to invasive mechanical ventilation (Group NIV+IMV) whereas 31/58 did not require subsequent invasive mechanical ventilation (Group NIV alone). Of note, 29/31 (94%) patients in Group NIV alone were discharged from hospital alive with the remaining 2/31 (6%) being alive in the ICU at the time of data collection. Of Cohort 2 patients, 4/24 (17%) were discharged from hospital alive whereas 20/24 (83%) died in hospital. In Group NIV+IMV, the median time to invasive mechanical ventilation was 17 h (4–31) and 55% failed within the first 24 h. For Group NIV alone, the median noninvasive ventilation duration was 3 days. The median age for patients in Group NIV alone was 50 yr compared with 57 yr in Group NIV+IMV. The clinical frailty scale, Charlson comorbidity index, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and sequential organ failure assessment (SOFA) score were similar between these two groups.

The only variable associated with risk of intubation was the admission SOFA score. In all patients who underwent a trial of noninvasive ventilation (Group NIV alone and Group NIV+IMV), univariate unadjusted logistic regression analysis showed increased SOFA scores on admission were associated with increased risk of tracheal intubation (odds ratio 2.4, 95% confidence interval 1.34–4.38, $P < 0.0001$). Among the patients eligible for escalation to invasive mechanical ventilation, the overall mortality was 9/61 (14%) patients with completed ICU episodes and 9/79 (11%) of all admitted patients including those remaining in the ICU. Overall, 23 patients (30%) remained hospitalised either in the ICU (20%) or on medical wards (10%), and 45 patients (57%) had been successfully discharged home. Two patients were transferred to another tertiary hospital for extracorporeal membrane oxygenation. Substantially higher mortality (83%) was noted among those patients who received noninvasive ventilation as ceiling of care.

Comparisons with published national critical care data for England, Wales, and Northern Ireland from the Intensive Care National Audit and Research Centre (ICNARC) provide interesting context to our data. It is important to emphasise that such comparisons are limited by the absence of comprehensive matching of the characteristics of our patients with those within the ICNARC dataset. APACHE-II and PaO₂/FiO₂ ratios for Cohort 1 (eligible for escalation to invasive mechanical ventilation) were similar to the ICNARC cohort. However, the use of basic respiratory support (noninvasive ventilation) was more common (73.4% for Cohort 1 vs 56.7% ICNARC).¹ In comparison with ICNARC mortality from completed episodes (discharged from hospital or dead) (3139/6860; 45.8%), there was a smaller proportion of deaths in all groups except for Cohort 2 (noninvasive ventilation as limit of ventilatory care):

Table 1 Patient characteristics and outcomes of all patients who received noninvasive and invasive ventilation. Data are presented as median (25th–75th centiles). All variables and scoring were performed at the time of the ICU admission. APACHE II, Acute Physiology and Chronic Health Evaluation II; ECMO, extracorporeal membrane oxygenation; IMV, invasive mechanical ventilation; INR, international normalised ratio; NIV, noninvasive ventilation; P_aO_2/FiO_2 , partial pressure of arterial oxygen to fraction of inspired oxygen ratio; SOFA, sequential organ failure assessment.

Patient characteristics and outcomes	Cohort 1 NIV only group (n=31)	Cohort 1 NIV+IMV group (n=27)	Cohort 1 IMV only group (n=21)	Cohort 2 NIV ceiling group (n=24)
Age (yr)	50 (45–60)	57 (50–64)	61 (18–65)	66 (54–72)
Female:Male	1:2	1:0.8	1:3.2	1:1.4
Symptomatic days before hospitalisation	7 (6–10)	9 (6.5–13)	5 (3–10)	4 (3–8)
Rockwood clinical frailty scale ⁶	2 (1–2)	2 (1–2.5)	2 (2–3)	6 (5–7)
Charlson comorbidity index ⁷	1 (0–2.5)	2 (1–3)	3 (1–3)	4 (3–7)
BMI >30 kg m ⁻² (%)	45	41	29	53
APACHE II	11 (8–12.5)	18 (13.0–24.5)	22 (15–25)	18 (16–20)
SOFA score	3 (4–3)	4 (3–6)	6 (4–8)	5 (4.5–6)
Worse P_aO_2/FiO_2 ratio at 24 h	17 (14.3–20.4)	13.9 (12.8–16.8)	15.3 (12.7–18.1)	10.1 (8.2–13.9)
Time (h) from hospitalisation to noninvasive ventilation initiation or intubation	18 (5–54)	1 (0–13)	1 (0–7)	26 (8–94)
Total noninvasive ventilation time (h)	72 (41–132)	17 (4–31)	N/A	44 (18–103)
Biochemical markers				
Creatinine (mM)	67 (60–90)	60 (48–91)	89 (74–142)	75 (57–125)
Bilirubin (mM)	11 (9–12.5)	13 (9–18)	9 (7–16)	11 (8–19)
White cell count (10 ⁹ L ⁻¹)	6.3 (5.3–10.8)	7.9 (5.7–13.4)	10.6 (8.1–12.6)	7 (4.6–9.9)
Lymphocytes (10 ⁹ L ⁻¹)	1 (0.8–1.4)	0.8 (0.6–1.0)	0.7 (0.6–1.1)	0.9 (0.5–1.0)
C-reactive protein (mg L ⁻¹)	120 (91–164)	158 (113–220)	179 (154–276)	118 (45–160)
INR	1.2 (1.1–1.2)	1.2 (1.1–1.3)	1.2 (1.1–1.4)	1.2 (1.1–1.3)
Ferritin (mg L ⁻¹)	1093 (451–2243)	1014 (542–1380)	754 (609–965)	326 (111–993)
Lactate dehydrogenase (U L ⁻¹)	888 (695–1332)	900 (752–1179)	1607 (1186–1884)	830 (488–1192)
Troponin (ng L ⁻¹)	9 (6–15)	13 (8–37)	64 (27–249)	18 (6–102)
D-Dimer (mg L ⁻¹)	420 (263–655)	540 (333–1057)	1677 (682–2884)	635 (364–1029)
Creatine kinase (U L ⁻¹)	242 (94–412)	109 (83–242)	247 (116–420)	91 (38–235)
Outcome (n [%])				
• Died	0 (0)	3 (11.1)	6 (28.6)	20 (83.3)
• Home	29 (93.5)	8 (29.6)	8 (38.1)	4 (16.7)
• Hospitalised (ICU)	2 (6.5)	9 (33.3)	5 (23.8)	0 (0)
• Hospitalised (ward)	0 (0)	5 (18.5)	2 (9.5)	0 (0)
• Transferred for ECMO	0 (0)	2 (7.4)	0 (0)	0 (0)

overall mortality 29/85 (34.1%); Cohort 1 mortality 9/61 (14.6%).¹

Despite the widespread use of noninvasive ventilation for the treatment of AHRF and acute respiratory distress syndrome, its utility in COVID-19 lung disease remains controversial.^{4,5,8} We report on 103 critically-ill patients with COVID-19 and moderate–severe hypoxaemic respiratory failure, including 24 patients who were offered noninvasive ventilation as a ceiling of ventilatory care. More than half of the patients eligible for escalation to invasive mechanical ventilation tolerated noninvasive ventilation well and avoided tracheal intubation at any time. Unsurprisingly, the mortality and clinical outcome of these patients were better than those patients who were subsequently intubated. In conclusion, noninvasive ventilation is a safe, feasible, and useful ventilatory strategy that may avoid the complications of tracheal intubation and ventilation in selected patients with COVID-19-associated respiratory failure. Our data from a single centre suggest that noninvasive ventilation has a role in the management of COVID-19-associated respiratory failure, but clarification of the nature of this role await the results of large RCTs. Patient selection, defining appropriate limits of care, and effective team working between critical care and respiratory specialists are important in the effective delivery of an integrated clinical ventilation strategy for COVID-19-associated respiratory failure.

Authors' contributions

Conception and design: AD, MG, SG, SF
 Data collection: AS, MN, MB, NA
 Manuscript preparation: AS, MB, AD, MG
 Critical revision of manuscript: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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Interdependence between elevated intra-abdominal, pleural, and airway opening pressure in severe acute respiratory distress syndrome with extracorporeal membrane oxygenation

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Keywords: airway opening pressure; ARDS; COVID-19; ECMO; SARS-CoV-2

Editor—Detection of airway opening pressure (AOP) above atmospheric pressure in patients with acute respiratory distress syndrome (ARDS) is a simple bedside measure with relevant physiological and clinical consequences.¹ Airway opening pressure is the threshold level for start of alveolar inflation, and when it is higher than externally set PEEP, undetected AOP can lead to overestimation of driving pressure² and to underestimation of the potential for lung recruitment.³ Several mechanisms contribute to the development of elevated AOP during ARDS, such as impaired surfactant.^{4,5} The recent coronavirus disease 2019 (COVID-19) pandemic led to a dramatic surge in intubated patients with ARDS admitted to intensive care.⁶ The number of patients, the stress on healthcare workers, and the need for careful isolation limited the ability to perform extensive clinical and physiological testing in these patients.⁷ We present here unique physiological measures on the interdependence between AOP, pleural pressure (P_{pl} , estimated from oesophageal pressure), and intra-abdominal pressure (IAP) obtained by standard bedside monitoring in a patient affected by COVID-19 ARDS fully supported by extracorporeal membrane oxygenation (ECMO). The institutional ethics board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy approved this study. The data used or analysed are available from the corresponding author on reasonable request.

A 46-yr-old intubated patient was admitted to the ICU of the Ospedale Maggiore Policlinico with a diagnosis of severe ARDS from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by reverse transcription–polymerase chain reaction. He had no comorbidities except for mild depressive state and obesity (BMI=32). After 8 days, oxygenation had not improved despite multiple sessions of prone positioning and administration of nitric oxide, and decreased compliance hindered application of protective mechanical ventilation. Thus, veno-venous ECMO was started through a femoral–femoral approach. Tidal volume (V_t) was reduced to keep driving pressure <14 cm H₂O and ventilatory frequency (VF) to 10 bpm with PEEP of 15 cm H₂O. Ten days later, respiratory conditions deteriorated further as a result of superinfection and alveolar bleeding, and a second ECMO system was added through a double-lumen jugular approach to produce peripheral oxygen saturation >80%. On ECMO Day 18, the patient developed abdominal compartment syndrome and oliguria. Possible causes included intestinal obstruction from opioid-induced constipation, hypoperfusion, or SARS-CoV-2 infection itself.^{8,9} The patient was ventilated on pressure-controlled mode, and as V_t became minimal (0.7 ml kg⁻¹ predicted body weight; [Supplementary Table S1](#)) in association with development of abdominal hypertension, we performed comprehensive bedside physiological measures to monitor the clinical evolution and confirm