Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Respiratory Medicine 185 (2021) 106481

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Short communication

Effects of non-invasive respiratory support on gas exchange and outcomes in COVID-19 outside the ICU

Ciara Gough [a,b,*,1], Michelle Casey [a,b,1], Thomas A. McCartan [a], Alessandro N. Franciosi [a], Derek Nash [d], Dominic Doyle [d], Neil Hyland [d], Grace Kavanagh [e], Sile Toland [f], Caleb Powell [f], Rhea O'Regan [g], Ruán Ó. Conluain [h], Garrett Greene [i], Grace Murray [a], Israa Fathi Hussein [a], Eoin Hunt [c], Fatma Gargoum [d], David Curran [e], Tidi Hassan [f], Liam Cormican [g], Richard W. Costello [a,b,1], Tom McEnery [c,1]

[a] Royal College of Surgeons in Ireland, Dublin, Ireland
[b] Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland
[c] Department of Respiratory Medicine, Mater Misericordiae University Hospital, Dublin, Ireland
[d] Department of Respiratory Medicine, University Hospital Galway, Ireland
[e] Department of Respiratory Medicine, Mercy Hospital, Cork, Galway, Ireland
[f] Department of Respiratory Medicine, Our Lady of Lourdes Hospital, Drogheda, Ireland
[g] Department of Respiratory and Sleep Medicine, James Connolly Memorial Hospital, Dublin, Ireland
[h] Trinity College Dublin, Ireland
[i] Department of Mathematics and Statistics, Royal College of Surgeons, Ireland

A B S T R A C T

Non-invasive respiratory support (NRS) outside of the ICU has played an important role in the management of COVID-19 pneumonia. There is little data to guide selection of NRS modality. We present outcomes of NRS outside the ICU and discuss the effects of NRS on gas exchange with implications for management.

1. Introduction

The SARS-CoV-2 pandemic has resulted in unprecedented demand on intensive care units (ICUs) [1]. Patients with COVID-19 related acute hypoxemic respiratory failure (AHRF) are frequently managed outside ICU [2], which data suggests is safe and may be necessary to conserve critical resources [3]. Use of non-invasive respiratory support (NRS) including high flow nasal cannulae (HFNC) and positive end-expiratory pressure (PEEP) may support oxygenation and avoid invasive mechanical ventilation (IMV) [4], allowing time for recovery. Selection of optimal modality remains unclear, with a need for reliable non-invasive bedside monitoring to recognise treatment failure and avoid delayed intubation.

In mechanically ventilated patients disease-course and effects on respiratory dynamics and gas exchange have been well described [5]. Comparatively little data is available for self-ventilating patients outside the ICU. Anecdotal observation of highly variable change in ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (P:F) following initiation of continuous positive airway pressure (CPAP), led us to suspect that a subgroup may respond better via known physiological effects of PEEP.

We hypothesised that analysis of gas exchange abnormalities prior to- and post-initiation of NRS (5 and 6 on the WHO Clinical Progression Scale respectively) could characterise a phenotype more likely to respond to greater PEEP afforded by CPAP. Our aims were to guide selection of optimal respiratory support modality and parameters for monitoring treatment outside the ICU.

2. Methods

We performed a longitudinal observational cohort study of consecutive patients admitted to 6 centres in Ireland in March and April 2020 with COVID-19 (confirmed by nasopharyngeal polymerase chain reaction for SARS-CoV-2) and a radiographic diagnosis of pneumonia causing AHRF (>4L/min oxygen to maintain peripheral O_2 saturation (SpO_2) above 92%). The study was approved by the National Research

* Corresponding author. 31 St Joseph's Square, Dublin, Ireland.
E-mail address: Ciaragough007@gmail.com (C. Gough).
[1] CG and MC share joint first authorship. TM and RWC share joint senior authorship.

https://doi.org/10.1016/j.rmed.2021.106481
Received 22 February 2021; Received in revised form 20 May 2021; Accepted 21 May 2021
Available online 25 May 2021

Ethics Board (ref 20-NREC-COV-001) and consent waived. CPAP was administered via face mask with minimum PEEP of 10cmH_2O. Flow rate for HFNC was capped at 30L/min, limiting PEEP to <3cmH_20. Data from first presentation to time of death, intubation or recovery was collected. We calculated P:F and SpO_2:FiO_2 (S:F) prior to initiation of CPAP or HFNC and within 24hrs.

3. Results

169 patients were included, with useable data in 164 (Table 1). 33.5% (55/164) had a do not resuscitate order (DNR), established at admission. 71.3% (117/164) received NRS, of whom 72.6% (85/117) received CPAP. Overall 45.9% (50/109) of individuals without DNR received IMV. Rates were similar across treatment groups (47.5%, 44.4% and 43.8% for CPAP, HFNC and COT respectively). There was no difference in time to intubation (median days (IQR) 2 (1–3.75) for CPAP, 3 (1-4) for HFNC and 1 (0–2.5) for COT, p = 0.29, Kruskall-Wallis) or number of days on IMV (data available for 35/50, median days 7 (3.5–10) for CPAP, 7 (2-20) for HFNC, 9 (7-11) for COT, p = 0.3). Mortality in those with a DNR order was 56.4% (31/55) and was similar across groups (57.7% for CPAP, 50% for HFNC, 60% for COT).

Table 1
Demographics, admission respiratory parameters and biomarkers for the entire group and according to oxygen delivery modality. Kruskal-Wallis test for continuous and Chi-square test for categorical variables. IQR, interquartile range. Cardiac disease includes heart failure and ischaemic heart disease. Respiratory disease includes COPD, asthma or interstitial lung disease.

	Total n = 164	Any CPAP n = 85	HFNC only n = 32	COT only n = 47
Demographics and Comorbidities				
Age, median (IQR), yrs	61.5 (50-74)	61 (51-73)	73 (56-93)	62 (48-75)
Male, %	50.9	43.4	51.6	60.9
BMI, median (IQR)	30 (27-35)	29.7 (27-34)	28.7 (25-35)	31.4 (23-38)
Rockwood Clinical Frailty Score, median (IQR)	3 (2-5)	3 (2-4)	4 (2-5)	3.5 (2-6)
Respiratory Disease, n (%)	47/134 (35.1)	23/73 (31.5)	8/22 (36.4)	16/39 (41)
Cardiac Disease, n (%)	40/134 (29.9)	21/73 (28.8)	5/22 (22.8)	14/39 (35.9)
Hypertension, n (%)	70/134 (52.2)	38/73 (52.1)	12/22 (54.5)	20/39 (51.3)
Diabetes, n (%)	27/134 (20.1)	10/73 (13.7)	5/22 (22.7)	12/39 (30.8)
DNR order, n (%)	55 (33.5)	26 (30.6)	14 (43.8)	15 (29.8)
Admission Respiratory Parameters				
Respiratory Rate, median (IQR)	24 (20-28)	24 (20-30)	22 (20-25)	22 (20-25)
PaO2, median (IQR), mmHg	60 (53.5–71.3)	60* (52.3–70.7)	63.8 (55.9–80.9)	66.8 (56.6–77.3)
PaCO2, median (IQR), mmHg	36 (31.5–37.5)	33.4 (30.4–37.8)	34.4 (29.5–44.6)	32.8 (29.3–37.1)
Initial P:F ratio, median (IQR)	207 (197.3–264)	191.3 (108–242.3)	183 (82.5–275.3)	286.5 (225–351.8)
Initial ROX score, median (IQR)	12.1 (8–16.3)	10.5 (7-14)	13.0 (10.2–17.4)	14.7 (10.5–18.3)
Admission Biomarkers				
CRP, median (IQR), mg/L	143 (66-247)	147 (78-238)	193 (84-270)	114 (45-252)
Ferritin, median (IQR), ng/mL	1044 (555-2026)	1130 (644-2074)	927 (534-927)	1032 (500-2023)
Dimer, median (IQR), mg/L	1.03 (0.65–2.03)	1.02 (0.65–1.78)	1.56 (0.67–4.68)	1.09 (0.62–1.93)
Lymphocytes, median (IQR), 10^9/L	0.795 (0.55–1.22)	0.79 (0.54–1.16)	0.8 (0.5–1.37)	0.76 (0.55–1.5)

Change in P:F ratio (ΔP:F) after transitioning between respiratory support modalities are demonstrated in Fig. 1. Transitioning from COT to CPAP was associated with ΔP:F of +79.4 mmHg (±15.7, P < 0.0001, Wilcoxon matched-pairs signed rank test). Changes in $PaCO_2$ were minimal (mean 36.8 ± 1.3 mmHg on COT/HFNC and 38 ± 1 mmHg after commencing CPAP). 17 of 49 patients initially treated with HFNC received 'rescue' CPAP, but this was not associated with significant change in P:F (mean + 29.4 ± 30.5 mmHg, P = 0.36). 10 (59%) of these individuals were subsequently intubated and two died.

For the non-DNR group ΔP:F within 24hrs of commencing CPAP or HFNC was compared according to subsequent requirement for IMV (Fig. 1B), and did not differ significantly. Greater improvement in P:F after initiation of CPAP did not correlate significantly with BMI, age, duration since symptom onset or biomarkers. Nadir P:F *was* correlated with IMV, with 59.3% of patients with P:F ≤ 150 mmHg subsequently intubated, compared to 15.3% with P:F nadir >150 mmHg (unadjusted risk ratio 8.06, 95% CI 3.88–16.78). The relationship of S:F to P:F was described by the equation SF = 1.167*P:F + 47.99 (p < 0.0001, R^2 0.76, Fig. 2A). An S:F cut-off of 225 had 88% sensitivity and specificity of 92% to determine P:F < 150 mmHg (area under the ROC curve 0.9476, Fig. 2B).

4. Discussion

Effects of CPAP include lung recruitment, preservation of pulmonary surfactant and redistribution of perfusion [6], whereas loss of surfactant, atelectasis and worsening V:Q mismatch/shunt have been implicated in COVID-19 AHRF [7]. WHO COVID-19 guidelines recommend CPAP in 'selected patients', however selection criteria are not defined [8]. RCT data suggest that non-invasive PEEP may reduce risk of IMV [9]. Though unlikely to modify the disease course, this may allow time for recovery to occur and aid resource allocation.

Increased BMI is associated with worse outcomes in COVID-19 and with increased lung atelectasis [10]. Contrary to our original hypothesis, elevated BMI was not associated with augmented response to PEEP/CPAP in our study. We did not identify a distinct 'PEEP/CPAP responder' phenotype and initial improvement in gas exchange was not associated with overall improved outcome. S:F correlated well with P:F ratio and offers a non-invasive method of assessing treatment response. S:F ratio <225 predicted P:F < 150 mmHg, which was associated with increased risk of intubation and may serve as a useful benchmark. Rates of IMV were similar across oxygen delivery groups but comparison is precluded by differences in disease severity. We did not observe increased duration of mechanical ventilation in patients intubated following treatment with CPAP.

Limitations of this study include its observational nature and lack of data on pharmacological treatment. Our study illustrates the effect of NRS on indices of gas exchange in COVID-19 AHRF. We believe that a trial of CPAP in those with more severe degree of shunt with careful bedside assessment of response is reasonable, albeit recognising that improvement in oxygenation within the first 24 h is not necessarily reassuring. S:F can be used in lieu of P:F, with a threshold of 225 prompting more intensive monitoring or escalation. Logistical and patient factors should be considered when starting NRS outside ICU, with bedside assessment of respiratory rate, pulse oximetry and work of breathing prioritised over routine arterial blood gas sampling.

Author contributions

CG, MC, AF, RWC and TMcE designed the study, co-ordinated data collection, analysed data and wrote the manuscript. TMcC, GG and RO'C analysed data and provided statistical input. All other authors co-ordinated data collection, provided editorial input and approved the final manuscript.

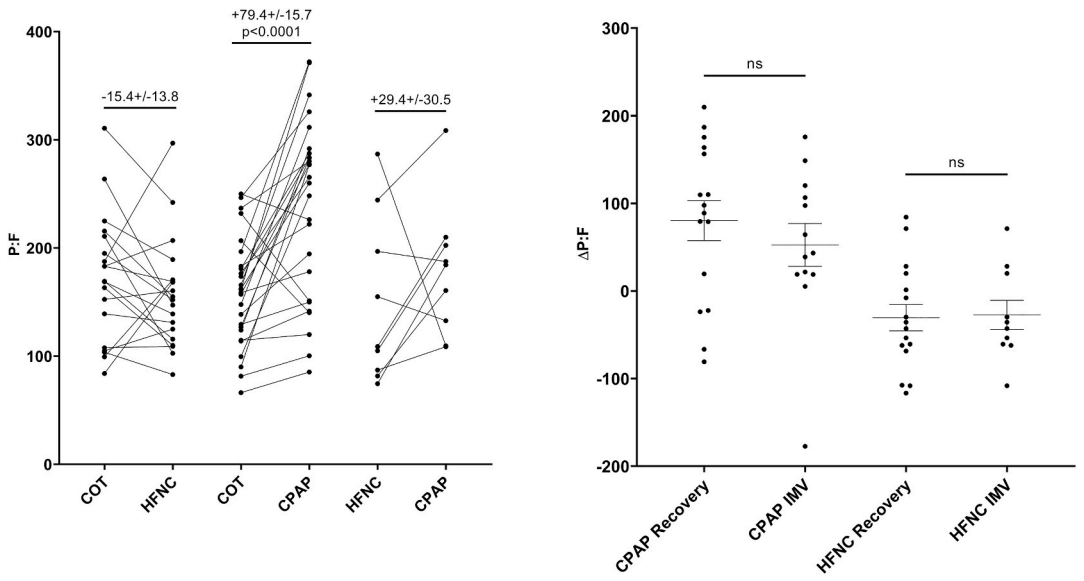

Fig. 1. A P:F ratios within 24hrs of transitioning between conventional oxygen and CPAP or HFNC (score of 5/moderate and 6/severe on the WHO Clinical Progression Scale respectively). Data normally distributed, mean change ± SEM, Wilcoxon matched-pairs signed rank test. Figure 1B ΔP:F within 24hrs of commencing CPAP or HFNC stratified according to subsequent intubation or recovery without IMV.

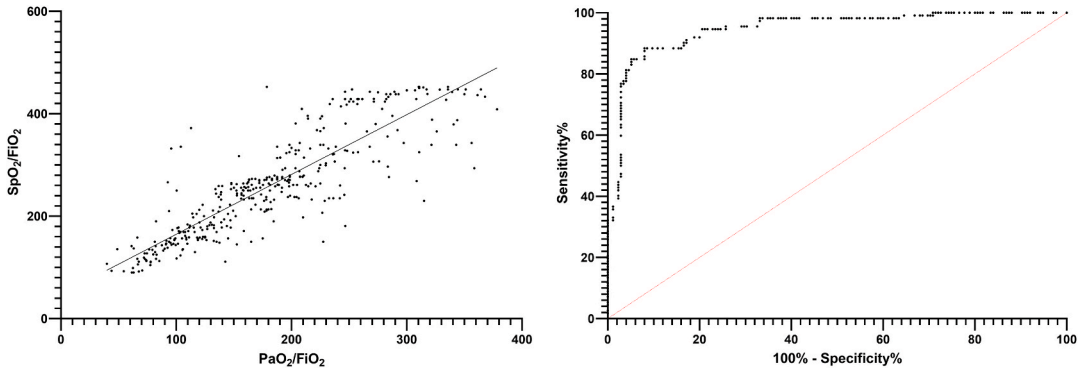

Fig. 2. A Simple linear regression of S:F and P:F (mmHg). Slope 1.167 (95% CI 1.106 to 1.229), S:F = 1.167*P:F + 47.99, R^2 0.76, $p < 0.0001$. Figure 2B Receiver operating characteristic (ROC) curve for S:F ratio to determine a P:F < 150 mmHg. Area under the curve 0.9476.

Credit author statement

CG: Conceptualization, methodology, investigation, writing – original draft, writing-review and editing. MC: Conceptualization, methodology, investigation, writing-original draft, writing-review and editing. TMcC: Methodology, formal analysis, writing-review and editing. AF: Methodology, investigation, writing-review and editing. DN, DD, NH, GK, ST, CP, RO'R, RO'C,GM, IFH: Investigation, resources. EH, FG, DC, TH, LC: Supervision, resources, investigation. GG: Supervision, formal analysis. RWC: Methodology, writing-review and editing, supervision and project administration. TMcE: Methodology, investigation, writing-original draft, writing-review and editing, formal analysis, visualisation, supervision and project administration.

Descriptor

Ventilation: Non-Invasive/Long-Term/Weaning.

Declaration of competing interest

No authors declare any competing interests relevant to the submitted work. No external funding was provided for this study.

RWC reports grants and personal fees from Aerogen, grants and personal fees from GSK, personal fees from Novartis, personal fees from TEVA, grants from Vitalograph, outside the submitted work. TMcE reports personal fees from Pfizer, outside the submitted work.

Acknowledgements

We would like to acknowledge colleagues who assisted with data collection, in particular Carol Buckley, Paula Hallahan, Lavinia McLeod, Lynn Fox, Ciara O'Grady, Claire Sheridan, Deirdre O'Flaherty, Catherine Geoghegan, Helen McCarthy, Deirdre Long, Claire Bolton and Dr Helen O'Brien.

References

[1] E. Tan, J. Song, A.M. Deane, M.P. Plummer, Global impact of coronavirus disease 2019 infection requiring admission to the ICU: a systematic review and meta-analysis, Chest 159 (2) (2020) 524–536, https://doi.org/10.1016/j.chest.2020.10.014.

[2] T. McEnery, C. Gough, R.W. Costello, COVID-19: respiratory support outside the intensive care unit, Lancet Respir Med 8 (2020) 538–539.

[3] C. Franco, N. Facciolongo, R. Tonelli, R. Dongilli, A. Vianello, et al., Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19 related pneumonia, Eur. Respir. J. 56 (5) (2020) 2002130, https://doi.org/10.1183/13993003.02130-2020.

[4] M. Oranger, J. Gonzalez-Bermejo, P. Dacosta-Noble, C. Llontop, et al., Continuous positive airway pressure to avoid intubation in SARS-CoV-2 pneumonia: a two-period retrospective case-control study, Eur. Respir. J. 56 (2) (2020).
[5] L. Gattinoni, D. Chiumello, P. Caironi, M. Busana, et al., COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 46 (2020) 1099–1102.
[6] N.R. MacIntyre, Physiologic effects of noninvasive ventilation, Respir. Care 64 (6) (2019) 617–628.
[7] P. Schousboe, L. Wiese, C. Heiring, H. Verder, et al., Assessment of pulmonary surfactant in COVID-19 patients, Crit. Care 24 (2020) 552.
[8] WHO: CLinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: interim guidance 28 January 2020.
[9] D.L. Grieco, L.S. Menga, M. Cesarano, T. Rosà, et al., COVID-ICU gemelli study group. Effect of helmet non-invasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial, J. Am. Med. Assoc. 325 (17) (2021 May 4) 1731–1743.
[10] A. Hussain, K. Mahawar, Z. Xia, W. Yang, et al., Obesity and mortality of COVID-19. Meta-analysis, Obes. Res. Clin. Pract. 14 (2020) 295–300.