Pulmonology Journal

volume 27 / number 5 / September/October 2021

PULMONOLOGY JOURNAL

Previously **Revista Portuguesa de Pneumologia**

volume 27 / number 5 / September/October 2021

Original articles

Special article

Reviews

ISSN 2531-0437

www.journalpulmonology.org

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

CSL Behring

PORTUGAL

DAATNEWS

NOTÍCIAS SOBRE A DEFICIÊNCIA DE ALFA1-ANTITRIPSINA

Newsletter sobre novidades em deficiência de Alfa1-antitripsina

Subscreva-se na *DAAT News* para estar a par das notícias mais relevantes **sobre Deficiência de Alfa1-Antitripsina.** Esta *newsletter* compila de forma trimestral as notícias mais relevantes nesta área publicadas recentemente em revistas de prestígio da especialidade.

Em cada edição, 4 artigos são comentados por médicos especialistas com vasta experiência no tratamento desta doença.

Coordenação Científica:

Dra. Joana Maria Lobo Gomes
MD, Departamento Pneumologia
Centro Hospitalar do Porto

Dra. Catarina Sofia Romano Gonçalves Guimarães
MD, Departamento Pneumologia
Hospital Senhora da Oliveira- Guimarães

Como fazer a subscrição?

Para poder disfrutar deste serviço basta registar-se na plataforma e começará a receber as seguintes edições da *Newsletter*

A subscrição pode ser feita de duas formas:

1. Acedendo ao formulário de registo neste serviço através da leitura do código QR
2. Inscrevendo-se através do link da nossa página web: **www.daatnews.pt**

Esperamos que este serviço que a **CSL Behring** lhe oferece seja do seu interesse.

Biotherapies for Life™ CSL Behring

Acesse diretamente através da leitura do código QR através do seu telemóvel

PRT-RPZ-0066

SPP SOCIEDADE PORTUGUESA DE PNEUMOLOGIA

www.sppneumologia.pt

Published every 2 months (6 issues per year).
www.journalpulmonology.org

Reprints information:
Clarissa Felix: c.felix@elsevier.com

Subscription of printed version available

One issue	30.00 € (VAT not included)
Anual	120.00 € (VAT not included)

(prices valid only for Portugal)

Subscriptions orders: sppneumologia@mail.telepac.pt

ELSEVIER
Av. Josep Tarradellas, 20-30, 1°
08029 Barcelona (Spain)
Phone: +34 932 000 711
Paseo de la Castellana, 163
28046 Madrid (Spain)
Phone: +34 914 021 212

Data protection: Elsevier España, S.L.U.. declares that it complies with that established by Organic Law 3/2018, of December 5, Protection of Personal Data and Guarantee of Digital Rights (LOPDGDD).

Indexed in: Science Citation Index Expanded (SCIE), Journal of Citation Reports (JCR), Index Medicus/MEDLINE, Scopus, EMBASE/Excerpt Medica
ISSN 2531-0437 (online)

Register 122.190 of Gabinete para os Meios de Comunicação Social

Printed in Spain
Printed in acid free paper
Legal deposit: B-20.760-2019

PULMONOLOGY

CK

The ClinicalKey Mobile App is here!

Leverage insights for better patient outcomes anytime, anywhere with the ClinicalKey mobile app – available for both Apple® and Android™ devices.

ClinicalKey helps clinicians rapidly access evidence-based, peer reviewed information to improve speed to accurate diagnosis and treatment, with the goal of improving patient outcomes and lowering the high cost of care.

Start your ClinicalKey mobile experience today!

- Open the App Store on your mobile device
- Search for "ClinicalKey" and install at no charge
- Once in the app, two options will appear – Click on ClinicalKey
- Enter your ClinicalKey username and password used for remote access and start using the ClinicalKey App!

Your institution must subscribe to ClinicalKey in order for you to use the app.
To sign up for a free 30-day trial, visit clinicalkey.com.au/info

Lead with answers.

ELSEVIER

PULMONOLOGY

www.journalpulmonology.org

Volume 27. Number 5. September-October 2021

CONTENTS

Letters to the Editor

Correspondence

Images

Pulmonology 27 (2021) 383—385

PULMONOLOGY

www.journalpulmonology.org

COMMENTARY

FeNO testing in severe asthma: A clinical argument or an access constraint?

Pedro Carreiro-Martins[a,b], Frederico S. Regateiro[c,d,e], Jorge Ferreira[f], José Luís Plácido[g], Rita Gerardo[h,i], Cláudia Loureiro[j,k,*]

[a] *Comprehensive Health Research Center (CHRC), NOVA Medical School, Lisbon, Portugal*
[b] *Immunoallergy Department, Hospital de Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal*
[c] *Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[d] *Institute of Immunology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*
[e] *Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal*
[f] *Pneumology Service, Hospital de São Sebastião - Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira, Portugal*
[g] *Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de S. João, Porto, Portugal*
[h] *Pneumology Unit, Hospital de Santa Marta, Centro Hospitalar e Universitário de Lisboa Central, Lisbon, Portugal*
[i] *NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal*
[j] *Pneumology Unit, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[k] *Centre of Pneumology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*

Received 9 April 2021; accepted 3 May 2021
Available online 14 June 2021

KEYWORDS
FeNO testing;
SEVERE ASTHMA;
Endotypes

Abbreviations

ATS — American Thoracic Society
FeNO —Fractional exhaled nitric oxide
GINA — Global Initiative for Asthma
ICS —Inhaled corticosteroids
IgE —Immunoglobin E
NICE — National Institute for Health and Care Excellence

* Corresponding author at: Pneumology Unit, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Praceta Professor Mota Pinto, 3004-561 Coimbra, Portugal.
E-mail address: cl_loureiro@hotmail.com (C. Loureiro).

Text

Asthma is one of the most common chronic diseases, causing significant burden to healthcare systems and societies.[1] The prevalence of asthma is increasing in many countries, especially among children. In Portugal, asthma affects 6,8% of the population.[2]

Severe asthma, according to the Global Initiative for Asthma (GINA), is a subset of difficult-to-treat asthma, defined as "asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased".[3,4] Severe asthma affects approximately 5—10%

https://doi.org/10.1016/j.pulmoe.2021.05.002

of asthma patients and is associated with increased morbidity, risk of hospitalization from exacerbations, mortality, and related healthcare costs.[5]

Type 2 inflammation-driven asthma (type 2 asthma) is mediated by type 2 cytokines (e.g. IL-4, IL-5, IL-13) and is very heterogeneous in nature.[3] Type 2 asthma is present in most asthmatic children and about 50% of asthmatic adults.[6,7] There is a high proportion of type 2 asthma among patients with severe asthma. Type 2 asthma is usually associated with increased eosinophilic inflammation, raised serum immunoglobin E (IgE) and raised fractional exhaled nitric oxide (FeNO) levels. Because Type 2 inflammation results from complex pathophysiologic mechanisms involving both innate and cellular immunity, the criteria to define type 2 asthma is still a matter of debate. According to GINA, either refractory or underlying type 2 inflammation should be considered if: (i) blood eosinophils $\geq$150/μl, and/or (ii) FeNO $\geq$20ppb, and/or (iii) sputum eosinophils $\geq$2%, and/or (iv) asthma is clinically allergen-driven.[3]

All guidelines recommend the use of biomarkers, such as FeNO, IgE or blood eosinophil counts, to characterize severe asthma, although there is still disagreement regarding the cut-off values.[3,8,9] Biomarkers are important tools to classify asthma patients into phenotypes. Asthma phenotypes do not define asthma severity, as the correlation between biomarker levels and disease severity is limited, and, for some uncontrolled patients, there are no detectable changes in biomarker levels. However, biomarker-based phenotyping of asthma patients, in association with detailed clinical evaluation, is essential for the proper characterization of the patient and to define the most appropriate therapeutic strategy. This is particularly important considering the high proportion of uncontrolled asthma patients in many countries, including Portugal.

Nitric oxide is a key modulator of immune responses and is overproduced in the airways of type 2 asthma patients. FeNO levels have long been recognized as a valid biomarker for the clinical management of severe asthma, not only for the phenotypic characterization of the disease, but also for assessing the disease evolution and treatment strategies.[3,8,10] FeNO levels are particularly useful as a diagnostic tool in ICS-naïve patients, to monitor patient compliance with treatment, and are good predictors of response to ICS, asthma exacerbations and decline of lung function.[11] In particular, the combination of elevated FeNO levels and an elevated blood eosinophil count is a good indicator of the higher exacerbation burden in severe asthma.[12] FeNO levels are also useful to monitor and guide the therapeutic strategy, and to predict the responsiveness to some biological therapies.[13] In short, FeNO evaluation is a low-cost, non-invasive procedure that is useful as a surrogate biomarker for the assessment and management of severe asthma. Therefore, the routine use of FeNO testing can play an important role in effective asthma control.

Interpreting FeNO levels is not straightforward as there are many possible underlying causes for variations in FeNO levels: smoking habits, diet, respiratory tract infections, time of day, height, gender, age, etc.[11] This precludes the use of this biomarker alone to define type 2 severe asthma and most specialists rely on several biomarkers simultaneously in endotype assessment. FeNO levels are easier to interpret when very high levels are observed.

In Portugal, biomarker-based asthma phenotyping assays are reimbursed by the public national health service. However, FeNO testing is not reimbursed by private insurance companies. In addition, FeNO testing is not available at all

Table 1 Summary of the answers to the online survey regarding FeNO testing clinical practice in Portugal.

Question	Answers			
		Immunoallergology panel (n = 18)	Pneumology panel (n = 12)	Total (n = 30)
Is FeNO typing a routine procedure, in your hospital/center?	Yes	9 (50.0%)	3 (25.0%)	12 (40.0%)
	No	9 (50.0%)	9 (75.0%)	18 (60.0%)
	Total	18	12	30
If yes to question 1, do you use FeNO typing for all asthma patients?	Yes	6 (66.7%)	2 (66.7%)	8 (66.7%)
	No	3 (33.3%)	1 (33.3%)	4 (33.3%)
	Total	9	3	12
If yes to question 2, for what purpose?	Diagnostic & monitoring	0 (0.0%)	1 (50.0%)	1 (12.5%)
	Monitoring only	6 (100.0%)	1 (50.0%)	7 (87.5%)
If no to question 1, why not?	No apparatus available	8 (88.9%)	8 (88.9%)	16 (88.9%)
	No technician available	1 (11.1%)	0 (0.0%)	1 (5.6%)
	Lack of consumables	0 (0.0%)	1 (11.1%)	1 (5.6%)

Note: A panel of immunoallergologists and pulmonologists was informally invited to answer an online survey in order to assess the clinical practice of FeNO testing in Portugal; a total of 30 valid answers were obtained.

hospitals/centers. In order to assess clinical practice of FeNO testing in Portugal, a panel of immunoallergologists and pulmonologists was informally invited to participate anonymously in an online survey. The data obtained (see Table 1), demonstrates that FeNO testing is still not routinely used in clinical practice in Portugal mainly due to access constraints: the lack of devices or consumables for FeNO measurement. Interestingly, for those who reported using FeNO testing with all asthma patients, the biomarker is mainly used for disease activity monitoring purposes, and for those who use FeNO routinely but not for all patients, the reported criteria for testing included severe and type 2 asthma patients.

In conclusion, although FeNO testing appears to be recognized by Portuguese asthma specialists as an important tool for disease management, particularly in patients with severe and/or type 2 asthma, there are access constraints to this assay that need to be addressed in Portugal. Generalized access to FeNO testing will add value to the clinical management of asthma patients and improve symptom control. FeNO testing is also particularly relevant in severe asthma patients as it can serve to predict responsiveness to some new biological therapies and contribute to more cost-effective therapeutic options: e.g., high FeNO levels are one of the prescription criteria for dupilumab, a novel biologic for the treatment of severe asthma. We thus recommend that FeNO testing should be established as a routine procedure in clinical practice in Portugal for the diagnosis and management of asthma patients or at least be available in all reference centers.

Declaration of Competing Interest

In the preparation of this article, the authors received collaboration from the medical writer Duarte Oliveira (W4Research) financially supported by Sanofi. Sanofi had no role in the preparation of the manuscript or in the decision to submit the manuscript for publication. All authors declare collaborating and receiving fees from Sanofi and other pharmaceutical companies either through participation in advisory boards or consultancy, congress symposia, conducting clinical trials, investigator-initiated trials or grants.

References

1. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990—2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5(9):691—706.
2. Sa-Sousa A, Morais-Almeida M, Azevedo LF, Carvalho R, Jacinto T, Todo-Bom A, et al. Prevalence of asthma in Portugal — the Portuguese National Asthma Survey. Clin Transl Allergy. 2012;2 (1):15.
3. GINA - Global Initiative for Asthma. In: Difficult-to-treat & severe asthma in adolescent and adult patients — diagnosis and management; 2019. https://ginasthma.org/severeasthma/ last accessed on 19 April 2021.
4. GINA - Global Initiative for Asthma. In: Global strategy for asthma management and prevention; 2020. https://ginasthma.org/gina-reports/ last acessed on 19 April 2021.
5. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of severe asthma worldwide: data from the international severe Asthma Registry. Chest. 2020;157(4):790—804.
6. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391(10122):783—800. Feb.
7. Fahy J V. Type 2 inflammation in asthma—present in most, absent in many. Nat Rev Immunol. 2015;15(1):57—65.
8. NICE - National Institute for Health and Care Excellence. In: Asthma: diagnosis, monitoring and chronic asthma management (NICE guideline NG80); 2020. https://www.nice.org.uk/guidance/ng80 last accessed on 19 April 2021.
9. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2): 343—73.
10. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602—15. Sep.
11. Menzies-Gow A, Mansur AH, Brightling CE. Clinical utility of fractional exhaled nitric oxide in severe asthma management. Eur Respir J. 2020;55(3):1—13.
12. Soma T, Iemura H, Naito E, Miyauchi S, Uchida Y, Nakagome K, et al. Implication of fraction of exhaled nitric oxide and blood eosinophil count in severe asthma. Allergol Int. 2018;67S: S3—11.
13. Loureiro CC, Amaral L, Ferreira JA, Lima R, Pardal C, Fernandes I, et al. Omalizumab for severe asthma: Beyond allergic asthma. Biomed Res Int. 2018. 2018.

Pulmonology 27 (2021) 386–393

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Noninvasive ventilatory support in morbid obesity

J.R. Bach[a,*], A.W. Kazi[a], T. Pinto[b,c], M.R. Gonçalves[b,c]

[a] *Department of Physical Medicine and Rehabilitation, Rutgers University - New Jersey Medical School, United States*
[b] *Pulmonology Department, University Hospital of São João, Porto, Portugal*
[c] *Faculty of Medicine, University of Porto, Porto, Portugal*

Received 7 January 2020; accepted 6 December 2020
Available online 11 January 2021

KEYWORDS
Obesity associated respiratory failure;
Morbid obesity;
Noninvasive ventilator support;
Noninvasive ventilation;
Mechanical insufflation-exsufflation

Abstract
Background: In the conventional management of the morbidly obese that normalizes the apnea-hypopnea index (AHI), CO2 levels often remain elevated.
Methods: A retrospective review of morbidly obese patients using volume preset settings up to 1800 ml to positive inspiratory pressures (PIPs) of 25–55 cm H2O, or pressure control at 25–50 cm H2O pressure via noninvasive interfaces up to continuously (CNVS).
Results: Twenty-six patients, mean 55.6 ± 14.8 years of age, weight 108–229 kg, mean BMI 56.1 (35.5–77) kg/m^2, mean AHI 69.0 ± 24.9, depended on up to CNVS for 3 weeks to up to 66 years. There were eleven extubations and seven decannulations to CNVS despite failure to pass spontaneous breathing trials. Thirteen were CNVS dependent for 92.2 patient-years with little to no ventilator free breathing ability (VFBA). Six used NVS from 10 to 23 h a day, and others only for sleep. Fifteen patients with cough peak flows (CPF) less than 270 L/m had access to mechanical insufflation-exsufflation (MIE) in the peri-extubation/decannulation period and long-term. The daytime end-tidal (Et)CO2 of 14 who were placed on sleep NVS without extubation or decannulation to it decreased from mean EtCO2 61.0 ± 9.3–38.5 ± 3.6 mm Hg and AHI normalized to 2.2. Blood gas levels were normal while using NVS/CNVS. Pre-intubation PaCO2 levels, when measured, were as high as 183 mm Hg before extubation to CNVS.
Conclusions: Ventilator unweanable morbidly obese patients can be safely extubated/decannulated and maintained indefinitely using up to CNVS rather than resort to tracheotomies.

* Corresponding author at: Department of Physical Medicine and Rehabilitation, Behavioral Health Sciences Building, 183 South Orange Ave., Newark, NJ 07103, United States.
E-mail address: bachjr@njms.rutgers.edu (J.R. Bach).

https://doi.org/10.1016/j.pulmoe.2020.12.003

Introduction

Morbid obesity is defined by having a body mass index (BMI) of 40 kg/m^2 or more, and is associated with a number of comorbid conditions which can adversely impact survival. Increased work of breathing and 'resetting' of hypothalamic respiratory drive can result in hypoventilation and in cor pulmonale.[1,2] Morbidly obese individuals, with or without complicating conditions, can become continuously ventilator dependent, that is, dependent on noninvasive ventilatory support (CNVS) or on tracheostomy mechanical ventilation (CTMV).

''NIV'' has come to be synonymous with continuous positive airway pressure (CPAP) and bi-level PAP at spans that can normalize AHI without providing full NVS to normalize CO2 and optimally rest inspiratory muscles.[2] Bi-level PAP became available in 1990 and often better normalized AHIs than CPAP but it has not been used at full ventilatory support settings aimed at normalization of CO2 in patients with ventilatory pump failure.[3] Mokhlesi et al. reported that eight of 34 patients (23%) who used sleep bi-level PAP did not have a significant improvement in their $PaCO_2$ despite normalization of their AHIs from 44 ± 45.[4] Likewise, Bouloukaki et al.[5] evaluated CPAP and typical bi-level therapy and reported that around 20% of individuals had a CO2 > 45 mm Hg after two years of therapy. Greater than the usual bi-level spans can be needed to normalize CO2.

The positive inspiratory pressures (PIPs) of mechanical ventilation during general anesthesia and neuromuscular blockade for patients with normal BMI are 17–25 cm H2O as are PIPs for any patients with little or no measurable vital capacity (VC) but normal pulmonary compliance.[6] However, patients with poor lung and chest wall compliance may require much higher pressures to normalize ventilation. The aim of this study is to demonstrate that NVS can at times be required to pressures over 50 cm H2O for the morbidly obese to normalize CO2 levels and avoid the need for O2 therapy and tracheotomy. Ventilator dependent patients can also be extubated or decannulated to it. This study was approved by the Rutgers University Institutional Review Board as No. Pro2018001071.

Methods

This is a retrospective study describing the use of NVS with high PIPs for morbidly obese patients presenting to two NVS centers over a 12 year period who required NVS support due to ongoing hypercapnic respiratory failure despite NIV use. Patients 1–17 presented to Center A and patients 18–26 to Center B. Vital capacity (VC) (measured to correlate with weight but not reported here), cough peak flows (CPF), End-tidal (Et)CO2, and oximetry were measured at every visit Thirteen of the 17 patients of center A underwent bariatric surgery but subsequently regained weight. All were offered ketogenic diets and exercise programs, but none continued these therapies long-term. Introduction of NVS was indicated by symptomatic hypoventilation with decreased VC.

The therapeutic goals were: (1) normalization of PaCO2 and/or end-tidal carbon dioxide (EtCO2) or transcutaneous CO2 (TcCO2) tensions and oxyhemoglobin saturation (SpO2) during wakefulness and sleep to relieve symptoms of hypoventilation; (2) to extubate and/or decannulate those failing ventilator weaning parameters and spontaneous breathing trials to CNVS.

We define NVS as the use of portable ventilators, volume or pressure preset or bi-level machines, at at least full ventilatory support settings to normalize CO2 levels as opposed to ''NIV'' settings to only normalize AHI. Although volumes were initially prescribed for the patient to choose over a range from 700 to 1500 ml, one patient increased his to 1800 ml. Pressure support/control for drive pressures of 20–55 cm H2O were used for patients with abdominal distension. The goal was to normalize PaCO2 around the clock. Patients used sleep-only NVS, sleep plus daytime NVS for up to 23 h/day, or CNVS with little or no VFBA.

All patients were prescribed NVS, which was preferentially volume preset with physiologic back-up rates, that is, normal respiratory rates for age or about 12−16. Portable ventilators were used with active ventilator circuits with or without minimal EPAP/PEEP. Volume preset was preferred since lung volume recruitment cannot be performed when using pressure preset ventilation.[6,7] Intubated patients and those using tracheostomy mechanical ventilation (TMV) were extubated/decannulated to up to CNVS with weaning, as possible.

Sleep NVS users who continued to gain weight tended to become dyspneic upon discontinuing NVS in the morning and developed fatigue, somnolence, and dyspnea when daytime hypercapnia was associated with decreases in SpO2 below 95% during the day, especially late in the day. As previously described, increased daytime use of mouthpiece/nasal NVS at that point was facilitated by using oximetry feedback. This renormalized blood gases and relieved dyspnea. Nasal or oronasal interfaces were used for sleep, although patients who required daytime as well as sleep NVS used oronasal interfaces with straps tightly applied during sleep for a more ''closed system'' to maintain normal blood gases. With nasal NVS during sleep large leak resulted in difficulty maintaining adequate PIPs and normal SpO2.[8] Any supplemental O2 and sedating medications were discontinued to avoid increased NVS leakage out of the mouth.[9,10] Patients' cough peak flows (CPF) were measured and when less than 270 L/m mechanical insufflation-exsufflation (MIE) was made available to decrease the risk of intercurrent pneumonias.[11,12]

Although pre-NVS AHI measurements were by polysomnography, subsequent measurements were estimated by ventilator flow and pressure sensors that store the data for analysis on personal computers. Compliance, average tidal volume, minute ventilation, respiratory rate, leaks, percent of spontaneous inspirations, and indices of residual apnea and hypopnea were monitored during sleep. However, only SpO2 and EtCO2 or TcCO2 levels were used as indications to adjust ventilator settings and interfaces, for example, whether to use nasal or oronasal interfaces. The reliability of the AHI by ventilator software has been reported to be sufficient for monitoring subjects on long-term NIV/NVS.[11,13,14]

Results and outcomes

The patients' demographics, anthropometric data, any complicating neurological conditions, and whether extubated

Table 1 Demographic Data, Extubations and Decannulations for Patients with Morbid Obesity.

Case	Age	Sex	BMI	Complicating conditions	BiPAP to intubation	Required Extubation/Decannulation to CNVS
1[a]	71	M	77	None	1 year 3 intubations	Extubation & Decannulation
2[a]	24	M	54.4	Spina bífida paraplegia	2 years 3 intubations	No
3	43	F	41.4	None	NVS to intubation	Extubation x 2
4	72	F	43.9	Post-poliomyelitis	No	Extubation to CNVS for Surgery
5[a]	32	F	75	None	2 years 2 intubations	Extubation & Decannulation
6[a]	59	F	57.5	None	2 years 2 intubations	Extubation & Decannulation
7	71	M	35.5	Diabetic neuropathy	No	Extubation
8[a]	53	F	53.1	None	1 intubation	Extubation x 2 & Decannulation
9[a]	62	F	48.1	None	14 years 2 intubations	Decannulation
10[a]	81	F	54	None	8 years	No
11[a]	59	F	46.3	None	2 intubations	Decannulation
12	58	F	N/A	None	No	No
13	37	F	44	diabetic neuropathy	No	No
14	30	F	47	Hypopituitarism, Cushingoid	No	No
15	53	F	61.8	None	No	No
16	71	M	48	MND	4 years	No
17	52	F	68	None	No	No
18	64	F	75	None	No	No
19	66	F	58	None	No	No
20	61	M	49	Post-Polio	No	No
21	50	F	67	None	No	No
22	66	F	56.3	None	No	No
23	69	M	58.6	None	No	No
24	42	M	74	None	No	No
25	37	F	66.8	None	No	No
26	59	M	55	Polyneuropathy	No	No

CNVS — continous noninvasive ventilatory support; BMI — body mass index.

BiPAP to intubation—''No'' denotes patients who were placed on NVS settings from outset, otherwise patients developed acute on chronic respiratory failure with or without using bi-lovel PAP with seven requiring intubation then extubation to CNVS and five of the seven failing a total of nine extubation attempts at other hospitals before transfer for successfully extubation to CNVS and mechanical insufflation-exsufflation (MIE). One local patient required extubation to CNVS and MIE twice.

Required extubation/decannulation to CNVS – except where noted, all intubations were for acute on chronic respiratory failure and extubation attempts to CPAP, bi-level PAP, and O2 failed or were not attempted do to inability to pass ventilator weaning parameters and spontaneous breathing trials. The patients had to be extubated to CNVS and MIE.

[a] Denotes patients who had been successfully extubated to low span bi-level PAP and O2 but remained extremely hypercapnic despite sleep bi-level PAP until being transitioned to NVS settings, in 5 cases, after being intubated again, undergoing tracheotomies, then being decannulated to CNVS in our center. Patient 9, however, only required sleep NVS post-decannulation.

or decannulated to CNVS or simply maintained on NVS settings following polysomnography with or without transition from low span bi-level PAP are noted in Table 1. Eighteen were female and eight male, mean age 55.6 ± 14.8 years. Weights ranged from 108 to 229 kg and BMI a mean of 61.1 (range 35.5–77) kg/m^2. Twenty presented with symptomatic hypercapnia or were intubated, ventilator unweanable, and wanted extubation to CNVS and MIE rather than tracheotomy and six presented using tracheostomy mechanical ventilation (TMV) (Table 1).

Patients' initial presentation, clinical management, and transition to NVS are described in a flow diagram in Fig. 1. Diurnal CO2 and SpO2 levels, mean sleep SpO2 levels, and AHI for those undergoing polysomnograms before introduction to NVS are noted in Table 2. Extent of NVS dependence (VFBA) between NVS to CNVS varied with patients' weight (Table 2).

Table 3 denotes extent of daytime use of NVS. Five intubated patients were transferred, including two on two occasions, from other critical care units after failing weaning and a total of 15 extubation attempts. Two intubated

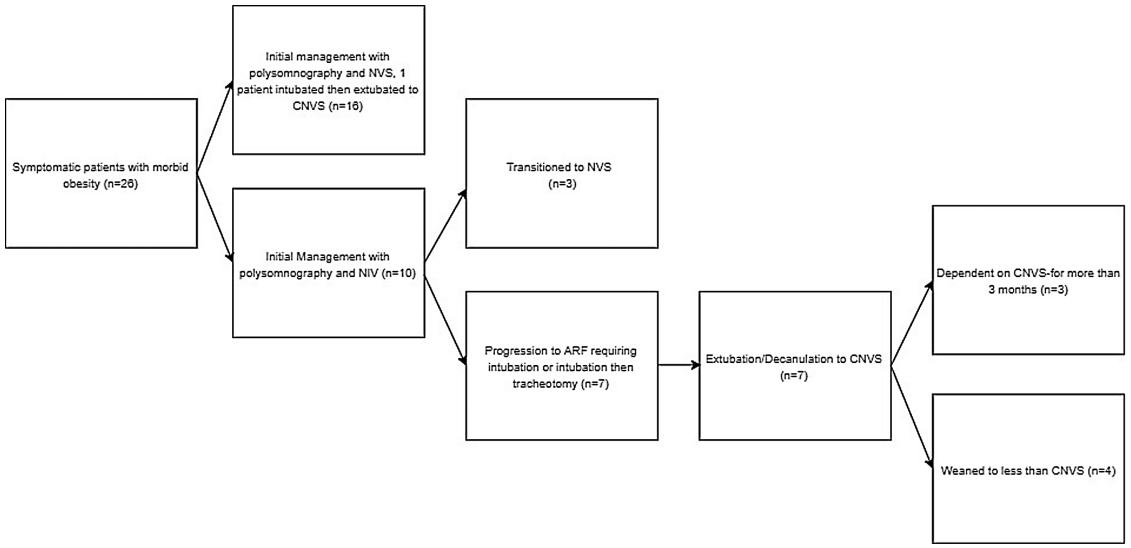


Figure 1 Patients' Initial Presentation, Management, and Transition to Noninvasive Ventilatory Support (NVS). NIV- noninvasive ventilation; ARF- acute respiratory failure; CNVS- continuous noninvasive ventilatory support.

Table 2 Pre-Noninvasive Ventilatory Support (NVS) Assessment.

Case	Pre-NVS			
	Daytime O2 Sat	Daytime EtCO2/TcCO2	Sleep mean O2 Sat	AHI
1	88–94%	51		
2	92%	71		81
3	88–94%	63		
4	75–90%		90%	
5	79–83			
6	85–91%	59	93%	
**7	**			
8	96–98%	47		
9	94–95%	44		
10	83–85%	54	89%	67
11	86–88%	51		
12	79–89%	56		
13	98%	33	92–93%	81
14	90–92%	52	90%	79
15	83–84%	65		74
16	91–94%	48	89%	40
17	78–82%	103	55.2%	
18	87%	64	81%	113
19	91%	58	87%	68
20	86%	68	83%	32
21	90%	50	86%	79.5
22	94%	49	88%	56.2
23	96%	60	87%	50.8
24	89%	55	77%	19.3
25	92%	49	83%	88.7
26	90–94%	94	84%	105

EtCO2 — End-tidal carbon dioxide in mm Hg; TcCO2 — transcutaneous CO2 mm Hg; Daytime O2 sat and EtCO2 — O2 sat and EtCO2 while stable; AHI — apnea hypopnea index; NVS settings — ** indicates pre-hospitalization blood gases unknown; the patient was transferred for extubation to CNVS after failing two extubation attempts and passing no ventilator weaning parameters; post-extubation was discharged using sleep NVS.

Table 3 Duration of Noninvasive Ventilatory Support (NVS) Use and Post-NVS Parameters While Using NVS at the Noted Settings.

Case	NVS extent and duration			NVS outcomes				
	Sleep only NVS	Night NVS + Day	CNVS	O2 Sat	EtCO2/TcCO2	AHI with NVS	Day and Sleep NVS PIP (cmH20)	Sleep Bi-level Pressure mm Hg
[a]1	None	5 years	5 year	95–100%	39		48–52[a]	
[a]2	None	None	1 year	95–100%	40	3	48–55[a]	
3	None	None	1 year	95–100%	39	0.9	36–45	42/4
[a]4	None	None	65 years	95–100%	41		35–40[a]	
[a]5	None	1 year	1 year	91–92%	40		40–45[a]	
[a]6	8 years	None	Only for Ext/Dec	95–97%	42		25–28[a]	
[a]7	None	None	Only for Ext/Dec	97–98%	32		25–32[a]	
[a]8	4 years	None	None	96–98%	47		32–38[a]	
[a]9	None	None	1 month	95–97%	42		25–30[a]	
10	9 years	None	2 years	93–95%	35	0.9	26–30	22/3
11	3.6 years	6.4 years	None				35–44	30/4
[a]12	None	2.4 years	None	94–95%	44		32–36[a]	
13	6 months	None	None	98%	33	0.8	26–32	18–25/2
14	None	9 years	None	98–99%	39	2.3	25	20/2
15	None	2.5 years	3 months	94–95%	44	2.1	48–55[a]	
[a]16	2 years	1 year	9 months	95–100%	37	3.1	34–39[a]	
[a]17	None	None	3 months	95–100%	35		48–55[a]	
18	None	5 years	4 years	97%	33	2	40	35/4
19	None	4 years	4 years	97%	42	3.8	30	24/4
20	None	12 years	None	98%	35	1.3	60	35/4
21	2 years	None	5 years	95%	42	4.4	30	25/5
22	6 years	None	None	96%	38	1.8	0	24/4
23	3 years	3 years	None	98%	40	3.5	34	28/4
24	None	None	2 years	96%	36	1.1	38	28/4
25	None	6 years	6	97%	39	4.8	30	23/4
26	1 year	None	None	98%	38		0	30/4

(C)NVS — (continuous) noninvasive ventilatory support; EtCO2 — end-tidal carbon dioxide in mm Hg; TcCO2 — transcutaneous CO2 mm Hg; NVS extent and duration — the total duration of use of sleep-only NVS, NVS use up to 23 h a day, and CNVS with little or no ventilator free breathing ability, however, patients often varied from one category to another as their weights and vital capacities increased or decreased.

[a] Indicates patients who used volume preset NVS with a range of 800–1800 ml, mean 1280 ml, that resulted in the positive inspiratory pressures (PIPs) noted for both daytime and sleep NVS, others used pressure control NVS.

patients were local. All seven unweanable patients were successfully extubated to CNVS and MIE, including Cases 3 and 8 on two occasions, and discharged home. Three of the seven eventually weaned, at least temporarily, to nighttime-only NVS. Their CPF averaged 208 L/m (70 L/m Case 8) and only one patient had flows over 270 L/m (Case 15) so 15 needed access to MIE long-term as well as for extubation and/or decannulations.[15–17]

All six patients who presented using up to continuous TMV (CTMV) were successfully decannulated to NVS/CNVS and MIE including 3 CTMV users who had no VFBA. All six subsequently weaned to have at least some daytime VFBA. Two patients who were decannulated to CNVS but then used sleep-only NVS, subsequently developed pneumonia and required re-intubation but were successfully re-extubated to CNVS (Table 1: Cases 1, 5). One patient who was extubated to CNVS developed sepsis from a hand infection, underwent tracheotomy, and was subsequently decannulated to CNVS.

Dyspnea was relieved and blood gases normalized for all patients. For the eleven who used only sleep NVS the initial daytime EtCO2 of 61.5 ± 6.3 decreased to 39.5 ± 3.3 mm Hg, and SpO2 normalized before increasing weight resulted in their need to extend NVS into daytime hours. The EtCO2 and SpO2 were always normal while using NVS during the day at PIPs of 25–55 cm H2O. The mean pre-NVS AHI of 69.0 ± 24.9 decreased to 2.3 ± 1.4 during sleep NVS. Four required CNVS only for days to months following extubation or decannulation before weaning to less than full-time NVS was achieved. Using oximetry as feedback, all patients were able to maintain normal daytime SpO2 in ambient air by using NVS and MIE.[17]

For Center A, the 17 patients' mean VC was 1409 ± 871 (range 200–2680) ml when sitting, and 1029 ± 764 (range 200–2060) ml when supine with a mean decrease of 27% from sitting to supine for these patients who could not tolerate reclining supine without using NVS. In the overall group, 18 patients used nasal and eight patients used oronasal interfaces for sleep NVS (Table 2). Four patients died; three predominantly from diabetes, hypertension, and renal failure including one with sickle cell anemia and aortic stenosis. Contact was lost with Case 8 who had liver cirrhosis and severe diabetes mellitus, and with case 13.

No patients were intubated due to failure of CNVS, however, two using less than CNVS, because of its inconvenience while walking, developed CO2 narcosis, required hospitalization and intubation for ARF, and had to be extubated back to CNVS.

Fourteen patients were CNVS dependent for 7.3 ± 16.1 (range from 3 months to 66 years) years with little to no VFBA for a total of 92.2 patient-years. Six others predominantly used NVS day and night with some VFBA and the others predominantly for sleep-only (Table 2).

Discussion

These results demonstrate that: (1) volume or pressure preset NVS settings can normalize blood gases day and night and AHIs without EPAP or PEEP; (2) ventilator unweanable patients with morbid obesity can be extubated/decannulated to, and depend on, CNVS for years to maintain normal blood gases without supplemental O2 despite having little or no autonomous ability to breathe, (3) CNVS can be safely provided day and night to PIPs over 40 and even over 50 cm H2O for the morbidly obese, (4) morbidly obese patients are good candidates for mouthpiece and nasal CNVS because of intact bulbar-innervated musculature that permits them to comfortably use NVS settings, (5) and morbidly obese patients with respiratory orthopnea can use NVS for sleep reclining.

In many studies on managing morbid obesity, supplemental O2 and bi-level PAP at less than NVS settings are used rather than correcting SpO2 and CO2 levels by using NVS settings.[18–24] Residual hypercapnia can be symptomatic and cause morbidity.[9,25] Outside of academic circles, CO2 levels are often not routinely monitored during polysomnography. None of the patients we switched to active ventilator circuits with 0 ml of PEEP had CO2 monitored during their sleep studies. While morbidly obese patients can obstruct inspiration during sleep and they may not exhale to atmospheric pressures, the air delivered at PIPs of 30–50 cm H2O was unobstructed on flow signals from the ventilator download. Increasing the IPAP to compensate for the EPAP to achieve the same support as with EPAP increases mean thoracic pressures and possibly discomfort sometimes without obvious clinical benefit. Although the airway obstruction of patients with bulbar amyotrophic lateral sclerosis (ALS) is certainly pathologically distinct from that of the morbidly obese, Crescimanno et al. titrated the AHIs of patients with ALS then repeated the studies with 0 EPAP and reported that even 4 cm H2O produced more leak than no EPAP, along with poorer sleep quality, more arousals, and a higher occurrence of patient-ventilator dyssynchrony without improving oxygen saturation.[26] Thus, EPAP may also be unnecessary to treat the morbidly obese when NVS settings are used, since airflow was unobstructed, blood gases normalized, and symptoms relieved. Future studies will be needed to confirm this observation.

Pressure preset CNVS at 18–50 cm H2O and volume preset CNVS at 700–1800 ml have now been used to sustain life for over 65 years for some of the 257 post-poliomyelitis mouthpiece CNVS users described in 1993,[27] for up to 28 years for 59 high level traumatic tetraplegics,[28] for over 30 years for patients with Duchenne muscular dystrophy,[15] for over 25 years for severe spinal muscular atrophy (SMA) type 1[29,33] for up to 13 years for ALS,[30] as well as for others. None received EPAP, PEEP, or supplemental O2. Likewise, many morbidly obese patients with no VFBA and immediate apnea when unaided, may also be managed by NVS without EPAP or PEEP.

Six patients were decannulated despite dependence on up to CTMV with limited VFBA. Although these patients could not be weaned from ventilatory support, this is not unprecedented. Perhaps the first decannulated CTMV dependent patient was a 17 year old high level spinal cord injured patient with 420 ml of VC seated but 0 ml supine. He had had a C1 fracture in March of 1967. He was decannulated to CNVS using a mouthpiece during the day. The ostomy closed in April 1969. He was euthanized after 38 years of CNVS in 2006. Another 91 TMV dependent patients, including two with 0 ml of VC, were subsequently decannulated to CNVS in reports in 1988 and 1990.[27,28,31] Seven remained CNVS dependent for 12.4 ± 6.3 (range 1–22) years. Another 61

decannulated patients ventilator unweanable patients were reported in 2014,[16] and in another report, Ceriana et al. decannulated 46 patients with at least 8 h of VFBA to bi-level NIV in 2019.[32]

No baro or volutrauma was observed in our patients nor in many hundreds of patients with ventilatory pump failure dependent on CNVS for decades, many of whom, as with some of these patients, have performed LVR to pressures of 60–90 cm H2O three times daily for decades.[6,7] Thus, statements like ''when 'NIV' becomes ineffective or is needed all day tracheotomy is necessary'' need to be re-thought.[33,34] Although the use of long-term CNVS and extubation to it along with MIE instead of TMV has now expanded to over 30 centers around the world,[3] this is its first description for the morbidly obese. Other than this report there are as yet no other reports of continuous ventilatory support via noninvasive interfaces for any morbidly obese patients with little to no VFBA, and none have been reported to use MIE to increase cough flows to expel airway debris.[18–24] However, eight of the 17 patients, for whom it was measured, had CPF less than 250 L/m and, at times, as low as 130 L/m.

Limitations of this study were that it was retrospective with data from 2 different centers (not always the same data points available), not all patients underwent polysomnography which could have been used to determine the effect on blood gases and sleep of adding EPAP/PEEP to the high inspiratory pressures that normalized CO2, the accuracy of ventilator software is speculative, and forms of bariatric surgery were not documented. Polysomnograms offer information about sleep architecture and arousals and can be instructive even when CO2 is not monitored. However, since blood gases were normalized and symptoms of dyspnea and somnolence relieved, it is clear that morbidly obese patients can become continuously ventilator dependent using noninvasive interfaces rather than tracheostomy tubes or supplemental O2 provided that oximetry is used as feedback. Leaks at any pressures or volumes are controlled largely by ventilatory drive with sedative medications and O2 avoided.[10]

In this paper we have described the use of NVS with high PIP or tidal volumes for patients with morbid obesity who continued to have daytime hypercapnia and symptoms despite nocturnal ventilatory support using bi-level ventilation. This strategy was also used for a group of morbidly obese patients who were unweanable from ventilator use. Using the NVS strategy, in some patients on a continuous basis, we were able to normalize daytime blood gases and relieve symptoms associated with respiratory insufficiency. No patient has required tracheostomy or oxygen therapy. Future studies need to compare the use of NVS to NIV in those with symptomatic hypercapnic morbid obesity to systematically evaluate the impact of this approach on health care resource use, quality of life, tolerance and survival. Continuous NVS is preferable to continuous TMV.[35]

Conflicts of interest

Financial disclosure statements have been obtained and the authors have no conflicts of interest to declare.

Acknowledgements

JB and MG have been treating and managing all the patients, contributed to the writing of the paper, and confirm the study objectives, procedures, and data are honestly disclosed. A.K. analyzed the data and contributed to the writing. T.P. is a respiratory therapist and PhD student who gathered and analyzed the data for the Center B subjects and contributed to the writing.

References

1. Chau EH, Lam D, Wong J, Mokhlesi B, Chung F. Obesity hypoventilation syndrome: a review of epidemiology, pathophysiology, and perioperative considerations. Anesthesiology. 2012;117(1):188–205.
2. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome. A reevaluation of the ''Pickwickian syndrome''. Chest. 1986;89(5):627–35.
3. Bach JR, Goncalves MR, Hon A, et al. Changing trends in the management of end-stage neuromuscular respiratory muscle failure: recommendations of an international consensus. Am J Phys Med Rehabil. 2013;92(3):267–77.
4. Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani A-A, Hassaballa HA, et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med. 2006;2(1):57–62.
5. Bouloukaki, I, Mermigkis C, Michelakis S, Moniaki V, Mauroudi E, Tzanakis N, Schiza SE. The association between adherence to positive airway pressure therapy and long-term outcomes in patients with obesity hypoventilation syndrome: a prospective observational study. J Clin Sleep Med. 2018;14(9):1539–50.
6. Kang SW, Bach JR. Maximum insufflation capacity: vital capacity and cough flows in neuromuscular disease. Am J Phys Med Rehabil. 2000;79(3):222–7.
7. Kang SW, Bach JR. Maximum insufflation capacity. Chest. 2000;118(1):61–5.
8. Bach JR. Noninvasive respiratory management of patients with neuromuscular disease. Ann Rehabil Med. 2017;41(4):519–38.
9. Chiou M, Bach JR, Saporito LR, Albert O. Quantitation of oxygen-induced hypercapnia in respiratory pump failure. Rev Port Pneumol (2006). 2016;22(5):262–5.
10. Bach JR, Robert D, Leger P, Langevin B. Sleep fragmentation in kyphoscoliotic individuals with alveolar hypoventilation treated by NIPPV. Chest. 1995;107(6):1552–8.
11. Aarrestad S, Qvarfort M, Kleiven AL, Tollefsen E, Skjonsberg OH, Janssens JP. Sleep related respiratory events during non-invasive ventilation of patients with chronic hypoventilation. Respir Med. 2017;132:210–6.
12. Bach JR. Update and perspectives on noninvasive respiratory muscle aids. Part 1: the inspiratory aids. Chest. 1994;105(4):1230–40.
13. Georges M, Adler D, Contal O, et al. Reliability of apnea-hypopnea index measured by a home bi-level pressure support ventilator versus a polysomnographic assessment. Respir Care. 2015;60(7):1051–6.
14. Gonzalez-Bermejo J, Perrin C, Janssens JP, Pepin JL, Mroue G, Leger P, et al. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. Thorax. 2012;67(6):546–52.
15. Bach JR, Tran J, Durante S. Cost and physician effort analysis of invasive vs. noninvasive respiratory management of Duchenne muscular dystrophy. Am J Phys Med Rehabil. 2015;94(6):474–82.
16. Bach JR, Saporito LR, Shah HR, Sinquee D. Decanulation of patients with severe respiratory muscle insufficiency: effi-

cacy of mechanical insufflation-exsufflation. J Rehabil Med. 2014;46(10):1037–41.
17. Bach JR, Goncalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness: a new management paradigm. Chest. 2010;137(5):1033–9.
18. Howard ME, Piper AJ, Stevens B, Holland AE, Yee BJ, Dabscheck E, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017;72(5):437–44.
19. Murphy PB, Davidson C, Hind MD, Simonds A, Williams AJ, Hopkinson NS, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012;67(8):727–34.
20. Priou P, Hamel JF, Person C, Meslier N, Racineux JL, Urban T, Gagnadoux F. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest. 2010;138(1):84–90.
21. Chouri-Pontarollo N, Borel JC, Tamisier R, Wuyam B, Levy P, Pepin JL. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. Chest. 2007;131(1):148–55.
22. Banerjee D, Yee BJ, Piper AJ, Zwillich CW, Grunstein RR. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. Chest. 2007;131:1678–84. United States.
23. Storre JH, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, Windisch W. Average volume-assured pressure support in obesity hypoventilation: a randomized crossover trial. Chest. 2006;130(3):815–21.
24. Perez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vazquez M, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005;128(2):587–94.
25. Shigemura M, Lecuona E, Sznajder JI. Effects of hypercapnia on the lung. J Physiol. 2017;595(8):2431–7.
26. Crescimanno G, Greco F, Arrisicato S, Morana N, Marrone O. Effects of positive end expiratory pressure administration during non-invasive ventilation in patients affected by amyotrophic lateral sclerosis: a randomized crossover study. Respirology. 2016;21(7):1307–13.
27. Bach JR, Alba AS, Saporito LR. Intermittent positive pressure ventilation via the mouth as an alternative to tracheostomy for 257 ventilator users. Chest. 1993;103(1):174–82.
28. Bach JR, Alba AS. Noninvasive options for ventilatory support of the traumatic high level quadriplegic patient. Chest. 1990;98(3):613–9.
29. Bach JR. POINT: is noninvasive ventilation always the most appropriate manner of long-term ventilation for infants with spinal muscular atrophy type 1? Yes, almost always. Chest. 2017;151(5):962–5.
30. Mahajan KR, Bach JR, Saporito L, Perez N. Diaphragm pacing and noninvasive respiratory management of amyotrophic lateral sclerosis/motor neuron disease. Muscle Nerve. 2012;46(6):851–5.
31. Bach JR. New approaches in the rehabilitation of the traumatic high level quadriplegic. Am J Phys Med Rehabil. 1991;70(1):13–9.
32. Ceriana P, Nava S, Vitacca M, Carlucci A, Paneroni M, Schreiber A, et al. Noninvasive ventilation during weaning from prolonged mechanical ventilation. Pulmonology. 2019;25(6):328–33.
33. Radunovic A, Annane D, Rafiq MK, Brassington R, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017;10:CD004427.
34. Toussaint M, Steens M, Wasteels G, Soudon P. Diurnal ventilation via mouthpiece: survival in end-stage Duchenne patients. Eur Respir J. 2006;28(3):549–55.
35. Bach Jr. A comparison of long-term ventilatory support alternatives from the perspective of the patient and care giver. Chest. 1993;104(6):1702–6.

Pulmonology 27 (2021) 394–402

PULMONOLOGY

www.journalpulmonology.org

ORIGINAL ARTICLE

Markers of cardiovascular risk and their reversibility with acute oxygen therapy in Kyrgyz highlanders with high altitude pulmonary hypertension

M. Furian[a,1], T.D. Latshang[a,1], S.S. Aeschbacher[a,1], U. Sheraliev[b,1], N.H. Marazhapov[b,1], E. Mirrakhimov[b,1], S. Ulrich[a,1], T.M. Sooronbaev[b,1], K.E. Bloch[a,*,1]

[a] *Pulmonary Division and Sleep Disorders Center, University Hospital of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland*
[b] *National Center for Cardiology and Internal Medicine, Department of Respiratory Medicine, 3 Togolok Moldo Str., Bishkek 720040, Kyrgyzstan*

Received 14 October 2020; accepted 3 February 2021
Available online 3 March 2021

KEYWORDS
QT prolongation;
Sudden cardiac death;
Highlanders;
Hypoxia;
Hyperoxia

Abstract
Background: High altitude pulmonary hypertension (HAPH), a chronic altitude related illness, is associated with hypoxemia, dyspnea and reduced exercise performance. We evaluated ECG and pulse wave-derived markers of cardiovascular risk in highlanders with HAPH (HAPH+) in comparison to healthy highlanders (HH) and lowlanders (LL) and the effects of hyperoxia.
Methods: We studied 34 HAPH+ and 54 HH at Aksay (3250 m), and 34 LL at Bishkek (760 m), Kyrgyzstan. Mean pulmonary artery pressure by echocardiography was mean ± SD 34 ± 3, 22 ± 5, 16 ± 4 mmHg, respectively ($p < 0.05$ all comparisons). During quiet rest, breathing room air or oxygen in randomized order, we measured heart-rate adjusted QT interval (QTc), an ECG-derived marker of increased cardiovascular mortality, and arterial stiffness index (SI), a marker of cardiovascular disease derived from pulse oximetry plethysmograms.
Results: Pulse oximetry in HAPH+, HH and LL was, mean ± SD, 88 ± 4, 92 ± 2 and 95 ± 2%, respectively ($p < 0.05$ vs HAPH+, both comparisons). QTc in HAPH+, HH and LL was 422 ± 24, 405 ± 27, 400 ± 28 ms ($p < 0.05$ HAPH+ vs. others); corresponding SI was 10.5 ± 1.9, 8.4 ± 2.6, 8.5 ± 2.0 m/s, heart rate was 75 ± 8, 68 ± 8, 70 ± 10 bpm ($p < 0.05$, corresponding comparisons HAPH+ vs. others). In regression analysis, HAPH+ was an independent predictor of increased QTc and SI when controlled for several confounders. Oxygen breathing increased SI in HH but not in HAPH+, and reduced QTc in all groups.

* Corresponding author.
E-mail address: Konrad.bloch@usz.ch (K.E. Bloch).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.pulmoe.2021.02.001

Conclusions: Our data suggest that HAPH+ but not HH may be at increased risk of cardiovascular mortality and morbidity compared to LL. The lack of a further increase of the elevated SI during hyperoxia in HAPH+ may indicate dysfunctional control of vascular tone and/or remodelling.

Introduction

Living at high altitude, where hypobaric hypoxia enhances sympathetic tone, hypoxemia and progressively increases mean pulmonary artery pressure (mPAP), residents may be exposed to increased risk for sudden cardiac death (SCD)[1] and cardiovascular disease (CVD).[2] Cardiac adaption and maladaptation to hypobaric hypoxia have been described previously.[3,4] Acute altitude exposure can prolong heart-rate corrected QT interval (QTc),[5,6] a validated marker for SCD.[7] Additionally, free reactive oxygen species are involved in the adaptive process to hypobaric hypoxia.[8] They act as signaling molecules to transcribe hypoxic-inducible factor $1-\alpha$. Unfortunately, excessive reactive oxygen species concentration can cause vascular endothelial dysfunction, the major underlying factor promoting atherogenesis and CVD.[9] Well acclimatized, healthy highlanders have elevated reactive oxygen species concentration without evidence of vascular dysfunction, which is in contrast to observations in highlanders with chronic mountain sickness (CMS).[10,11] CMS is characterized by polycythemia, pulmonary hypertension and severe chronic hypoxemia.[12] Apart from CMS, another chronic high altitude related illness is high altitude pulmonary hypertension (HAPH),[12] which is associated with elevated mPAP and moderate chronic hypoxemia but without polycythemia. Highlanders with HAPH may also be at increased risk of CVD and SCD with potential consequences for morbidity and mortality compared to healthy highlanders and lowlanders.[2,7,13]

Therefore, our aim was to examine indices of risk of CVD and SCD in highlanders with and without HAPH at their altitude of residence. To elucidate the role of altitude, a lowlander control group was assessed near sea level. We hypothesized, that highlanders with HAPH would reveal markers for elevated risk of CVD and SCD compared to healthy highlanders and healthy lowlanders.

Methods

Participants

Highlanders with HAPH (HAPH+) and HH, 21–75 y of age, both genders were recruited and studied at the Aksay health post (3250 m, barometric pressure 515 ± 1 mmHg, room temperature $24.2 \pm 3.2\,^{\circ}$C), Kyrgyzstan. Participants had to be of Kyrgyz ethnicity, born, raised and currently living at >2500 m. The diagnosis of HAPH was established by typical symptoms and a mPAP >30 mmHg in the absence of excessive erythrocytosis (hemoglobin concentration in females <19 g/dl, in males <21 g/dl), and other present or diagnosed diseases that lead to hypoxemia (i.e., such as cardio-pulmonary diseases).[12] Healthy lowlanders (LL), 21–75 y of age, both genders, of Kyrgyz ethnicity, born, raised and currently living in Bishkek (760 m barometric pressure 692 ± 2 mmHg, room temperature $25.8 \pm 1.2\,^{\circ}$C), formed the lowlander control group. To eliminate the influence of smoking on the cardiovascular system, current heavy smokers (>10 cigarettes per day), and subjects with a history of smoking >20 pack-years were excluded from the study. Other exclusion criteria were diagnosed comorbidities or drug therapies that may have interfered with control of breathing, or pulmonary hypertension other than HAPH, in particular from left ventricular failure, lung disease or other conditions listed in the guidelines on pulmonary hypertension of the European Society of Cardiology.[2] Data for the current study have been collected during the conduct of a previous study on HAPH, sleep apnea[14] and cerebral oxygenation[15] but the analysis of the ECG and pulse wave, the focus of the current study, have not been published. This study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained, and the ethics committee of the National Center of Cardiology and Internal Medicine, Bishkek, Kyrgyzstan, approved the study (No. 01-7/219).

Design and intervention

Highlanders traveled from their homes in the remote mountain areas by horse or car within one day to the study site at the Aksay health post. LL were studied in the National Center of Cardiology and Internal Medicine of Bishkek. The study design was according to a randomized single-blinded crossover protocol as detailed below. Participants rested in supine position breathing through a face-mask equipped with a reservoir bag and a one-way exhalation valve (non-rebreather oxygen mask, P.J. Dahlhausen & Co. GmbH, Cologne, Germany). Either ambient air (FiO_2 0.21) delivered by a continuous positive airway pressure generator (REMstar, Philips Respironics, Zofingen, Switzerland), or oxygen (FiO_2 1.0) at a flow rate of 10 l/min from a pressurized bottle were breathed through the mask. After a baseline period of at least 10 min, a 10 min recording period took place with ambient air (or oxygen, according to randomization). After a 10 min wash-out period with ambient air breathing (if FiO_2 1.0 was used first), the procedure was repeated with the alternate gas. Patients were not allowed to sleep during the experiment. Blinding of participants was achieved by placing the breathing gas source out of their view.

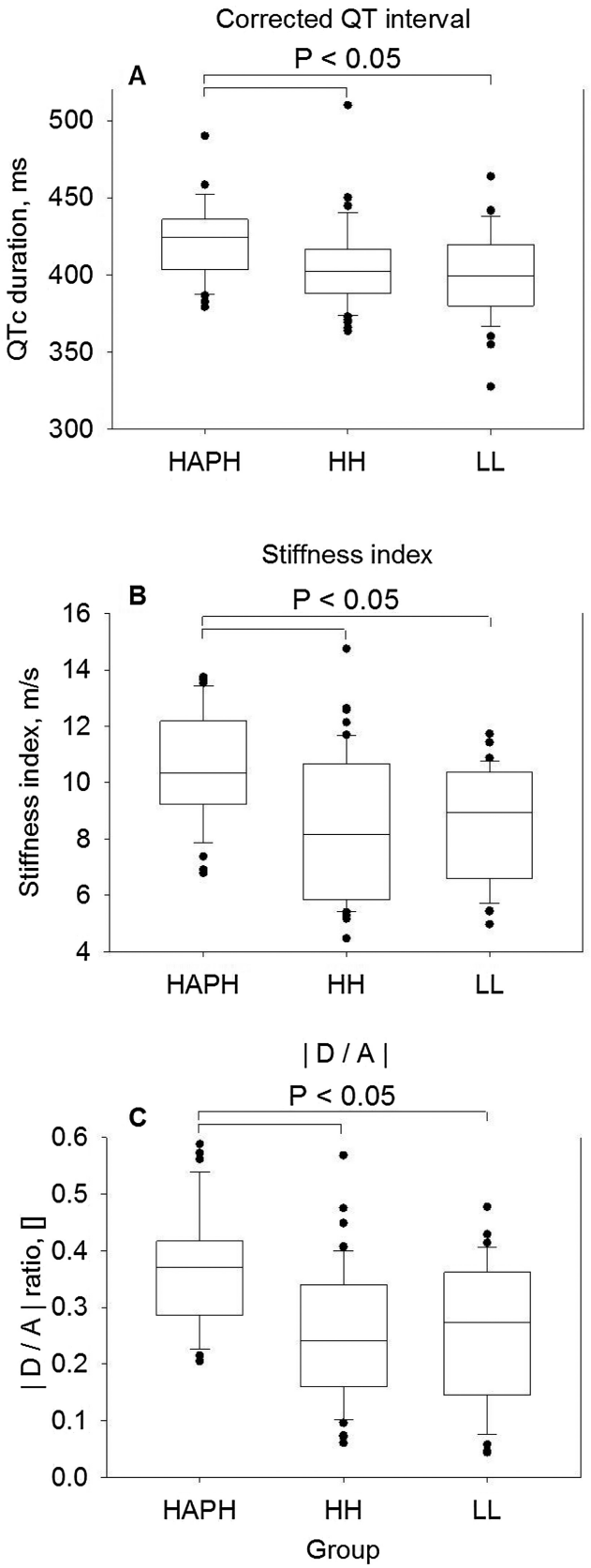


Figure 1 Comparison of baseline measurements under ambient air in highlanders with high altitude pulmonary hypertension (HAPH), healthy highlanders (HH) and healthy lowlanders (LL). Panel A: QT interval corrected for heart rate by the Bazett's formula.[16] Panel B: Stiffness index, calculated by the height of the participant in meters divided by the time delay in seconds between the

Measurements

A 4-lead electrocardiogram and the finger photoplethysmogram from pulse oximetry were continuously monitored with a sampling rate of 200 Hz. Arterial oxygen saturation (SpO_2) was assessed by finger pulse oximetry (Alice 5, Philips Respironics, Zofingen, Switzerland). QTc was calculated by the Bazett's formula.[16] Stiffness index (SI) and wave D to wave A ratio (DA) of the second derivative of the finger plethysmogram, both predictors for CVD were assessed.[17,18] SI was calculated as height of the participant divided by the time from the systolic to diastolic inflection point of the pulse waveform[19] whereas DA was calculated as described by Takada et al.[20] and Imanaga et al.[21] A clinical examination, measurement of systemic blood pressure, echocardiography and arterial blood gas analyses were obtained as reported previously.[14]

Statistics

Data are presented in median (quartiles). A per-protocol analysis was undertaken for the present study. Comparisons between groups were made with one-way ANOVA followed by post-hoc Scheffé multiple-comparisons or Kruskal–Wallis one-way analysis of variance followed by Mann–Whitney-*U* test as appropriate. Within group comparisons were made with dependent *t*-test or Wilcoxon signed ranks test as appropriate. ECG and pulse wave contour analysis was performed beat – by – beat over the last 2 min of breathing FiO_2 0.21 or 1.0, respectively. ECG/pulse wave analysis was performed with customized interactive software programmed in MatLab on mean waveforms ensemble-averaged by ECG triggering over 2 min. The number of participants exceeding the critical threshold of QTc prolongation of >440 ms was evaluated by the Pearson's Chi-squared test.[5,7]

In order to evaluate the effect of HAPH and residence at high altitude on QTc and SI independent of known confounders, such as age, gender, body mass index (BMI), mean arterial pressure and SpO_2 under ambient air, univariable and multivariable regression analyses were employed. A significance level of $p < 0.05$ was considered statistically significant.

Results

Of 232 highlanders invited to the study, 105 refused to participate, 37 had to be excluded due to relevant comorbidities or other exclusion criteria. Ninety consented to participate and could be examined. Of 39 LL invited to the study, 5 had to be excluded due to comorbidities or other exclusion criteria. Thirty-four consented to participate and could be examined. Two participants were excluded from the final analysis because of poor quality of ECG recordings; data from a total of 122 participants were included in the analysis. Demographics are presented in Table 1 . HAPH+ were slightly older and had a higher body weight than both control groups. In addition, HAPH+ were more hypoxemic and had a higher heart rate than HH and LL (Table 1).

During breathing ambient air (Fig. 1, Panel A–C) QTc duration of HAPH+, HH and LL was, median (quartiles), 424 (404; 436) ms, 402 (388; 417) ms and 400 (380; 420) ms, respectively ($p < 0.05$ vs HAPH+, all comparisons, p = NS between HH and LL). Correspondingly, SI of HAPH+, HH and LL were 10.4 (9.2; 12.2) m/s, 8.2 (5.9; 10.7) m/s and 9.0 (6.6; 10.4) m/s, respectively ($p < 0.05$ vs HAPH+, all comparisons, p = NS between HH and LL); corresponding DA were 0.37 (0.29; 0.42), 0.24 (0.16; 0.34) and 0.27 (0.14; 0.36), respectively ($p < 0.05$ vs HAPH+, all comparisons, p = NS between HH and LL). Critical QTc prolongation above 440 ms were observed in 6 of 34 (18%) in HAPH+, 5 of 54 (9%) in HH and 3 of 34 (9%) in LL (p = NS all comparisons).

Breathing oxygen FiO_2 1.0 (Fig. 2, Panel A–C) reduced QTc to a similar degree in HAPH+, HH and LL, i.e., by median difference (95% CI), −5 (−10 to −2) ms, −3 (−6 to −1) ms and −5 (−9 to −3) ms, respectively ($p < 0.05$ compared to ambient air values within the different groups, p = NS between groups, Fig. 2, Panel A), so that HAPH+ remained at prolonged QTc duration compared to HH and LL. SI did not change with breathing oxygen in HAPH+, 0.0 (−0.6 to 0.0), $p = 0.585$, and in LL, 0.0 (0.0 to 0.3), $p = 0.223$, but SI slightly increased in HH with breathing oxygen, 0.1 (0.0 to 0.8), $p < 0.05$, as shown in Fig. 2, Panel B. Ratio in DA remained stable in all 3 groups (Fig. 2, Panel C).

Regression analysis confirmed that HAPH+ was an independent predictor of increased QTc and SI even when controlled for age, gender, mean arterial blood pressure, BMI, and SpO_2 (Table 2).

Discussion

All three indices of cardiovascular risk studied, the QTc a predictor of sudden cardiac death (SCD), the SI and the wave D to wave A ratio of the second derivative of the pulse plethysmogram, were exclusively increased in highlanders with high altitude pulmonary hypertension compared to healthy highlanders and lowlanders. Furthermore, HAPH+ had a higher heart rate compared to HH. Thus, the current study suggests a higher risk for SCD and CVD in HAPH+ compared to HH and LL. With 20 min oxygen breathing (FiO_2 1.0), QTc was reduced in HAPH+, however, QTc remained prolonged compared to HH and LL. The elevated values of the SI in HAPH+ along with the lack of an acute change during oxygen breathing may indicate an altered autonomic control of vascular tone and/or structural vascular remodeling. Taken together, our findings raise concerns that HAPH+ may be at increased risk of SCD and CVD.

systolic and diastolic peaks (or, in the absence of a second peak, the point of inflection) of the pulse wave. Panel C: Wave D to wave A ratio of the second derivative of the finger plethysmogram. Boxes with lines represent medians and quartiles, whiskers represent the 10th and 90th percentiles, and dots represent individual values that fall outside the 10th–90th percentile range. Significant differences between groups are indicated. $p < 0.05$ was considered significant.

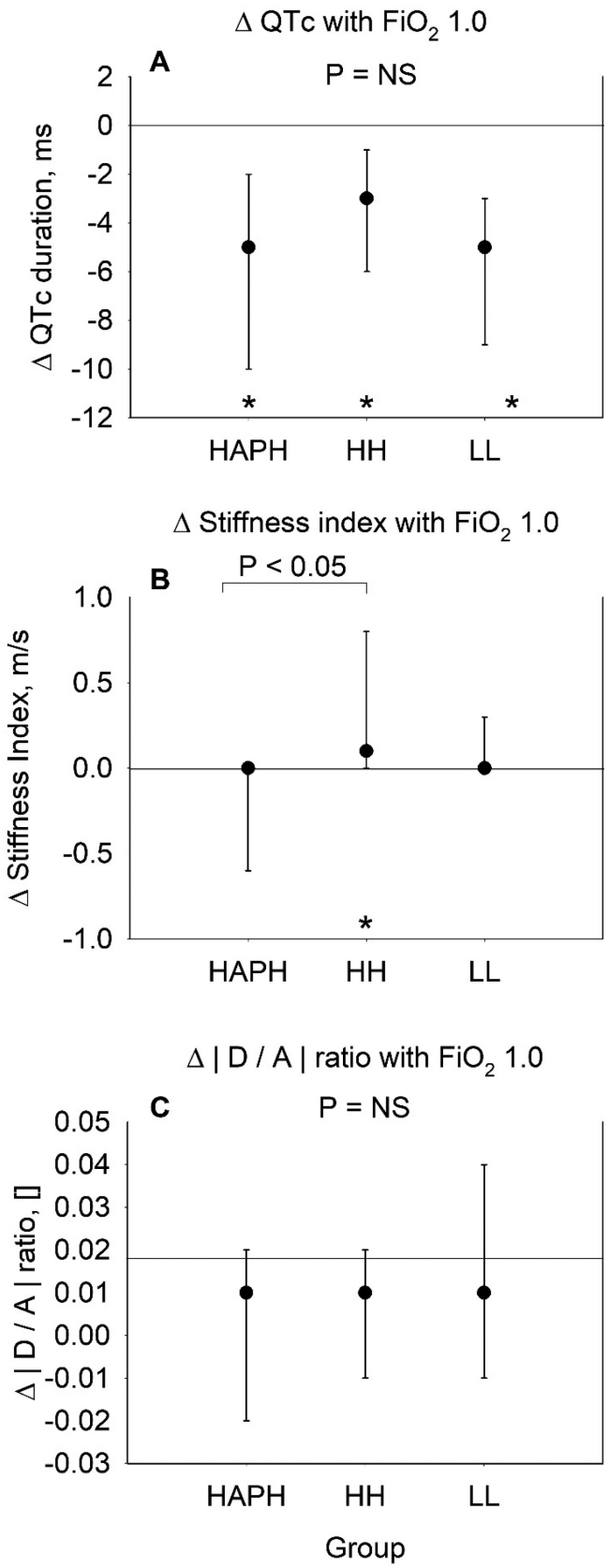


Figure 2 Changes with breathing oxygen (FiO_2 1.0) in highlanders with high altitude pulmonary hypertension (HAPH), healthy highlanders (HH) and healthy lowlanders (LL) in comparison to breathing ambient air (FiO_2 0.21). Panel A: Median change (95% confidence interval) in QT interval corrected for heart rate by the Bazett's formula.[16] Panel B: Median change (95% confidence

Table 1 Demographic characteristics of the participants.

	Healthy lowlanders	Healthy highlanders	Highlanders with HAPH
N (% female)	34 (35%)	54 (39%)	34 (47%)
Age, y	40 (30;47)	39 (32;48)	52 (47;58)*¶
BMI, kg/m^2	26.6 (23.1;27.8)	23.5 (21.3;25.6)*	29.0 (24.5;31.8)*¶
mPAP, mmHg	15 (12;19)	23 (19;26)*	33 (31;36)*¶
SpO_2, %	95 (94;97)	92 (90;94)*	89 (87;90)*¶
Heart rate, bpm	69 (62;75)	69 (62;73)	75 (70;80)*¶
Systolic BP, mmHg	117 (111;129)	105 (97;111)*	113 (103;127)¶
Diastolic BP, mmHg	76 (68;86)	68 (61;74)*	74 (65;84)¶
Mean BP, mmHg	89 (83;99)	80 (73;86)*	87 (78;99)¶
Smoking, pack-years	0 (0;2)	0 (0;4)	0 (0;5)

Data presented as median (quartiles); HAPH: high altitude pulmonary hypertension; BMI: body mass index; mPAP: mean pulmonary artery pressure; SpO_2: peripheral arterial oxygen saturation; BP: blood pressure.
*$p < 0.05$ vs healthy lowlanders.
¶$p < 0.05$ vs healthy highlanders.

Table 2 Regression analysis of corrected QT interval (QTc) and stiffness index (SI) with several predictors.

	Univariable regression				Multivariable regression			
	Coeff	SE	95% CI	*p* value	Coeff	SE	95% CI	*p* value
Dependent QTc, ms								
Age, y	0.74	0.19	0.37;1.12	<0.001	0.57	0.27	0.03;1.02	0.038
Female vs. male	15.07	4.57	6.01;24.12	0.001	12.06	4.70	2.75;21.38	0.012
BMI, kg/m^2	1.29	0.55	0.21;2.38	0.020	0.74	0.67	−0.59;2.07	0.273
SpO_2, %	−1.45	0.69	−2.82;0.08	0.038	0.79	0.78	−0.76;2.35	0.313
MAP, mmHg	−0.27	0.22	−0.70;0.17	0.227	−0.38	0.22	−0.82;0.06	0.089
Group membership								
HH vs LL	5.91	6.02	−6.02;17.84	0.329	5.83	6.54	−7.14;18.79	0.375
HAPH+ vs LL	22.5	6.30	10.08;35.04	<0.001	16.21	8.04	0.28;32.13	0.046
Intercept					300.4	84.2	133.6;467.2	0.001
Dependent SI, m/s								
Age, y	0.11	0.02	0.08;0.14	<0.001	0.12	0.02	0.08;0.16	<0.001
Female vs. Male	−0.11	0.44	−0.98;0.76	0.805	−0.18	0.39	−0.96;0.60	0.650
BMI, kg/m^2	0.05	0.05	−0.05;0.15	0.283	−0.13	0.05	−0.23;0.04	0.006
SpO_2, %	−0.13	0.04	−0.20;−0.05	0.001	0.11	0.08	−0.05;0.27	0.193
MAP, mmHg	0.05	0.02	0.01;0.09	0.012	0.03	0.02	−0.01;0.07	0.163
Group membership								
HH vs LL	−0.11	0.49	−1.08;0.85	0.814	0.34	0.58	−0.80;1.49	0.055
HAPH+ vs LL	2.04	0.47	1.11;2.97	<0.001	1.71	0.66	0.40;3.02	0.011
Intercept					−5.2	8.2	−21.3;11.0	0.527

All parameters from the univariate regression analyses were included in the multivariable models. BMI: body mass index; SpO_2: arterial oxygen saturation; MAP: mean arterial pressure; HH: healthy highlanders; LL: healthy lowlanders; HAPH: highlanders with high altitude pulmonary hypertension.

These results are novel and of clinical importance since HAPH is common among highlanders with an estimated prevalence of 5–18%.[22,23] With progressive increase of pulmonary artery pressure in untreated HAPH,[24] QTc and SI may rise simultaneously, indicating that highlanders with long-standing, untreated HAPH may be at increased risk of latent

interval) in stiffness index, calculated by the height of the participant in meters divided by the time delay in seconds between the systolic and diastolic peaks (or, in the absence of a second peak, the point of inflection) of the pulse wave. Panel C: Median change (95% confidence interval) in wave D to wave A ratio of the second derivative of the finger plethysmogram. Asterisks (*) indicate significant changes ($p < 0.05$) from baseline of the corresponding group. Significant differences between groups are indicated with horizontal lines. $p < 0.05$ was considered significant.

CVD and SCD. In remote areas such as Aksay – plateau treatment for HAPH+ is difficult due to insufficient medication supply and lack of knowledge of the potential risks, which can result in premature death.

To the best of our knowledge, no previous studies have elucidated the risk for CVD and SCD in HAPH+, although several studies have shown an increased risk for SCD in highlanders with CMS[7] and in travelers acutely exposed to high altitudes.[25,26]

Stiffness index and wave D to wave A ratio

Rimoldi et al. in 2012 and Bailey et al. in 2013, showed that highlanders with CMS had systemic vascular dysfunction, evidenced by impaired flow-mediated dilatation, increased vascular stiffness and increased carotid intima-media thickness, predisposing these patients to higher cardiovascular morbidity and mortality.[10,11] A correlation between SpO_2 and flow-mediated dilatation ($r = 0.62$) and its improvement 1 h after oxygen breathing in highlanders with CMS and in HH with moderate hypoxemia ($SpO_2 < 90\%$) led the authors to conclude that severity of hypoxemia was one of the underlying – and reversible – mechanisms responsible for the vascular dysfunction. However, they presented no results about mPAP and a possible correlation between mPAP and vascular dysfunction in CMS patients. In the current study we found high values of SI in HAPH+ comparable to those reported in patients with two or more cardiovascular risk factors,[19] but SI were only weakly correlated with SpO_2 ($R^2 = 0.045$, $p = 0.001$). The multivariable regression analysis revealed HAPH+, age and BMI as independent predictors of SI (Table 2). We found no impairments in the HH control group, which was in accordance with the cited study.[11] It has been shown that chronic hypoxemia induces vasodilatation in the peripheral blood vessels,[27] therefore, we assumed that baseline vessel diameter in the HAPH+ and HH would be larger compared to LL and would respond to breathing FiO_2 1.0 by hyperoxia-induced vasoconstriction and elevation of SI in HAPH+ and HH compared to LL. Interestingly, breathing FiO_2 1.0 increased SI in HH but not in HAPH+. This finding indicates that mildly hypoxemic HH have preserved vasomotor reactivity to breathing FiO_2 1.0. Indeed, acute supplemental oxygen has shown to increase vascular stiffness and reactivity in healthy subjects and in diseases associated with mild hypoxemia, such as in COPD,[28] indicating that breathing FiO_2 1.0 modulates the vasomotor activity by enhancing parasympathetic activity and reducing sympathetic activity (indicated in our study by a hyperoxia-induced median reduction in heart rate of −6 bpm (IQR, −8 to −5) and −7 bpm (IQR, −9 to −5) in HH and HAPH+, respectively), or by reducing the bioavailability of nitric oxide due to increased oxidative stress.[29] These changes towards higher vascular stiffness have been associated with enhanced spontaneous baroreflex sensitivity and restoration of vascular tone towards normal physiology in otherwise hypoxemic individuals.[28] Although, heart rate decreased similarly under breathing FiO_2 1.0 compared to room air in HH and HAPH+, the absence of hyperoxia-induced vascular stiffness as seen in HAPH+ might be due to only 20 min hyperoxic gas breathing compared to 30 min or 1 h in the cited studies,[11,29] or due to blunted vasoconstrictive mechanisms or even structural remodeling caused by more severe hypoxemia or pulmonary hypertension compared to HH. In LL, SI may possibly have remained unchanged due to the already well oxygenated blood under ambient air.

SI and wave D to wave A ratio of the second derivative of the finger plethysmogram, both predictors for CVD, correlated good to each other ($R^2 = 0.48$, $p < 0.001$).

In addition to the elevated mPAP, systemic blood pressure and heart rate were also elevated in HAPH+ compared to HH and LL. These findings are consistent with an elevated sympathetic tone.

Sudden cardiac death

QTc was prolonged in HAPH+ compared to HH and LL. Furthermore, QTc prolongation could be reduced with oxygen administration, but remained prolonged compared to the two control groups. Multivariable regression analysis revealed HAPH+, gender and age as independent factors influencing QTc. Our results are in accordance with past studies, showing an association between QTc and elevated pulmonary arterial pressure,[30] gender[31] and age.[32] Right ventricular strain and the association with sleep apnea with cyclic nocturnal deoxygenation contribute to impaired repolarization of cardiac muscles and may therefore reflect an increased risk of ventricular tachycardia and fibrillation.

Limitation

For logistical reasons, the current study in the remote mountain region could only include a relatively small sample of highlanders compared to previous low altitude studies.[33] Instead of a 12-lead ECG, we used a 4-lead ECG and were only able to analyze lead II ECG wave contour. SI assessed by digital volume pulse as a predictor for arterial stiffness is a common noninvasive technique to assess arterial stiffness and has been successfully validated against flow mediated dilatation[34] or tonometry-derived augmentation index.[19,34] HAPH+ were significantly older compared to the two control groups, however, in multivariable regression models controlling for age, gender and other confounders, HAPH+ remained an independent predictor for SCD and CVD.

Conclusion

ECG and pulse wave-derived indices studied in the current investigation in highlanders with high altitude pulmonary hypertension indicate that they may be at greater risk for cardiovascular diseases and sudden cardiac death compared to healthy highlanders and lowlanders in whom QTc and SI were normal. Breathing oxygen reduced QTc in all groups, however, this marker of sudden cardiac death remained elevated in HAPH+. Moreover, the elevated SI and A to D wave ratio derived from the finger pulse plethysmogram, both predictors of cardiovascular disease, remained unchanged in HAPH+ during hyperoxia consistent with altered vessel wall properties. In summary, our observations raise concerns that HAPH+ might be at increased risk of SCD and CVD.

Funding

This work was supported by the OPO Foundation and the Zurich-Lung-League.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The study was supported by grants from the OPO Foundation and the Lunge Zurich, Switzerland. Philips Respironics Switzerland contributed some of the measurement equipment used in this study. Siemens Healthcare Diagnostics AG, Zurich, Switzerland, provided the blood gas analyzer.

References

1. Akcay M. The effect of moderate altitude on Tp-e interval, Tp-e/QT, QT, cQT and P-wave dispersion. J Electrocardiol. 2018;51(6):929–33.
2. Galiè N, Humbert M, Vachiery J, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J. 2015;46(6):1855–6.
3. Windsor JS, Rodway GW, Montgomery HE. A review of electrocardiography in the high altitude environment. High Alt Med Biol. 2010;11(1):51–60.
4. Naeije R. Physiological adaptation of the cardiovascular system to high altitude. Prog Cardiovasc Dis. 2010;52(6):456–66.
5. Windsor JS, Rodway GW, Mukherjee R, Firth PG, Shattock M, Montgomery HE. Prolongation of the corrected QT complex – a cause of sudden cardiac death in the mountain environment? J R Army Med Corps. 2011;157(1):63–7.
6. Mantziari L, Styliadis C, Kourtidou-Papadeli C, Styliadis I. Arrhythmias, sudden cardiac death and incapacitation of pilots. Hippokratia. 2008;12 Suppl 1:53–8.
7. Straus SM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. J Am Coll Cardiol. 2006;47(2):362–7.
8. Guzy RD, Schumacker PT. Oxygen sensing by mitochondria at complex III: the paradox of increased reactive oxygen species during hypoxia. Exp Physiol. 2006;91(5):807–19.
9. Stocker R, Keaney JF. Role of oxidative modifications in atherosclerosis. Physiol Rev. 2004;84:1381–478.
10. Rimoldi SF, Rexhaj E, Pratali L, Bailey DM, Hutter D, Faita F, et al. Systemic vascular dysfunction in patients with chronic mountain sickness. Chest. 2012;141(1):139–46.
11. Bailey DM, Rimoldi SF, Rexhaj E, Pratali L, Salinas Salmón C, Villena M, et al. Oxidative-nitrosative stress and systemic vascular function in highlanders with and without exaggerated hypoxemia. Chest. 2013;143(2):444–51.
12. León-Velarde F, Maggiorini M, Reeves JT, Aldashev A, Asmus I, Bernardi L, et al. Consensus statement on chronic and subacute high altitude diseases. High Alt Med Biol. 2005;6(2):147–57.
13. Schumacher DS, Müller-Mottet S, Hasler ED, Hildenbrand FF, Keusch S, Speich R, et al. Effect of oxygen and acetazolamide on nocturnal cardiac conduction, repolarization, and arrhythmias in precapillary pulmonary hypertension and sleep-disturbed breathing. Chest. 2014;146(5):1226–36.
14. Latshang TD, Furian M, Aeschbacher SS, Ulrich S, Osmonov B, Mirrakhimov EM, et al. Association between sleep apnoea and pulmonary hypertension in Kyrgyz highlanders. Eur Respir J. 2017;49(2):1–10.
15. Furian M, Latshang TD, Aeschbacher SS, Ulrich S, Sooronbaev T, Mirrakhimov EM, et al. Cerebral oxygenation in highlanders with and without high-altitude pulmonary hypertension. Exp Physiol. 2015;100(8):905–14.
16. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart. 1920;7:353–70.
17. Millasseau SC, Ritter JM, Takazawa K, Chowienczyk PJ. Contour analysis of the photoplethysmographic pulse measured at the finger. J Hypertens. 2006;24(8):1449–56.
18. Hashimoto J, Chonan K, Aoki Y, Nishimura T, Ohkubo T, Hozawa A, et al. Pulse wave velocity and the second derivative of the finger photoplethysmogram in treated hypertensive patients: their relationship and associating factors. J Hypertens. 2002;20:2415–22.
19. Clarenbach CF, Stoewhas A-C, van Gestel AJR, Latshang TD, Lo Cascio CM, Bloch KE, et al. Comparison of photoplethysmographic and arterial tonometry-derived indices of arterial stiffness. Hypertens Res. 2012;35(2):228–33.
20. Takada H, Washino K, Harrell JS, Iwata H. Acceleration plethysmography to evaluate aging effect in cardiovascular system. Med Prog Technol. 1997;21:205–10.
21. Imanaga I, Hara H, Koyanagi S, Tanaka K. Correlation between wave components of the second derivative of plethysmogram and arterial distensibility. Jpn Heart J. 1998:775–84.
22. Aldashev AA, Kojonazarov BK, Amatov TA, Sooronbaev TM, Mirrakhimov MM, Morrell NW, et al. Phosphodiesterase type 5 and high altitude pulmonary hypertension. Thorax. 2005;60(8):683–7.
23. Lichtblau M, Saxer S, Furian M, Mayer L, Bader PR, Scheiwiller P, et al. Cardiac function and pulmonary hypertension in Central Asian highlanders at 3250 m. Eur Respir J. 2020;56(2).
24. Sooronbaev T, Osmonov B, Furian M, Aeschbacher SS, Latshang TD, Ulrich S, et al. Time course of pulmonary artery pressure and clinical characteristics in Kyrgyz highlanders. Eur Respir J. 2015;46 suppl 59:PA3761.
25. Sherry E, Clout L. Deaths associated with skiing in Australia: a 32-year study of cases from the Snowy Mountains. Med J Aust. 1988;149:615–8.
26. Burtscher M, Philadelphy M, Likar R. Sudden cardiac death during mountain hiking and downhill skiing. N Engl Med J. 1993;329(23):1738–9.
27. Maher AR, Milsom AB, Gunaruwan P, Abozguia K, Ahmed I, Weaver RA, et al. Hypoxic modulation of exogenous nitrite-induced vasodilation in humans. Circulation. 2008;117:670–7.
28. Bartels MN, Jelic S, Basner RC, Ngai P, Gonzalez JM, De Meersman RE. Supplemental oxygen increases arterial stiffness in chronic obstructive pulmonary disease. Respir Med. 2004;98(1):84–9.
29. Vucinovic Z, Duplancic D, Seselja-Perisin A, Kukoc-Modun L, Gunjaca G, Radman M, et al. Acute application of antioxidants protects against hyperoxia-induced reduction of plasma nitrite concentration. Clin Physiol Funct Imaging. 2015;35(1):76–80.
30. Rich JD, Thenappan T, Freed B, Patel AR, Thisted RA, Childers R, et al. QTc prolongation is associated with impaired right ventricular function and predicts mortality in pulmonary hypertension. Int J Cardiol. 2013;167(3):669–76.
31. Larsen JA, Kadish AH. Effects of gender on cardiac arrhythmias. J Cardiovasc Electrophysiol. 1998;9:655–64.
32. Rijnbeek PR, van Herpen G, Bots ML, Man S, Verweij N, Hofman A, et al. Normal values of the electrocardiogram for ages 16–90 years. J Electrocardiol. 2014;47(6):914–21.

33. Niemeijer MN, van den Berg ME, Deckers JW, Franco OH, Hofman A, Kors JA, et al. Consistency of heart rate-QTc prolongation consistency and sudden cardiac death: the Rotterdam Study. Heart Rhythm. 2015;12(10):2078–85.

34. Woodman RJ, Kingwell BA, Beilin LJ, Hamilton SE, Dart AM, Watts GF, et al. Assessment of central and peripheral arterial stiffness: studies indicating the need to use a combination of techniques. Am J Hypertens. 2005;18 2 Pt 1:249–60.

Pulmonology 27 (2021) 403–412

PULMONOLOGY

www.journalpulmonology.org

SPECIAL ARTICLE

Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort

S. Koirala[a,*], S. Borisov[b,*], E. Danila[c,*], A. Mariandyshev[d], B. Shrestha[e], N. Lukhele[f], M. Dalcolmo[g], S.R. Shakya[h], S. Miliauskas[i], L. Kuksa[j], S. Manga[k], A. Aleksa[l], J.T. Denholm[m], H.B. Khadka[n], A. Skrahina[o], S. Diktanas[p], M. Ferrarese[q], J. Bruchfeld[r], A. Koleva[s], A. Piubello[t], G.S. Koirala[u], Z.F. Udwadia[v], D.J. Palmero[w], M. Munoz-Torrico[x], R. GC[y], G. Gualano[z], V.I. Grecu[A], I. Motta[B], A. Papavasileiou[C], Y. Li[D], W. Hoefsloot[E], H. Kunst[F], J. Mazza-Stalder[G], M.-C. Payen[H], O.W. Akkerman[I,J], E. Bernal[K], V. Manfrin[L], A. Matteelli[M], H. Mustafa Hamdan[N], M. Nieto Marcos[O], J. Cadiñanos Loidi[P], J.J. Cebrian Gallardo[Q], R. Duarte[R], N. Escobar Salinas[S], R. Gomez Rosso[T], R. Laniado-Laborín[U,V], E. Martínez Robles[W], S. Quirós Fernandez[X], A. Rendon[Y], I. Solovic[Z], M. Tadolini[aa,bb], P. Viggiani[cc], E. Belilovski[b], M.J. Boeree[E], Q. Cai[dd], E. Davidavičienė[ee,ff], L.D. Forsman[r], J. De Los Rios[gg], J. Drakšienė[p], A. Duga[hh,ii], S.E. Elamin[N], A. Filippov[b], A. Garcia[w], I. Gaudiesiute[i], B. Gavazova[jj], R. Gayoso[g], V. Gruslys[c], J. Jonsson[kk], E. Khimova[d], G. Madonsela[ll], C. Magis-Escurra[E], V. Marchese[M], M. Matei[mm,nn], C. Moschos[C], B. Nakčerienė[ee,ff], L. Nicod[G], F. Palmieri[z], A. Pontarelli[oo], A. Šmite[j], M.B. Souleymane[t], M. Vescovo[w], R. Zablockis[c], D. Zhurkin[o], J.-W. Alffenaar[pp,qq,rr], J.A. Caminero[ss,tt], L.R. Codecasa[q], J.-M. García-García[uu], S. Esposito[vv], L. Saderi[ww], A. Spanevello[xx,yy], D. Visca[xx,yy], S. Tiberi[F,zz], E. Pontali[AA], R. Centis[BB], L. D'Ambrosio[CC], M. van den Boom[DD], G. Sotgiu[ww], G.B. Migliori[BB,*]

[a] *Damien Foundation Nepal, Kathmandu, Nepal*
[b] *Moscow Research and Clinical Center for TB Control, Moscow Government's Health Department, Moscow, Russian Federation*
[c] *Clinic of Chest Diseases, Immunology and Allergology, Vilnius University Medical Faculty, Centre of Pulmonology and Allergology, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*
[d] *Northern State Medical University, Northern (Arctic) Federal University, Arkhangelsk, Russian Federation*
[e] *Kalimati Chest Hospital/GENETUP/Nepal Anti Tuberculosis Association, Kathmandu, Nepal*
[f] *TB/HIV, Hepatitis, & PMTCT Department, World Health Organization, Eswatini WHO Country Office, Mbabane, Eswatini*
[g] *Reference Center Hélio Fraga, Fundação Oswaldo Cruz (Fiocruz)/Ministry of Health, Rio de Janeiro, Brazil*
[h] *Lumbini Provincial Hospital, Butwal, Nepal*

* Corresponding author at: Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS, Via Roncaccio 16, Tradate, Varese, 21049, Italy.
E-mail address: giovannibattista.migliori@icsmaugeri.it (G.B. Migliori).
* These authors equally contributed

https://doi.org/10.1016/j.pulmoe.2021.02.006

[i] *Department of Pulmonology, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[j] *MDR-TB Department, Riga East University Hospital for TB and Lung Disease Centre, Riga, Latvia*
[k] *Department of Infectious Diseases, University National San Antonio Abad Cusco, Cusco, Peru*
[l] *Department of Phthisiology and Pulmonology, Grodno State Medical University, Grodno, Belarus*
[m] *Victorian Tuberculosis Program, Melbourne Health, Department of Infectious Diseases, University of Melbourne, Melbourne, Australia*
[n] *Nepalgjunj TB Referral Center, TB Nepal, Nepalgunj, Nepal*
[o] *Republican Research and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus*
[p] *Tuberculosis Department, 3rd Tuberculosis Unit, Republican Klaipėda Hospital, Klaipėda, Lithuania*
[q] *TB Reference Centre, Villa Marelli Institute, Niguarda Hospital, Milan, Italy*
[r] *Division of Infectious Diseases, Department of Medicine, Solna, Karolinska Institute, Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden*
[s] *Pulmonology and Physiotherapy Department, Gabrovo Lung Diseases Hospital, Gabrovo, Bulgaria*
[t] *Damien Foundation, Niamey, Niger*
[u] *Nepal Anti Tuberculosis Association, Morang Branch, TB Clinic, Biratnagar, Province 1, Nepal*
[v] *Department of Respiratory Medicine, P.D. Hinduja National Hospital and MRC, Mumbai, India*
[w] *Pulmonology Division, Municipal Hospital F. J. Muñiz, Buenos Aires, Argentina*
[x] *Clínica de Tuberculosis, Instituto Nacional De Enfermedades Respiratorias Ismael Cosio Villegas, Ciudad De Mexico, Mexico*
[y] *Damien Foundation, Midpoint District Community Memorial Hospital, Danda, Nawalparasi, Nepal*
[z] *Respiratory Infectious Diseases Unit, National Institute for Infectious Diseases 'L. Spallanzani', IRCCS, Rome, Italy*
[A] *National Programme for Prevention, Surveillance and Control of Tuberculosis, Dolj Province, Romania*
[B] *Department of Medical Science, Unit of Infectious Diseases, University of Torino, Italy*
[C] *Department of Tuberculosis, Sotiria Athens Hospital of Chest Diseases, Athens, Greece*
[D] *Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China*
[E] *Radboud University Medical Center, Center Dekkerswald, Nijmegen, The Netherlands*
[F] *Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom*
[G] *Division of Pulmonary Medicine, University Hospital of Lausanne CHUV, Lausanne, Switzerland*
[H] *Division of Infectious Diseases, CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium*
[I] *University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands*
[J] *University of Groningen, University Medical Center Groningen, TB Center Beatrixoord, Haren, The Netherlands*
[K] *Unidad de Enfermedades Infecciosas, Hospital General Universitario Reina Sofia, Murcia, Spain*
[L] *Infectious and Tropical Diseases Operating Unit, S. Bortolo Hospital, Vicenza, Italy*
[M] *Clinic of Infectious and Tropical Diseases, WHO Collaborating Centre for TB Elimination and TB/HIV Co-infection, University of Brescia, Brescia, Italy*
[N] *MDR-TB Department, Abu Anga Teaching Hospital, Khartoum, Sudan*
[O] *Internal Medicine Department, Hospital Doctor Moliner, Valencia, Spain*
[P] *Internal Medicine Department, Hospital General de Villalba, Collado Villalba, Spain*
[Q] *Unidad de Neumología, Agencia Sanitaria Costa del Sol, Marbella, Spain*
[R] *National Reference Centre for MDR-TB, Hospital Centre Vila Nova de Gaia, Department of Pneumology, Public Health Science and Medical Education Department, Faculty of Medicine, University of Porto, Porto, Portugal*
[S] *Division of Disease Prevention and Control, Department of Communicable Diseases, National Tuberculosis Control and Elimination Programme, Ministry of Health, Santiago, Chile*
[T] *National Institute of Respiratory and Environmental Diseases Ïprof. Dr. Juan Max BoettnerÄsunción, Paraguay*
[U] *Universidad Autónoma de Baja California, Baja California, Mexico*
[V] *Clínica de Tuberculosis del Hospital General de Tijuana, Tijuana, Baja California, Mexico*
[W] *Internal Medicine Department, Hospital de Cantoblanco- Hospital General Universitario La Paz, Madrid, Spain*
[X] *Pneumology Department, Tuberculosis Unit, Hospital de Cantoblanco- Hospital General Universitario La Paz, Madrid, Spain*
[Y] *Centro de Investigación, Prevención y Tratamiento de Infecciones Respiratorias CIPTIR, University Hospital of Monterrey UANL (Universidad Autonoma de Nuevo Leon), Monterrey, Mexico*
[Z] *National Institute for TB, Lung Diseases and Thoracic Surgery, Vysne Hagy, Catholic University Ruzomberok, Slovakia*
[aa] *Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Policlinico di Sant'Orsola, Bologna, Italy*
[bb] *Department of Medical and Surgical Sciences Alma Mater Studiorum University of Bologna, Bologna, Italy*
[cc] *Reference Center for MDR-TB and HIV-TB, Eugenio Morelli Hospital, Sondalo, Italy*
[dd] *Zhejiang Integrated Traditional and Western Medicine Hospital, Hangzhou, China*
[ee] *National TB Registry, Public Health Department, Ministry of Health, Vilnius, Lithuania*
[ff] *Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania*
[gg] *Centro de Excelencia de TBMDR, Hospital Nacional Maria Auxiliadora, Lima, Peru*
[hh] *Baylor College of Medicine, Children's Foundation, Mbabane, Eswatini*
[ii] *National Pharmacovigilance Center, Eswatini Ministry of Health, Matsapha, Eswatini*
[jj] *Improve the Sustainability of the National TB Programme, Sofia, Bulgaria*

[kk] *Department of Public Health Analysis and Data Management, Public Health Agency of Sweden, Solna, Sweden*
[ll] *Eswatini National Aids Programme, Mbabane, Eswatini*
[mm] *Hospital of Pneumophtisiology Leamna, Dolj Province, Romania*
[nn] *University of Medicine and Pharmacy, Craiova, Romania*
[oo] *Respiratory Infectious Diseases Unit, Cotugno Hospital, A.O.R.N. dei Colli, Naples, Italy*
[pp] *University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, Australia*
[qq] *Westmead Hospital, Sydney, Australia*
[rr] *Marie Bashir Institute of Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia*
[ss] *Pneumology Department, Hospital General de Gran Canaria ''Dr. Negrin'', Las Palmas de Gran Canaria, Spain*
[tt] *Vital Strategies, New York, USA*
[uu] *Tuberculosis Research Programme (PII-TB), SEPAR, Barcelona, Spain*
[vv] *Pediatric Clinic, Pietro Barilla Children's Hospital, University of Parma, Parma, Italy*
[ww] *Clinical Epidemiology and Medical Statistics Unit, Department of z, University of Sassari, Sassari, Italy*
[xx] *Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy*
[yy] *Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Tradate, Varese-Como, Italy*
[zz] *Department of Infection, Royal London and Newham Hospitals, Barts Health NHS Trust, London, United Kingdom*
[AA] *Department of Infectious Diseases, Galliera Hospital, Genova, Italy*
[BB] *Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri IRCCS, Tradate, Italy*
[CC] *Public Health Consulting Group, Lugano, Switzerland*
[DD] *World Health Organization Regional office for Europe, Copenhagen, Denmark*

Received 15 February 2021; accepted 15 February 2021
Available online 19 March 2021

KEYWORDS
Tuberculosis;
MDR-TB;
Delamanid;
Bedaquiline;
Treatment outcomes;
Prevention of TB sequelae

Abstract The World Health Organization (WHO) recommends countries introduce new anti-TB drugs in the treatment of multidrug-resistant tuberculosis.

The aim of the study is to prospectively evaluate the effectiveness of bedaquiline (and/or delamanid)- containing regimens in a large cohort of consecutive TB patients treated globally.

This observational, prospective study is based on data collected and provided by Global Tuberculosis Network (GTN) centres and analysed twice a year.

All consecutive patients (including children/adolescents) treated with bedaquiline and/or delamanid were enrolled, and managed according to WHO and national guidelines.

Overall, 52 centres from 29 countries/regions in all continents reported 883 patients as of January 31st 2021, 24/29 countries/regions providing data on 100% of their consecutive patients (10–80% in the remaining 5 countries).

The drug-resistance pattern of the patients was severe (>30% with extensively drug-resistant -TB; median number of resistant drugs 5 (3—7) in the overall cohort and 6 (4—8) among patients with a final outcome).

For the patients with a final outcome (477/883, 54.0%) the median (IQR) number of months of anti-TB treatment was 18 (13—23) (in days 553 (385–678)). The proportion of patients achieving sputum smear and culture conversion ranged from 93.4% and 92.8% respectively (whole cohort) to 89.3% and 88.8% respectively (patients with a final outcome), a median (IQR) time to sputum smear and culture conversion of 58 (30—90) days for the whole cohort and 60 (30—100) for patients with a final outcome and, respectively, of 55 (30—90) and 60 (30—90) days for culture conversion.

Of 383 patients treated with bedaquiline but not delamanid, 284 (74.2%) achieved treatment success, while 25 (6.5%) died, 11 (2.9%) failed and 63 (16.5%) were lost to follow-up.

Introduction

The World Health Organization (WHO) estimated that about half million people suffer from multidrug- (MDR-) or rifampicin-resistant (RR-) tuberculosis (TB) in 2019, of whom 38% accessed treatment and, among them, 57% were successfully treated.[1,2]

Effective treatment, coupled with rapid and accurate diagnosis, of both drug-susceptible and -resistant (MDR- and extensively drug-resistant, XDR-) TB cases is an essential

intervention to curb the TB epidemic and prevent further development and transmission of drug-resistant *Mycobacterium tuberculosis* strains.[3,4]

New drugs (*i.e.*, delamanid and bedaquiline) have been recently licensed to manage MDR- and XDR-TB[2]; they were included into a new WHO drug classification where bedaquiline belongs to Group A and delamanid to Group C.[5–18]

Although more evidence is becoming available from experimental and observational studies on the efficacy and effectiveness of new drugs,[19–23] programmatic information on their effectiveness is still incomplete worldwide.[1]

The Global Tuberculosis Network (GTN) project,[24] which recently reported on the safety of these drugs, allowed to shed further light on the effectiveness of these drugs in a large cohort of patients (Table 1, Fig. 1).[24–26]

The aim of the study is to prospectively evaluate the effectiveness of bedaquiline and/or delamanid- containing regimens in a cohort of consecutive TB patients treated globally.

Methods

Study design

The study is observational, prospective and based on the collection twice a year and analysis of data provided by GTN centres.

Following a pilot study implemented in 2015 to pre-test the project's feasibility, the results of the project (management of adverse events) was published elsewhere.[25,26]

The study was approved by the Ethics Committee of the coordinating centre, and the participating centres obtained ethical clearance based on local regulations and signed a data-sharing agreement.[25,26]

All consecutive patients (including children and adolescents) treated with bedaquiline and/or delamanid were enrolled either from the beginning of the study or from the time the drugs under study were introduced in the respective country centre (*e.g.* in Mexico, Nepal, Paraguay, Spain, Slovakia and Sudan).[25,26]

In all participating countries, the patients were managed according to WHO and National guidelines, under supervision of a coordinating team supervising the patients' clinical management and validation of data.[27] Investigators were contacted by the coordinating centre to ensure accuracy after recoding and validation of the dataset before final analysis was conducted. Discrepancies were resolved by consensus.

WHO case and treatment outcome definitions were used.[1,5,6,28,29]

The present manuscript reports the results of the interim analysis conducted on the data collected up to the 31st January 2021.

Variables collected

The data were collected *via* an *ad hoc* developed collection form in electronic format.[25,26]

The information collected (from the clinical files of the participating centres) included, among others, anonymized patient's demographic data, bacteriological, radiological and clinical status at diagnosis, and details on bacteriological conversion and final treatment outcomes.

The study coverage and number of patients treated per centre are reported in Table 1.

Table 1 Participating countries, estimated coverage and number of cases enrolled.

Countries	Estimated coverage[a] %	Cases enrolled N
Argentina	100	11
Australia[c]	100[e]	26
Belarus[b]	80	53
Belgium	60	3
Brazil	100	39
Bulgaria	100	17
Chile	100	1
China[c]	100[d]	5
Eswatini	100	41
Greece	100	6
India	100[e]	15
Italy[g]	80	40
Latvia	100	30
Lithuania[h]	100	160
Mexico[i]	100	11
Nepal[h]	100	125
Netherlands[b]	100	6
Niger	100	17
Paraguay	100	1
Peru	80	29
Portugal	100	1
Romania[c]	100[f]	7
Russian Federation[b]	100[j]	202
Slovakia	100	1
Spain[g]	100	8
Sudan	100	2
Sweden	100	19
Switzerland	100[d]	3
United Kingdom	10	4
Total 29	Range 10%–100%	Total 883

Legend:
[a] Countries' estimate of the national coverage of the aDSM project on new drugs;
[b] 2 centres;
[c] 1 centre;
[d] in the Province/Canton reporting;
[e] in the State reporting;
[f] in the Province reporting;
[g] 7 centres;
[h] 5 centres;
[i] 3 centres;
[j] in the 2 Oblasts reporting.

Data analysis

A descriptive analysis was performed to evaluate the characteristics of the cohort.

Qualitative and quantitative variables were summarised using absolute and relative (percentage) frequencies, medians with interquartile ranges (IQR), and means with standard

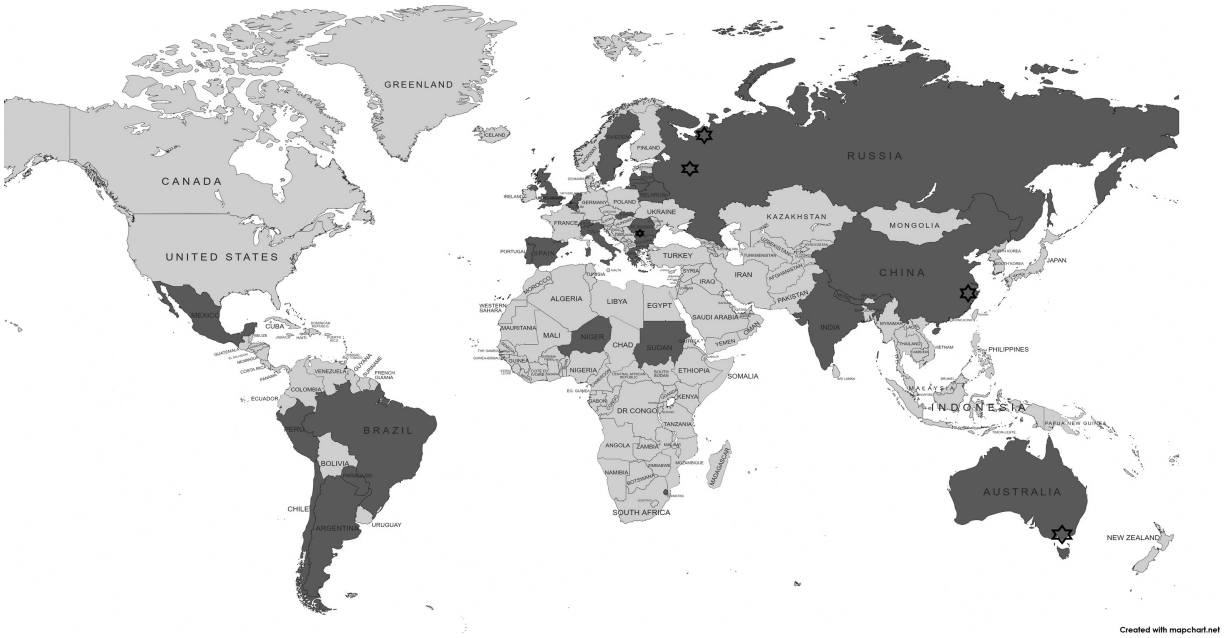


Figure 1 Global distribution of the clinical centres participating in the study.

☆ The following States/Regions are covered in the study: Australia (State of Victoria); China (Zhejiang Province); Romania (Dolj Region); Russian Federation (Arkhangelsk, Moscow Oblasts).

deviations (SD). Sputum smear and culture conversion (as well as the time to sputum and culture conversion) were evaluated in the whole cohort and in those completing their prescribed regimen.

Treatment outcomes were evaluated only in patients who completed the prescribed treatment regimen (separately for the entire cohort and in patients treated with bedaquiline but not delamanid) to favour international comparisons.

Results

Overall, 52 centres from 29 countries/regions in all continents reported 883 patients as of January 31st 2021 (Fig. 1).

Argentina, Australia (State of Victoria), Brazil, Bulgaria, Chile, Eswatini, China (Zhejiang Province), Greece, India, Latvia, Lithuania, Mexico, Nepal, The Netherlands, Niger, Paraguay, Portugal, Romania, Russian Federation (Moscow and Arkhangelsk Oblasts), Slovakia, Spain, Sudan, Sweden and Switzerland (Vaud county) reported 100% of the patients treated with new drugs in the country/region, while Belarus, Belgium, Italy, Peru and the United Kingdom reported a proportion of national patients ranging from 10% to 80% (Table 1).

Demographic, epidemiological, and clinical characteristics of the patients are summarised in Table 2. The bacteriological conversion rates and the time to sputum smear and culture conversion are reported in Table 3 separately for the entire cohort and for the patients completing their prescribed treatment regimen. The final treatment outcomes of the entire cohort (477/883, 54.0%) are summarized in Table 4, while Table 5 is reporting the patients treated with bedaquiline only who have a final outcome assigned.

Overall, 883 patients were treated with bedaquiline and/or delamanid, 477 of them with a final outcome assigned (Table 2).

Most patients were male (n = 602, 68.2% in the overall cohort and n = 333, 69.8% with a final outcome assigned) and the median (IQR) age was 38 (28–49) years for the entire cohort and (30–50) years for those with a final outcome.

The proportion of foreign born was 13.4% in the overall cohort and 12.8% in the group of patients with a final outcome. The main co-morbidities and risk factors are summarized in Table 2.

Pulmonary TB was diagnosed in 97% patients, and cavity lesions were found in over 60% of the patients' radiographs. Overall, there were 575/883 (65%) patients with MDR/RR-TB in the overall cohort, of whom 300/477 (62.9%) with a final outcome. Among them the XDR-TB cases were, respectively 289/883 (32.7%) and 169/477 (35.4%). Other resistance patterns were present only in 19/883 (2.2%) and 8/477 (1.7%), respectively.

The median (IQR) number of drugs for which resistance was detected was 5 (3—7) in the overall cohort and 6 (4—8) among patients with a final outcome.

Bedaquiline was administered to 782/883 patients in the entire cohort (88.6%), of whom 416/477 (87.2%) with a final outcome. The patients undergoing treatment with delamanid were, respectively 167/883 (18.9%) and 94/477 (19.7%), some of them having been treated also with bedaquiline.

The median (IQR) number of months of anti-TB treatment was 18 (13—23) (in days 553 (385–678)) among patients with a final outcome.

Bedaquiline was prescribed for 180 (168—264) days in the whole cohort and 183 (168–364) among patients with a final outcome. Delamanid was prescribed for 168 (144—184) days

Table 2 Characteristics of 883 patients undergoing treatment with bedaquiline and delamanid in the cohort, including 477 who completed the prescribed regimen.

Variable	All patients (n = 883)	Patients with final outcome (N = 477)
Male, n (%)	602/883 (68.2)	333/477 (69.8)
Median (IQR) age, years	38 (28—49)	39 (30—50)
Foreign born n (%)	118/882 (13.4)	61/477 (12.8)
Diabetes Mellitus, n (%)	79/880 (9.0)	40/476 (8.4)
People living with HIV, n (%)	67/871 (7.7)	27/473 (5.7)
Thyroid disease, n (%)	25/795 (3.1)	17/399 (4.3)
Alcohol misuse, n (%)	186/879 (21.2)	112/475 (23.6)
Injecting drug user n (%)	48/880 (5.5)	30/475 (6.3)
Methadone user, n (%)	10/787 (1.3)	4/395 (1.0)
Previous anti-TB treatment, n (%)	544/880 (61.8)	329/474 (69.4)
Surgical therapy, n (%)	90/814 (11.1)	59/449 (13.1)
Pulmonary TB, n (%)	857/883 (97.1)	463/477 (97.1)
Extra-pulmonary TB, n (%)	72/882 (8.2)	39/476 (8.2)
Cavitary lesions, n (%)	523/831 (62.9)	295/448 (65.8)
MDR/RR-TB, n (%)	575/883 (65.1)	300/477 (62.9)
XDR-TB, n (%)	289/883 (32.7)	169/477 (35.4)
Other drug-resistance patterns, n*(%)	19/883 (2.2)	8/477 (1.7)
Median (IQR) number of reported drug-resistances	5 (3—7)	6 (4—8)
Bdq administration, n (%)	782/883 (88.6)	416/477 (87.2)
Dlm administration, n (%)	167/883 (18.9)	94/477 (19.7)
Median (IQR) months anti-TB treatment duration	–	18 (13—23)
Median (IQR) days Bdq administration	180 (168—264)	183 (168—363,5)
Median (IQR) days Dlm administration	168 (144—184)	168 (136—186)

TB: tuberculosis; IQR: interquartile range; Bdq: bedaquiline; Dlm: delamanid; MDR/RR-TB: multi-drug resistant /rifampicin-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

* Including 3 susceptible cases treated with second-line drugs due to AEs first-line drugs.

Table 3 Sputum smear and culture conversion and median time to bacteriological conversion in 883 patients treated with new anti-tuberculosis drugs.

Variable	All patients (n = 883)	Patients with final outcome (N = 477)
Sputum smear conversion, n (%)	467/500 (93.4)	274/307 (89.3)
Sputum culture conversion, n (%)	532/573 (92.8)	324/365 (88.8)
Median (IQR) days sputum smear conversion	58 (30—90)	60 (30—100)
Median (IQR) days sputum culture conversion	55 (30—90)	60 (30—90)

IQR: interquartile range.

in the entire cohort and 168 (136—186) days to patients with a final outcome.

The proportion of patients achieving sputum smear conversion was 93.4% in the whole cohort and 89.3% among the patients with a final outcome, with a median (IQR) time to sputum smear and culture conversion of 58 (30—90) days for the whole cohort and 60 (30—100) for patients with a final outcome and, respectively, of 55 (30—90) and 60 (30—90) days as far as culture conversion is concerned (Table 3).

The final treatment outcomes of the entire cohort (477/883, 54.0%) are summarized in Table 4; 344/477 patients (72.1%) achieved treatment success, 38 died (8%), 20 failed (4.2%) and 75 (15.7%) were lost to follow-up.

Among the 383 patients treated with bedaquiline but not delamanid, 284 (74.2%) achieved treatment success, while 25 (6.5%) died, 11 (2.9%) failed and 63 (16.5%) were lost to follow-up (Table 5).

Discussion

The aim of the present study was to prospectively evaluate the outcome of a global cohort of patients treated with new anti-TB drugs.

Although new research results (some summarized in a special bedaquiline series of the IJTLD)[19–23,30–35] have been recently published, to the best of our knowledge this is the first global study prospectively reporting detailed information on treatment outcomes; the report of the safety profile of the new drugs was published elsewhere.[25,26]

The results of our study show that ~90% of patients from 29 countries in all continents, with a severe pattern of drug resistance (>30% with XDR-TB; median number of resistances: 5–6) achieved sputum smear and culture conversion within 60 days of treatment with new anti-TB drugs. The success rates achieved were 72.1% in the full cohort (patients

Table 4 Treatment outcomes of the 477 patients who completed the prescribed regimen including new anti-tuberculosis drugs.

Treatment Outcome	n/N (%)
Treatment success (cured + treatment completed)	344/477 (72.1)
Cured	281/477 (58.9)
Treatment completed	63/477 (13.2)
Died	38/477 (8.0)
Failure	20/477 (4.2)
Lost to follow-up	75/477 (15.7)

Table 5 Treatment outcomes of the 383 patients treated with bedaquiline (but no delamanid) who completed the prescribed regimen.

Treatment outcome	n/N (%)
Treatment success (cured + treatment completed)	284/383 (74.2)
Cured	226/383 (59.0)
Treatment completed	58/383 (15.1)
Died	25/383 (6.5)
Failure	11/383 (2.9)
Lost to follow-up	63/383 (16.5)

with a final outcome) and 74.2% among the patients (the vast majority) treated with bedaquiline. This second outcome is particularly relevant for international comparisons. Importantly, in this specific group of patients the death rate was 6.5%, the failure rate 2.9% and the lost to follow-up rate 16.5%; these outcomes need to be read considering that this cohort has been programmatically managed in many different settings, with a relatively low prevalence of HIV infection (5.7%). In a previous study by the GTN with different patients treated with bedaquiline,[9] the culture conversion rate was similar (90%) and the overall success rate 76.9%

The study stratified the success rates by geographical area, showing that in austral Africa (where the HIV prevalence is higher) it was lower (64.6%) than in Niger (76.5%) where HIV prevalence is low, Europe (76.5%) and elsewhere (77.6%). Specifically in XDR-TB patients, the success rate was 77.6% in Africa, 80.4% in Europe and 77.7% elsewhere; these peculiar results, with treatment outcomes higher among XDR- than MDR-TB patients, have been caused by the fact that the XDR-TB patients had access to better drugs in the regimen (*e.g.* linezolid, clofazimine) which were not available in all countries (at the time the study was conducted) for MDR-TB patients. The WHO has from January 2021 updated its DR-TB definitions[36] to include the term pre-XDR for patients with an MDR-TB strain resistant to later generation fluoroquinolone and XDR-TB which is MDR-TB plus resistance to two group A drugs (fluoroquinolone plus bedaquiline or linezolid resistance). The MDR-TB definition remains the same.[28,36]

Similarly, the death rate was much higher in Africa (23.9%) than in Europe (3.5%) and elsewhere (6.1%).

In a sub-group analysis of the 57 severe patients undergoing adjuvant surgery, the culture conversion rate was similar (90%) and the overall success rate 69.1%.[37]

A South African study on 19,617 patients showed a 3-fold reduction of all-cause mortality among individuals treated with bedaquiline when compared with those treated without new drugs.[38]

In the large individual patient data meta-analysis on 12,030 MDR-TB patients[18] a small proportion of patients was treated with bedaquiline: 431/491 (87.8%) achieved treatment success (aOR, 95% CI: 2.0, 1.4–2.9) and 59/550 (10.7%) died (aOR, 95% CI: 0.4, 0.3—0.5).

The preliminary results of the Challenge-TB Project[30] reported, among bedaquiline-treated patients, a culture conversion of 71% at months 6, with 58.8% treatment success, 11.8% failure, 23.5% died, 4.7% lost to follow-up and 1.2% still on treatment after 24 months (2016 cohort data). The patients' drug resistance profile was not reported.[30] The project involved 23 countries with 9389 patients enrolled between 2016 and mid-2019. Among the most relevant problems encountered, the Authors identified the limited in-country coordination and the absence of a robust clinical and laboratory network and the difficulties of implementing effective monitoring of adverse events related to the new drugs.[25,26]

A report from India (interim analysis) showed 83% culture conversion rate among the patients treated with bedaquiline within a median time of 60 days, while the final outcomes were not yet available.[33]

In Eswatini, between 2015 and 2018, 355 patients started treatment with new drugs (bedaquiline and/or delamanid), of whom 109 were treated with bedaquiline only and with final outcomes.[35] Out of 109 patients, 80 were treated successfully (73.4%, a result consistent with that of our study), 18 died (16.5%, higher than our death rate but the HIV prevalence was higher in Eswatini, 72.3%), 1 failed, 1 was lost to follow-up (both 0.9%) and 9 were still in treatment after 24 months (8.3%). In the Eswatini cohort the proportion of males (58—7%), the median (IQR) age (35 (29–44) years) and the proportion of pre-XDR-/XDR-TB patients (26—1%) was consistent with our study.

Although without reporting details on treatment outcomes some studies have started reporting on the modified shorter regimens, which include bedaquiline ro replace the injectable drug in the former Bangladesh regimen.[20,31,34]

The project worked as a 'register' reporting treatment outcomes (and aDSM findings)[25,26] twice a year so as to support countries in implementing quality monitoring and evaluation of the process of introducing new anti-TB drugs under programmatic conditions.

The study has several strengths, including the number of countries participating (29) from all continents, a large sample size (as far we know one of the largest studies of its kind), the prospective design, and the accuracy of the information collected. Last but not least, the majority of countries/states/regions (24/29) provided data on all the consecutive patients treated with bedaquiline and delamanid during the study period.

One limitation (common to all the studies of this kind) is the impossibility of attributing the outcomes to a specific drug, as treatment regimens are inherently polypharmacological.

A second limitation is that few paediatric patients (twenty-seven individuals aged less than 18 years) and people living with HIV (n = 67; 7.7%) were included in the cohort to allow specific sub-analyses.

The study will continue to evaluate early and final treatment outcomes as periodic updates occur and the 'cohort' is therefore a 'living' one. This cohort allows evaluation of novel treatments and combinations in a relatively short time-frame – particularly important given the substantial variation in international practice and guidelines recommending person-centered therapy for MDR-TB.[4,5,39–41]

This approach will allow the participating countries to evaluate the 'quality' of their treatment services and minimise the risk of post-treatment sequelae responsible of functional damage and impaired quality of life.[42–48]

In conclusion, our Global TB Network study further supports the importance of access to lifesaving anti-TB drugs like bedaquiline to improve outcome of drug-resistant (DR) TB patients. Bedaquiline has allowed for an all-oral, less toxic shorter regimen which significantly improves survival, and it is becoming more widely available globally.[49] Future cohort reviews will show a reduction of treatment duration from 18 months to 6 months. This global study shows that even when there is access to the same WHO DR TB regimen, outcomes can still differ greatly, highlighting that managing MDR-/DR-TB is not only a question of better detection of DR-TB and starting treatment. Even though the WHO has shortened treatment considerably for the majority of DR-TB patients, it is very likely that more work and investment are required, especially in resource limited settings and treatment of people living with HIV and to combat the small but concerning number of XDR-TB patients.

Authors'contribution

The manuscript was conceived, planned, written, edited and approved using a collaborative approach, following the internal GTN (Global Tuberculosis Network) and internationally acknowledged rules on Authorship, based on major intellectual contribution to the steps mentioned above. The study represents a global effort involving 26 countries in all continents.

Giovanni Sotgiu, Simon Tiberi, Rosella Centis, Lia D'Ambrosio and Giovanni Battista Migliori wrote the protocol. Giovanni Sotgiu, Laura Saderi and Raquel Duarte revised it for the methodological content.

Giovanni Sotgiu, Laura Saderi, Rosella Centis and Lia D'Ambrosio performed the analysis.

Simon Tiberi, Rosella Centis, Lia D'Ambrosio, Emanuele Pontali, Jan-Willem Alffenaar, Jose A. Caminero, Giovanni Sotgiu and Giovanni Battista Migliori wrote the first draft of the manuscript.

Sushil Koirala, Sergey Borisov, Judith Bruchfeld, Alberto Piubello, Onno Akkermann, Justin Denholm, José-María García-García, Rafael Laniado-Laborín, Jesica Mazza-Stalder, Alberto Matteelli, Marcela Munoz-Torrico, Martin van den Boom, Dina Visca, Jose A. Caminero, Giovanni Sotgiu wrote the sections of the manuscript (second draft).

Antonio Spanevello, José-María, García-García Zarir Farokh Udwadia, Edvardas Danila, Andrei Maryandyshev, Susanna Esposito and Margareth Dalcolmo provided comments to the second draft (third draft).

Bhabana Shrestha, Satya Raj Shakya, Hikmat Bahadur Khadka, Ghan Shyam Koirala, Rajesh GC, Skaidrius Miliauskas, Liga Kuksa, Selene Manga, Alena Skrahina, Saulius Diktanas, Luigi Ruffo Codecasa, Alena Aleksa, Antoniya Koleva, Evgeny Belilovski, Enrique Bernal, Martin J Boeree, Julen Cadiñanos Loidi, Qingshan Cai, Jose Joaquín Cebrian Gallardo, Moschos Charalampos, Edita Davidavičienė, Lina Davies Forsman, Jorge De Los Rios Jefe, Alemayehu Duga, Seifeldin Eltaeb Elamin, Nadia Escobar Salinas, Maurizio Ferrarese, Aleksey Filippov, Blagovesta Gadzheva, Ana Garcia, Ieva Gaudiesiute, Regina Gayoso, Roscio Gomez Rosso, Vygantas Gruslys, Gina Gualano, Wouter Hoefsloot, Victor Ionel Grecu, Jerker Jonsson, Elena Khimova, Heinke Kunst, Yang Li, Nomthandazo Lukhele, Cecile Magis-Escurra, Gugulethu Madonsela, Vinicio Manfrin, Valentina Marchese, Elena Martínez Robles, Andrei Maryandyshev, Marius Matei, Ilaria Motta, Hamdan Mustafa Hamdan, Birutė Nakčerienė, Lauren Nicod, Magnolia Nieto Marcos, Domingo Juan Palmero, Fabrizio Palmieri, Apostolos Papavasileiou, Marie-Christine Payen, Agostina Pontarelli, Sarai Quirós, Adrian Rendon, Laura Saderi, Agnese Šmite, Ivan Solovic, Mahamadou Bassirou Souleymane, Marina Tadolini, Marisa Vescovo, Piero Viggiani, Rolandas Zablockis, Dmitry Zhurkin and provided additions to the fourth draft.

Simon Tiberi and Justin Denholm proof read the manuscript.

All co-Authors approved the final manuscript.

Funding sources

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

Ethical approval

Ethical approval was obtained by the coordinating centre and in each country as per national regulations in force.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The project is supported by the Global Tuberculosis Network (GTN; Committees on TB Treatment, Clinical trials and Global TB Consilium) and was part of the European Respiratory Society Latin American project in collaboration with ALAT (Asociación Latino Americana de Torax - Latino American Thoracic Association) and SBPT (Brazilian Society of Pulmonology and Tuberculosis).

This article belongs to the scientific activities of the WHO Collaborating Centre for Tuberculosis and Lung Diseases, Tradate, ITA-80, 2017-2020- GBM/RC/LDA.

The Authors wish to thank Dr. Algirdas Gauronskis, Dr.Vita Globytė (Clinic of Tuberculosis and Pulmonology, Republican Šiauliai county hospital, Šiauliai, Lithuania), Dr. Antanas Strazdas (Department of Tuberculosis, Alytus

County Tuberculosis Hospital, Alytus, Lithuania), Dr. Paola Castellotti (Regional TB Reference Centre, Villa Marelli Institute, Niguarda Hospital, Milan, Italy), Ms. Samriddhi Karki (Kalimati Chest Hospital/ GENETUP NATA, Nepal), Dr Andrea Calcagno, Alberto Gaviraghi and Francesca Alladio (Department of Medical Science, Unit of Infectious Diseases, University of Torino, Italy) for their contribution.

References

1. World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf Accessed 9 December 2020.
2. Pontali E, Raviglione MC, Migliori GB, The writing group members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev. 2019;28(152):190035, http://dx.doi.org/10.1183/16000617.0035-2019.
3. Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, et al. Reducing tuberculosis transmission: a consensus document from the World Health Organization Regional Office for Europe. Eur Respir J. 2019;53(6):1900391, http://dx.doi.org/10.1183/13993003.00391-2019.
4. Migliori GB, Tiberi S, Zumla A, Petersen E, Chakaya JM, Wejse C, et al. MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network. Int J Infect Dis. 2020;92S:S15–25, http://dx.doi.org/10.1016/j.ijid.2020.01.042.
5. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
6. Migliori GB, Global Tuberculosis Network (GTN). Evolution of programmatic definitions used in tuberculosis prevention and care. Clin Infect Dis. 2019;68(10):1787–9, http://dx.doi.org/10.1093/cid/ciy990.
7. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723–32, http://dx.doi.org/10.1056/NEJMoa1313865.
8. Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, et al. TMC207-C209 Study Group. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J. 2016;47(2):564–74.
9. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study. Eur Respir J. 2017;49(5):1700387, http://dx.doi.org/10.1183/13993003.00387-2017.
10. Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and MDR-TB: a systematic and critical analysis of the evidence. Eur Respir J. 2016;47:394–402.
11. Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistance tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. Eur Respir J. 2017;49(3):1700146, http://dx.doi.org/10.1183/13993003.00146-2017.
12. Mbuagbaw L, Guglielmetti L, Hewison C, Bakare N, Bastard M, Caumes E, et al. Outcomes of Bedaquiline Treatment in Patients with Multidrug-Resistant Tuberculosis. Emerg Infect Dis. 2019;25(5):936–43, http://dx.doi.org/10.3201/eid2505.181823.
13. Chesov D, Heyckendorf J, Alexandru S, Donica A, Chesov E, Reiman M, et al. Impact of bedaquiline on treatment outcomes of multidrug-resistant tuberculosis in a high-burden country. Eur Respir J. 2020, http://dx.doi.org/10.1183/13993003.02544-2020. Dec 17:2002544.
14. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366(23):2151–60, http://dx.doi.org/10.1056/NEJMoa1112433.
15. Kim CT, Kim CTO, Shin HJ, Ko YC, Hun Choe Y, Kim HR, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis:a multi-center cohort study in Korea. Eur Respir J. 2018;51(3):1702467, http://dx.doi.org/10.1183/13993003.02467-2017.
16. Kuksa L, Barkane L, Hittel N, Gupta R. Final treatment outcomes of multidrug and extensively drug-resistant tuberculosis patients in Latvia receiving delamanid-containing regimens. Eur Respir J. 2017;50(5):1701105, http://dx.doi.org/10.1183/13993003.01105-2017.
17. Mohr E, Hughes J, Reuter A, Trivino Duran L, Ferlazzo G, Daniels J, et al. Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa. Eur Respir J. 2018;51(6):1800017, http://dx.doi.org/10.1183/13993003.00017-2018.
18. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821–34, http://dx.doi.org/10.1016/S0140-6736(18)31644-1.
19. Bernal O, Lopez R, Montoro E, Avedillo P, Westby K, Ghidinelli M. Introduction and scaling up of new drugs for drug-resistant TB: experiences from the Americas. Int J Tuberc Lung Dis. 2020;24(10):1058–62, http://dx.doi.org/10.5588/ijtld.20.0111.
20. Cox H, Shah NS, Castro KG. Discovering a new drug is only the beginning: progress and challenges in expanding access to BDQ for MDR-TB treatment. Int J Tuberc Lung Dis. 2020;24(10):985–6, http://dx.doi.org/10.5588/ijtld.20.0562.
21. Rutta E, Kambili C, Mukadi Y. The Bedaquiline donation program: progress and lessons learned after 4 years of implementation. Int J Tuberc Lung Dis. 2020;24(10):1039–45, http://dx.doi.org/10.5588/ijtld.20.0134.
22. Lachenal N, Hewison C, Mitnick C, Lomtadze N, Coutisson S, Osso E, et al. Setting up pharmacovigilance based on available endTB Project data for bedaquiline. Int J Tuberc Lung Dis. 2020;24(10):1087–94, http://dx.doi.org/10.5588/ijtld.20.0115.
23. Seung KJ, Khan U, Varaine F, Ahmed S, Bastard M, Cloez S, et al. Introducing new and repurposed TB drugs: the endTB experience. Int J Tuberc Lung Dis. 2020;24(10):1081–6, http://dx.doi.org/10.5588/ijtld.20.0141.
24. Silva DR, Rendon A, Alffenaar JW, Chakaya JM, Sotgiu G, Esposito S, et al. Global TB Network: working together to eliminate tuberculosis. J Bras Pneumol. 2018;44(5):347–9, http://dx.doi.org/10.1590/S1806-37562018000000279.
25. Akkerman O, Aleksa A, Alffenaar JW, Al-Marzouqi NH, Arias-Guillén M, Belilovski E, et al. Members of the International Study Group on new anti-tuberculosis drugs and adverse events monitoring. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: a global feasibility study. Int J Infect Dis. 2019;83:72–6, http://dx.doi.org/10.1016/j.ijid.2019.03.036.
26. Borisov S, Danila E, Maryandyshev A, Dalcolmo M, Miliauskas S, Kuksa L, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculo-

sis: first global report. Eur Respir J. 2019;54(6):1901522, http://dx.doi.org/10.1183/13993003.01522-2019.
27. Tiberi S, Pontali E, Tadolini M, D'Ambrosio L, Migliori GB. Challenging MDR-TB clinical problems – the case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs. Int J Infect Dis. 2019;80S:S68–72, http://dx.doi.org/10.1016/j.ijid.2019.01.040.
28. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020). Geneva: World Health Organization; 2013. WHO/HTM/TB/2013.2. Available at: https://www.who.int/tb/publications/definitions/en Accessed 4 February 2021.
29. Avaliani Z, Gozalov O, Kuchukhidze G, Skrahina A, Soltan V, van den Boom M, et al. What is behind programmatic treatment outcome definitions for tuberculosis? Eur Respir J. 2020;56(1):2001751, http://dx.doi.org/10.1183/13993003.01751-2020.
30. Edwards CG, Wares DF, Dravniece G, Gebhard A, Tiemersma E, van der Grinten E, et al. Introducing bedaquiline: experiences from the Challenge TB Project. Int J Tuberc Lung Dis. 2020;24(10):1046–53, http://dx.doi.org/10.5588/ijtld.19.0790.
31. Zabsonre I, Thi SS, Cox V. Overcoming barriers to the access and uptake of newer drugs for multidrug-resistant TB. Int J Tuberc Lung Dis. 2020;24(10):1054–7, http://dx.doi.org/10.5588/ijtld.20.0226.
32. Santiago MR, Garfin AMC, Balanag VM. Introduction of bedaquiline for the treatment of drug-resistant TB in the Philippines. Int J Tuberc Lung Dis. 2020;24(10):1063–6, http://dx.doi.org/10.5588/ijtld.20.0359.
33. Sachdeva KS, Arora N, Solanki R, Singla R, Sarin R, Bhatnagar A, et al. Strengthened capacity of India's bedaquiline Conditional Access Programme for introducing new drugs and regimens. Int J Tuberc Lung Dis. 2020;24(10):1067–72, http://dx.doi.org/10.5588/ijtld.20.0136.
34. Ndjeka N, Hughes J, Reuter A, Conradie F, Enwerem M, Ferreira H, et al. Implementing novel regimens for drug-resistant TB in South Africa: what can the world learn? Int J Tuberc Lung Dis. 2020;24(10):1073–80, http://dx.doi.org/10.5588/ijtld.20.0174.
35. Vambe D, Kay AW, Furin J, Howard AA, Dlamini T, Dlamini N, et al. Bedaquiline and delamanid result in low rates of unfavourable outcomes among TB patients in Eswatini. Int J Tuberc Lung Dis. 2020;24(10):1095–102, http://dx.doi.org/10.5588/ijtld.20.0082.
36. World Health Organization. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. Geneva: World Health Organization; 2021. CC BY-NC-SA 3.0 IGO.
37. Borisov SE, D'Ambrosio L, Centis R, Tiberi S, Dheda K, Alffenaar JW, et al. Outcomes of patients with drug-resistant-tuberculosis treated with bedaquiline-containing regimens and undergoing adjunctive surgery. J Infect. 2019;78(1):35–9, http://dx.doi.org/10.1016/j.jinf.2018.08.003.
38. Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. Eur Respir J. 2018;52(6):1801528, http://dx.doi.org/10.1183/13993003.01528-2018.
39. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. STREAM Study Collaborators. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1201–13, http://dx.doi.org/10.1056/NEJMoa1811867.
40. Churchyard GJ. A short regimen for rifampin-resistant tuberculosis. N Engl J Med. 2019;380(13):1279–80, http://dx.doi.org/10.1056/NEJMe1902904.
41. Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of drug-resistant tuberculosis. An Official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2019;200(10):e93–142, http://dx.doi.org/10.1164/rccm.201909-1874ST.
42. Muñoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, et al. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis? J Bras Pneumol. 2016;42(5):374–85, http://dx.doi.org/10.1590/S1806-37562016000000226.
43. Tiberi S, Torrico MM, Rahman A, Krutikov M, Visca D, Silva DR, et al. Managing severe tuberculosis and its sequelae: from intensive care to surgery and rehabilitation. J Bras Pneumol. 2019;45(2):e20180324, http://dx.doi.org/10.1590/1806-3713/e20180324.
44. Visca D, Zampogna E, Sotgiu G, Centis R, Saderi L, D'Ambrosio L, et al. Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae. Eur Respir J. 2019;53(3):1802184, http://dx.doi.org/10.1183/13993003.02184-2018.
45. Visca D, Centis R, Munoz-Torrico M, Pontali E. Post-tuberculosis sequelae: the need to look beyond treatment outcome. Int J Tuberc Lung Dis. 2020;24(8):761–2.
46. Visca D, Centis R, D'Ambrosio L, Muñoz-Torrico M, Chakaya JM, Tiberi S, et al. The need for pulmonary rehabilitation following tuberculosis treatment. Int J Tuberc Lung Dis. 2020;24(7):720–2.
47. Muñoz-Torrico M, Cid-Juárez S, Gochicoa-Rangel L, Torre-Bouscolet L, Salazar-Lezama MA, Villarreal-Velarde H, et al. Functional impact of sequelae in drug-susceptible and multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2020;24(7):700–5.
48. Akkerman OW, Ter Beek L, Centis R, Maeurer M, Visca D, Muñoz-Torrico M, et al. Rehabilitation, optimized nutritional care, and boosting host internal milieu to improve long-term treatment outcomes in tuberculosis patients. Int J Infect Dis. 2020;92S:S10–4, http://dx.doi.org/10.1016/j.ijid.2020.01.029.
49. Natarajan S, Singla R, Singla N, Gupta A, Caminero JA, Chakraborty A, et al. Treatment interruption patterns and adverse events among patients on bedaquiline containing regimen underprogrammatic conditions in India. Pulmonology. 2020;S2531–0437(20), http://dx.doi.org/10.1016/j.pulmoe.2020.09.006, 30213-0.

Pulmonology 27 (2021) 413–422

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Use of Helmet CPAP in COVID-19 – A practical review

H. Amirfarzan[a,*], M. Cereda[b], T.G. Gaulton[b], K.B. Leissner[c], A. Cortegiani[d,e], R. Schumann[a], C. Gregoretti[d,f]

[a] *Tufts University School of Medicine, VA Boston Healthcare System, Anesthesiology and Perioperative Medicine, United States*
[b] *Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania, 3400 Spruce St, Dulles Bldg, Floor 7, Philadelphia, PA 19104, United States*
[c] *Harvard Medical School, VA Boston Healthcare System, Anesthesiology and Perioperative Medicine, United States*
[d] *Departmentof Surgical, Oncological and Oral Science (Di.Chir.On.S.), University of Palermo, Italy*
[e] *Department of Anesthesia Intensive Care and Emergency, Policlinico Paolo Giaccone, Palermo, Italy*
[f] *Fondazione 'Giglio', Cefalù, Italy*

Received 10 November 2020; accepted 23 January 2021

KEYWORDS
Helmet;
Non-invasive mechanical ventilation;
COVID-19;
ARDS;
Respiratory failure

Abstract Helmet CPAP (H-CPAP) has been recommended in many guidelines as a noninvasive respiratory support during COVID-19 pandemic in many countries around the world. It has the least amount of particle dispersion and air contamination among all noninvasive devices and may mitigate the ICU bed shortage during a COVID surge as well as a decreased need for intubation/mechanical ventilation. It can be attached to many oxygen delivery sources. The MaxVenturi setup is preferred as it allows for natural humidification, low noise burden, and easy transition to HFNC during breaks and it is the recommended transport set-up. The patients can safely be proned with the helmet. It can also be used to wean the patients from invasive mechanical ventilation. Our article reviews in depth the pathophysiology of COVID-19 ARDS, provides rationale of using H-CPAP, suggests a respiratory failure algorithm, guides through its setup and discusses the issues and concerns around using it.

Introduction

In 2019, a cluster of a novel acute atypical respiratory disease was described in Wuhan, China. A novel coronavirus was responsible for the outbreak and was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to its high homology with SARS-CoV, which also caused severe pulmonary involvement with a high mortality in 2002–03. The

* Corresponding author.
E-mail addresses: Houman.amirfarzan@va.gov (H. Amirfarzan), maurizio.cereda@pennmedicine.upenn.edu (M. Cereda), Timothy.Gaulton2@pennmedicine.upenn.edu (T.G. Gaulton), Kay.leissner@va.gov (K.B. Leissner), andrea.cortegiani@unipa.it (A. Cortegiani), Roman.Schumann@va.gov (R. Schumann), c.gregoretti@gmail.com (C. Gregoretti).

https://doi.org/10.1016/j.pulmoe.2021.01.008

new disease was named Coronavirus disease 19 (COVID-19) and in 2020 the World Health Organization (WHO) declared a pandemic impacting nearly the entire world.[1]

SARS-CoV2 primarily affects the respiratory system, but many additional organ systems can also be severely affected. A high percentage of COVID-19 patients admitted to an Intensive Care Unit (ICU) develop severe acute hypoxemic respiratory failure (AHRF) and fulfill criteria for COVID-19 acute respiratory distress syndrome (CARDS), requiring mechanical ventilation.[2–4]

For patients with COVID-19, use of noninvasive mechanical ventilation with face masks (FM) or high flow nasal therapy (HFNT) has been either reduced or restricted to airborne infection isolation rooms, due to the viral aerosolization potential with these techniques.[5,6] Therefore, across the Unites States (US), in hypoxemic patients who can no longer be sustained on conventional oxygen supplementation, the rate of intubation and mechanical ventilation remains high.[2,4,7]

In China and many European countries, noninvasive respiratory support (NRS) has been employed in up to 32.4% of COVID-19 patients requiring intensive care[1,3] and includes helmet-based methods as part of a respiratory failure management strategy.[8–11] Helmet Continuous Positive Airway Pressure (H-CPAP) was initially introduced in the 1990s using modifications of existing hyperbaric oxygen treatment devices, and thereafter the use expanded to NRS for additional indications.[12,13] H-CPAP has recently been reported to significantly reduce SARS-CoV-2 aerosolization and exposure risk for healthcare personnel compared to HFNT or FM.[6,9,10] When facility ICU bed and ventilator capacity has been temporarily expended, H-CPAP could be a lifesaving, easy to perform respiratory management tool for appropriate COVID-19 patients with respiratory failure and subsequently may not necessarily require an ICU stay. H-CPAP may avoid the need for intubation and ventilator associated problems in patients with CARDS altogether.[14,15]

This practical review summarizes the COVID-19 respiratory physiology, the evidence to date for helmet use as well as step-by-step instructions for clinicians to deliver CPAP with a helmet for patients requiring noninvasive respiratory support during a respiratory pandemic such as COVID-19.

Pathophysiology and respiratory mechanics of COVID-19 dyspnea

The pathophysiology of COVID-19 respiratory distress may best be described as an inflammatory induced pulmonary vasculitis, leading to varying degrees of lung collapse secondary to edema and microthrombosis,[16] characterized by bilateral ground glass opacities on CT-scan, resulting in ventilation perfusion ratio ($\dot{V}/\dot{Q}$) mismatching and a significant shunt fraction.[17,18]

Elevated clot waveform analysis parameters are consistent with hypercoagulability in critically ill COVID-19 patients.[19] CARDS is an ''atypical'' form of ARDS, leading to severe hypoxemia, dyspnea, impaired lung diffusion, formation of intravascular microthrombi hypoxic vasoconstriction, and intrapulmonary shunting.[19,20] As in the first days of the disease, the lung mechanics are well-preserved and there is usually no increased airway resistance or dead space ventilation, a disparity may be seen between the degree of hypoxemia and a clinically otherwise relatively unimpaired, ''happy'' patient.[21]

To better distinguish CARDS from classic ARDS, a continuum between 2 phenotypes of CARDS has been proposed to describe the pathophysiology, although not supported by any controlled trial and still in need of more precisely defined mechanisms. The early Type L is characterized by low elastance, (relatively high compliance, 50.2 ± 14.3 mL/cmH2O), low ventilation to perfusion ratio, limited PEEP response and low alveolar recruitability. The late type H is characterized by high elastance, high right-to-left shunt, high lung weight, better PEEP responsiveness, and high alveolar recruitability.[20,22] The two types are not mutually exclusive and overlap occurs during the course of the disease.

Improved arterial partial pressure of oxygen (PaO_2) by positive end-expiratory pressure (PEEP) may be explained not only by lung recruitment, but also by more even distribution of perfusion, diverting flow toward the high Va/Q areas.[23] The optimum level of PEEP to improve oxygenation still remains controversial and may depend upon presenting phenotype.

Rationale for Helmet CPAP in patients with hypoxemic respiratory failure

In a recent meta-analysis of trials of adults with AHRF, treatment with NRS including H-CPAP was associated with lower risk of death compared with standard oxygen therapy.[24]

In addition to the relative ease of use, H-CPAP may have physiological and biological advantages over the alternative strategies. H-CPAP decreases air leaks compared to face mask interfaces, potentially reducing viral transmission when used to treat patients with AHRF from COVID-19. In different forms of acute hypoxic respiratory failure, H-CPAP may increase recruitment of non-aerated alveoli in dependent pulmonary regions,[25,26] thereby increasing lung functional residual capacity and decreasing shunt. In theory, the tidal volume is shifted with H-CPAP to a more compliant part of the pressure-volume curve, thus reducing the patient's effort and work of breathing (WOB) and oxygen consumption[27,28] despite absence of ventilatory assistance. In the less severe forms of ARDS when spontaneous effort remains modest, there is an improved gas exchange and better lung aeration in CT analysis in experimental and clinical studies.[29] By decreasing alveolar collapse and inhomogeneity of pulmonary gas distribution without imposing a higher tidal volume, CPAP may decrease lung injury induced by vigorous diaphragmatic contraction in dorsal regions.[30] The presumed mechanism of diaphragmatic injury to the lungs is thought to be due to strong inspiratory efforts and large transpulmonary pressure swings that should be avoided to prevent an adverse effect of Pendelluft and large local tidal volume on baby lungs.[31] Comparative physiological studies have demonstrated the equal performance of helmet and mask CPAP for reducing the inspiratory effort and WOB[32]; however, H-CPAP may increase the duration of positive pressure application because of improved tolerability by patients.[33]

Table 1 Major benefits and challenges of H-CPAP compared to face mask.

• Reduce aerosolization and exposure to SARS-CoV-2 with proper fit[5,6]
• Allows enteral nutrition and hydration
• Limited air leaks with proper fitting[74]
• No facial skin lesions[12]
• Fitting independent of the patient's face anatomy
• Can be used without a ventilator
• Patient cooperation is likely improved with helmet
Challenges
• Large dead space needing fresh high flows
• Noise
• Possible Claustrophobia
• Armpits and neck skin breakdown
• Eye irritation
• Possible Claustrophobia
• Clinician team learning curve
• Achieving clinician education, engagement and acceptance of H-CPAP as a treatment option that improves outcomes

Currently, both noninvasive CPAP and HFNT are first-line treatments for AHRF in immunocompromised patients.[26] In several recent meta-analysis of trials in adults with AHRF, treatment with NRS including H-CPAP was associated with a lower risk of death, decreased intubation compared with standard oxygen therapy.[24,34]

The different considerations for H-CPAP use are summarized in Table 1.

In 2016, a major American academic medical center showed helmet NRS (pressure support ventilation) to decrease intubation rates and ICU length of stay in patients with mild to moderate ARDS when compared to mask NRS.[33]

Patients with COVID-19 and shunt-related hypoxemia may have a variable WOB and may respond favorably to CPAP, especially during type L CARDS and severe hypoxemia.[20] A successful response to CPAP can most likely be expected when lung elastance and congestion are still low and clinical signs of excessive inspiratory efforts (i.e. use of accessory muscles) are still absent.[20] Currently available data regarding the safety profile of H-CPAP mostly from Europe[15,35,36] suggests that H-CPAP is a helpful tool for NRS in mild to moderate CARDS and may mitigate the ICU bed shortage during a COVID surge as well as a decreased need for intubation/mechanical ventilation. Recently, Franco et al. reported using H-CPAP as a first line NRS in 49% of CARDS patients and only 25% of them required invasive mechanical ventilation after their initial treatment.[37]

Within the US, Gaulton et al. found that H-CPAP decreased the odds of intubation by over 80% compared to HFNT in obese and overweight patients with AHRF from COVID-19.[38] Additionally, H-CPAP as part of a ventilation strategy for COVID-19 patients has been supported by the Society for Critical Care Medicine and was integrated in their guidelines as early as March 2020.[39]

H-CPAP respiratory failure management for COVID-19 patients

The construction of the helmet typically includes a transparent, latex free, polyvinylchloride hood joined to a metal or plastic ring that incorporates a soft polyvinylchloride collar adjustable to different neck circumferences. Underarm straps may be attached to the front and back of the durable ring to prevent upward displacement of the helmet when gas flow is initiated.[32] Prior to the COVID-19 pandemic in the US, Food and Drug Administration (FDA) approval for helmets was limited to the use for gas delivery in a hyperbaric chamber. In response to the pandemic, the FDA has issued Emergency Use Authorizations (EUAs) to several manufacturers for helmet use in the treatment of AHRF from COVID-19. At the time of this publication, helmet EUAs have been granted to the StarMed CaStar R Hood (Intersurgical, Berkshire, UK) and the Subsalve Oxygen Treatment Hood (Lombardi Undersea LLC, Middletown, RI).[40] Additional US helmet manufacturers include Sea-Long Medical Systems, (Waxahachie, TX), and Amron International Inc., (Vista, CA) and non-US based H-CPAP options are also available.[41]

Setup and gas source

Several configurations are possible based on equipment availability (Fig. 1). The MaxVenturi setup (Fig. 2) is preferred as it allows for natural humidification, low noise burden, easy transition to HFNT during breaks and is a simple and safe set-up for patient movement and transport. PEEP may be selected to start at 5 cm H20 and can be titrated to a maximum of 15. For use in cases of COVID-19, a viral filter can be placed on the inspiratory and expiratory limbs to reduce viral transmission. An arterial blood gas analysis (ABG) prior to and after start of H-CPAP is desirable, but scheduled ABGs might not be necessary. Carbon dioxide rebreathing is common but can easily be mitigated by keeping continuous inspiratory flow >50 L per minute using the oxygen delivery systems shown in Fig. 1.[42] PEEP valve features may also affect CPAP performance. Precalibrated and water seal valves exhibit the best performance.[43]

H-CPAP management is most practically targeted to achieve peripheral oxygen saturation (SpO_2) > 92%. Initiating CPAP treatment should depend on the assessment of the PaO_2/FiO_2 ratio rather than on SpO_2 alone.[9] HCPAP treatment may be initiated and maintained based on the PaO_2/FiO_2 ratio, when there is a concern about falsely elevated SpO_2 from an early COVID-19 stage induced respiratory alkalosis and an associated left shift of the oxygen–hemoglobin dissociation curve.[11] A Respiratory Failure Management Algorithm for COVID-19 Patients that integrates H-CPAP is presented in Fig. 3.

Considerations specific to H-CPAP

Carbon dioxide rebreathing and tidal volume measurement

The degree of CO_2 rebreathing influencing the inspired partial pressure of CO_2 ($PiCO_2$) depends on the CO_2 produced

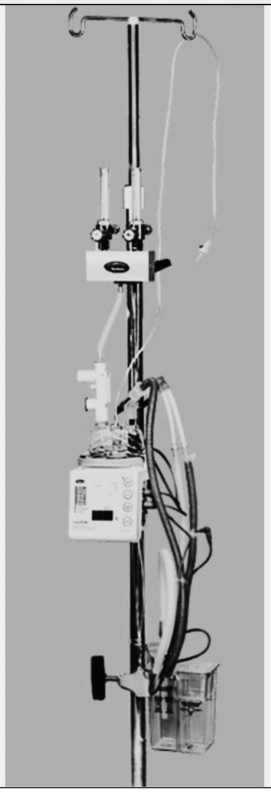
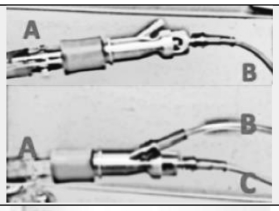
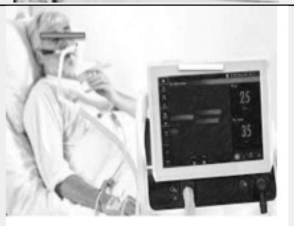
Device	Notes
	Venturi; Portable Flowmeters; setting 50 up to 100 LPM Can be coupled to an active humidifier. Easy transition to HFNT. See more specification in Figure 2A and 2B
	Venturi; (B) and (C) ports provides O_2 gas source to reach different FiO2. Both the (A) ports of Venturi systems are connected to the helmet. The amount of flow depends on the Venturi device performance No humidification is provided Cannot be use for HFNT
	The HFNT module of a ventilator can be used as a gas source (50-60 LPM) f0r the helmet Can be coupled to an active humidifier
	A turbine driven ventilator in intentional leak configuration. The arrow indicated the 6mmID intentional leak placed on the outlet helmet port (45) Can be coupled to an active humidifier It can be also used for HFNT if this module is provided inside the ventilator

Figure 1 O_2 delivery system configuration.

by the patient and the total fresh gas flow that clears the helmet. There are some data suggesting that reducing the internal volume of the helmet does not automatically prevent rebreathing but the increase in gas flow and the rate of CO_2 production will affect CO_2 rebreathing.[44,45]

Patroniti et al[45] found that with an increase of gas flow from 20 to 60 L/min and of 0 PEEP to 15 cmH2O during H-CPAP, the inspiratory CO_2 concentration was around 2.3 mmHg higher with helmet than with mask NRS. Increasing the gas flow rate significantly lowered

the inspiratory CO_2 concentration in patients with H-CPAP.

So far, H-CPAP does not allow tidal volume measurement during use due to its mechanical properties. However, in the setting of H-CPAP with a turbine driven ventilator, an intentional leak, and dedicated software, tidal volume can be estimated.[46–48]

Humidification

Although the optimal level of humidification of inspired gases during NRS is unknown, inadequate humidification can cause patient distress and NRS intolerance.[49,50] Adding active humidification set at body temperature may result in fogging of the helmet visor, which can also cause discomfort. When using a Venturi system, like the one shown in Fig. 2, to supply fresh gas, the entrained room air increases humidity compared to dry medical gas alone, depending on the chosen fraction of oxygen. Furthermore, the humidity and temperature of expired gas can mix with the dryer and cooler fresh gas, enhancing its temperature and humidity and reducing the need for active humidification. Chiumello et al.,[51] reported that during continuous flow H-CPAP and spontaneous breathing without active humidification, the temperature and humidity of the inspired gas was significantly higher compared to non-humidified medical gas alone. The magnitude of this effect was directly dependent on the gas flow passing through the helmet. Hence, in the absence of active humidification during high flow H-CPAP, insufficient humidification of gas may develop depending on the gas flow and oxygen fraction.[51,52] If humidification is chosen (e.g. when patients require more oxygen), the modern actively heated humidifiers are able to deliver an absolute humidity above 10 mgH_2O/L. The use of an active humidifier set at room temperature improves absolute and relative humidity inside the helmet and prevents insufficient humidification while reducing fogging.

Proning

Prone positioning in spontaneously breathing patients with AHRF may improve oxygenation and prevent intubation and has demonstrated utility in COVID-19.[53–56] Switching to prone position changes pulmonary perfusion, diverting blood flow toward the high Va/Q areas, and increases ventilation in the dorsal, now nondependent areas of the lung.[54] A redistribution of aerated and non-aerated areas of the lung occurs with proning. This maneuver improves oxygenation at a lower level of PEEP with more homogeneous distribution of ventilation and a decreased risk of ventilator–induced lung injury.[29,35] Anatomically, dorsal lung regions have a higher density of pulmonary vessels independent of gravity.[57,58]

Prone positioning in patients with COVID-19 who are receiving H-CPAP is safe, feasible, and may improve oxygenation and reduce work of breathing. In a study of 15 CARDS patients receiving H-CPAP in the prone position outside the ICU, a reduced respiratory rate compared to their baseline that was maintained after the end of pronation was observed.[36] All patients exhibited an improved PaO_2/FIO_2 ratio in the prone position and 12 patients (80%) had an enhanced PaO_2/FIO_2 ratio after the end of proning; 11 (73.3%) patients reported an improved level of comfort during proning in a very recent prospective study where H-CPAP was used in 79% of the patients. Moreover, Coppo et al. found that prone positioning with H-CPAP was feasible and effective in rapidly improving blood oxygenation in awake patients with COVID-19-related pneumonia requiring oxygen supplementation.[59]

Care should be taken to prevent inspiratory flow disconnection during positioning. A soft chest support may be placed under the patient so as to better align the head posi-

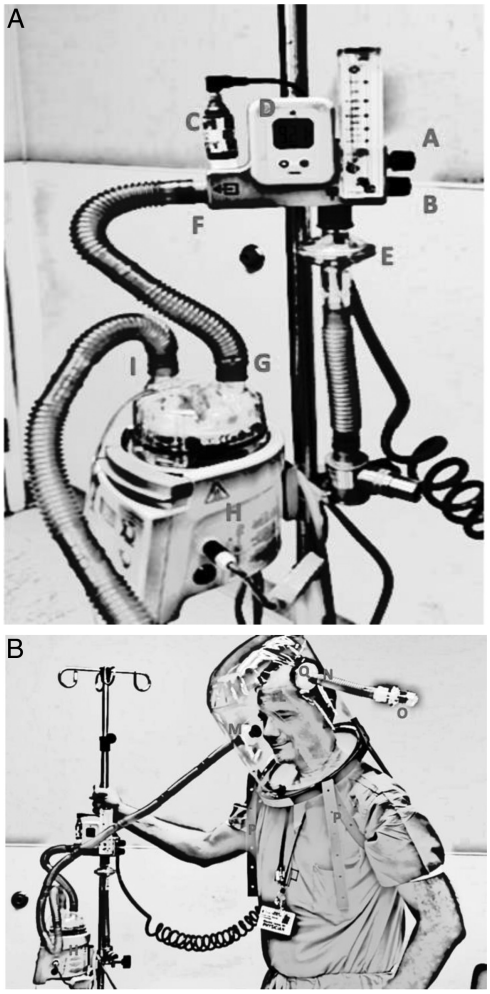


Figure 2 Flow delivery system configuration: MAX VENTURI System connected to a helmet.
A: A MAX VENTURI system is provided with 2 knobs to independently set oxygen and air. Knob (A) regulates oxygen percentage, Knob (B) regulates air, (C) oxygen cell and read on the display (D). protected by a HEPA filter (E). The outlet of the venturi system is connected to the inlet port (G) of the water chamber of an active humidifier (H) through an insulated circuit (F) From the outlet port of the water chamber another insulated circuit (I) connects the helmet inlet port as shown in B. B: A MAX VENTURI system is connected to the helmet (L) inlet port (M) through an insulated circuit (I) coming from the water chamber of the humidifier (H). The expiratory helmet port (N), protected with a HEPA filter (Q), is provided with a PEEP valve (O). Two armpit braces (P) keep the helmet in place. MAX VENTURI can be coupled to an active humidifier.

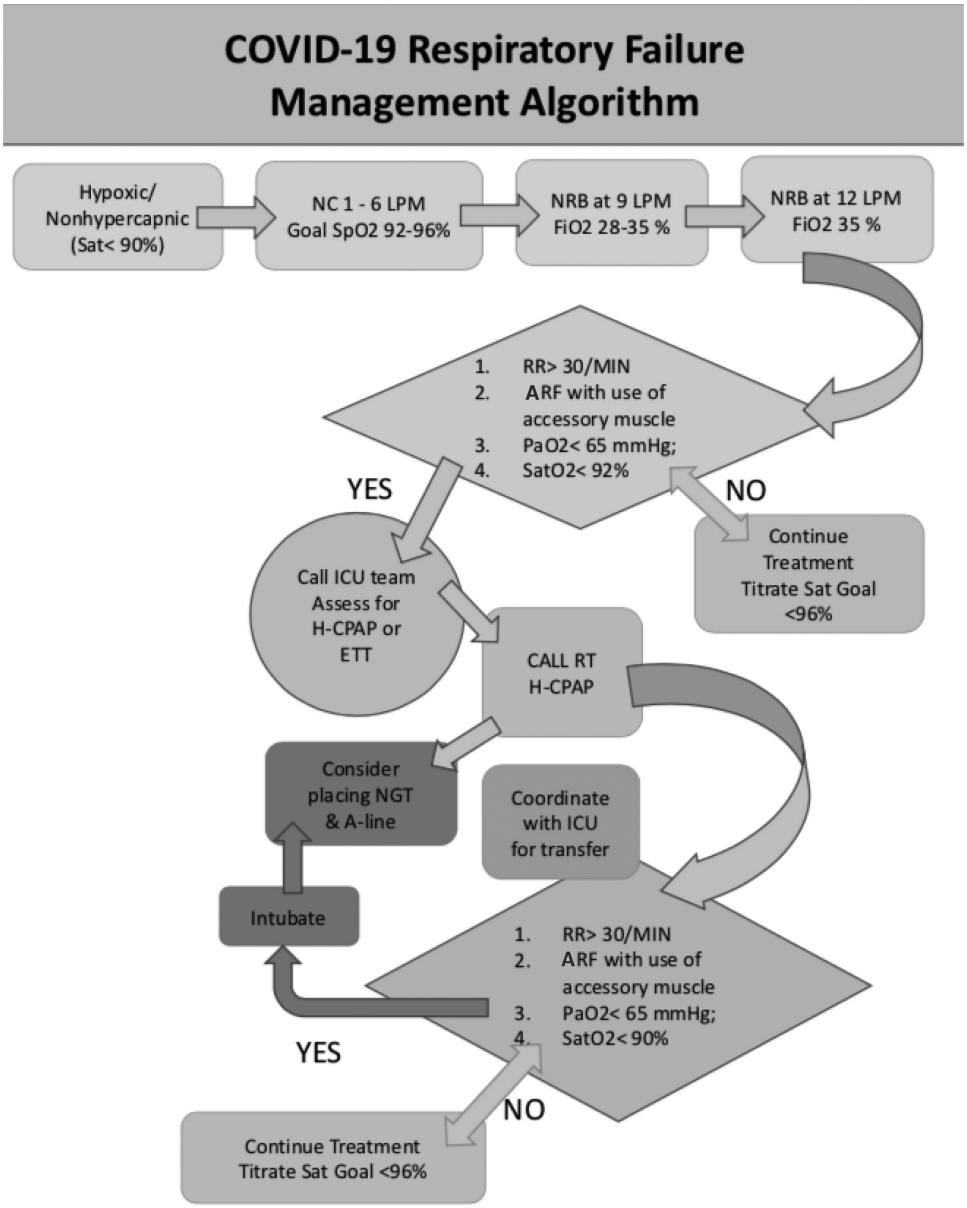


Figure 3 H-CPAP Respiratory Failure Management Algorithm for COVID-19 Patients.
The SpO_2 goals are based off SCCM COVID recommendations.
NC: Nasal Cannula; NRB: Non-Rebreather; ETT: Endotracheal intubation, ARF:acute respiratory failure, RR: respiratory rate

tion with the body axis when in a helmet. A towel may be placed inside the helmet to prevent head skin contact with the plastic neck rim for instances when the patient's head may rest against the mattress.

Like any other noninvasive ventilation technique, use of sedatives during H-CPAP application may trigger safety concerns of potential aspiration and hypoventilation.

Noise

Operating noise of helmets compared to masks has been reported as a barrier to helmet use.[60,61] Noise contributes to patient discomfort during the ICU stay,[62,63] and noise exposure during H-CPAP can be underestimated among the factors that influence the patient's well-being. The magnitude of gas flow is the origin of the noise generation for the different CPAP gas sources. High efficiency particulate air filters on the inspiratory limb of the gas circuit can help to reduce noise provided that active humidification is not used. Filters are recommended to reduce viral transmission. Ear plugs can be worn by patients during helmet use if so desired.

Nursing care and patient comfort

A well seated and maintained helmet is generally better tolerated than the mask NRS, especially for extended CPAP therapy over several days.[64–67] Use of H-CPAP compared to a face-mask interface may also reduce air leaks and thus potential health-care worker COVID-19 particle exposure

Table 2 Setup helmet and O_2 delivery.

- Prepare the helmet collar for the patient's neck size according to the manufacturer's specifications
- Connect the helmet to a gas source and connect a PEEP valve (if a turbine driven ventilator in single limb vented configuration set in CPAP mode is not used
- Place high efficiency particulate air (HEPA) filters in the correct positions.
- Connect inflow limb to humidifier outlet (Fig. 2A), set oxygen flow at 50-60 LPM and FiO_2 50%–60%.
- The helmet can also be utilized with flow meter blender devices (Fig. 1)
- The initial recommended FiO_2 is 0.5 with a CPAP of 5 cmH2O.
- Either follow ABG values to determine the optimal PO_2/FiO_2 ratio at the lowest level of CPAP or simply titrate per SpO_2 saturation
- If SaO_2 is >96%, down regulate the FiO_2 to reach closer to an SaO_2 of >92%.
- On the other hand, if the SaO_2 is <92%, adjust the FiO_2 to ideally no more than 0.6 and increase the CPAP to incrementally to no more than 14 cmH_2O to achieve adequate oxygenation.

and alleviate related anxiety triggered by the use of positive pressure NRS devices.[68] Helmet technology improves patients' comfort, allows patients' communication, interaction, coughing and oral feeding.[63] Rare problems of H-CPAP include dermal decubiti or even skin necrosis at the neck, gastric distension or eye irritation.[64,65] The helmet often features an anti-suffocation valve to allow air entry during any fresh gas flow interruption.[41] This feature is of utmost importance when helmet is used outside the ICU in the case gas source failure to prevent severe rebreathing.[45]

Appropriate patient selection and education of a cooperative patient and careful H-CPAP management are fundamental to minimize claustrophobia and preserve the patient's full visual contact and communication with health care providers and relatives.[45,52,69,70] H-CPAP is thought to also improve sleep possibly reducing the rate of delirium compared to intubation.[71] An H-CPAP bundle has been proposed by Lucchini et al. including noise reduction measures, a counter- weight fixation method and a heated wire active humidification system to further improve the patient's comfort.[72] H-CPAP should be maintained around the clock whenever possible. However, brief interruptions to improve the ease of feeding and provide a short H-CPAP holiday can be considered. A simple transition to HFNT is feasible with the MaxVenturi setup. This may reduce the amount of time a provider spends in a contaminated environment.

Typically, H-CPAP sessions last at least 6 h continuously followed by a break for meals (Table 2). Discomfort is a major cause of NRS failure.[69] Similar to invasive mechanical ventilation, sedation has been advocated to improve NRS success. However, patients undergoing CPAP therapy cannot be heavily sedated.[69] Dexmedetomidine is a preferred agent for sedating patients receiving H-CPAP in the ICU when necessary.[73]

Table 3 Indications for intubation.

- Inability to maintain a partial pressure of oxygen/FiO_2 ratio of 150, with no reduction in respiratory rate with use of accessory muscles and an increasing FiO_2 requirement, defined as an FiO_2 >80% after 1 h or at any time during H-CPAP therapy[75]
- Loss of ability to maintain ventilation to keep $PaCO_2$ <45
- Loss of protective airway gag reflex
- Respiratory or cardiac arrest
- Severe intolerance of the helmet
- Airway bleeding, persistent vomiting, or copious secretions

Special straps loop around the axilla to secure the helmet in a comfortable position on the patient's head. This configuration may cause dermal lesions despite padding and may result in H-CPAP discontinuation.[72] An alternative design is an opening ring deployed underneath an inflatable cushion to prevent leaks and secure the helmet without the need for axillary straps. This design also reduces the ventilation pressure swings during H-CPAP[74] and aerosolization.[5,9]

When to intubate

Intubation should not be delayed in patients with AHRF from COVID-19 if H-CPAP does not improve Arterial Blood Gas parameters or the clinical status (Fig. 3), and the indication is no different from AHRF from non-COVID-19 etiologies. (Table 3). When increased respiratory drive, WOB, persistent dyspnea, and use of accessory muscles are present in combination, invasive mechanical ventilation should be instituted.[75] Delayed intubation may increase the risk of clinical deterioration.[28]

Camporota et al.[76] suggest that as dead-space ventilation increases, a greater respiratory drive generates a greater minute ventilation and WOB. This in turn results in a higher transpulmonary pressure as in other forms of AHRF.[77] A greater contribution of viral aerosolization in this circumstance is also likely. These patients may be at higher risk of self-induced lung injury, which is thought to be caused by large diaphragmatic swings and increased WOB in patients receiving non-invasive mechanical ventilation.[31] Such a situation worsens their clinical status by prolonging H-CPAP and eventually leads to unfavorable outcomes.[76,78]

Specific to COVID-19, the airway team should be activated as soon as the need for mechanical ventilation is anticipated, to allow for the appropriate donning of personal protective equipment, optimize procedural control and avoid an emergency airway management scenario. Fi02 can be increased to 1, if using a MaxVenturi or ventilator setup, for pre-oxygenation. The helmet can be removed prior to or after induction ensuring that there are two providers available to assist in helmet removal.

Weaning

Currently, no general consensus exists regarding H-CPAP weaning process in COVID-19. Therefore, we propose a sound clinical approach with individualized care for patients with

AHRF due to CARDS based on comorbidities and the resolution of the respiratory impairment.

In our clinical experience, the patient can be gradually weaned from H-CPAP first by decreasing the PEEP, and FiO_2, followed by incrementally increasing the H-CPAP free time. H-CPAP can be discontinued by achieving respiratory distress improvement and an ability to maintain a SpO_2 > 96% on $Fi02_2 \leq 40\%$ and CPAP $0-5\,cmH_20$. When a PEEP of 5 cmH2O has been achieved, the H-CPAP may be replaced by an oxygen Venturi mask or HFNT if allowed (a surgical mask can decrease aerosol dispersion).[79]

Conclusions

H-CPAP is not intended to replace endotracheal intubation and mechanical ventilation in AHRF from COVID-19. Instead, as an option for respiratory support with evidence of effective and safe use in many parts of the world, it deserves consideration for more widespread use during a pandemic.[76]

H-CPAP, when properly fitted, is associated with minimal particle dispersion and air contamination,[5,6,9] reducing the risk of transmission to healthcare workers.

Clinician concerns with H-CPAP regarding the risk of viral contamination during use, the possibility of device malfunction, and patient decompensation can be alleviated with education, scientific evidence, and mentored experience.

Life-long learning, an open mind, and a positive attitude to new, life-saving treatments remain cornerstones for successful new program implementation. We must accept a learning curve for the benefit of many patients.

Funding

Support was provided solely from institutional and/or department resources. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. China Medical Treatment Expert Group for Covid-19, 2020. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20, http://dx.doi.org/10.1056/NEJMoa2002032.
2. Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. Am J Respir Crit Care Med. 2020;201:1560–4, http://dx.doi.org/10.1164/rccm.202004-1163LE.
3. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323:1574–81, http://dx.doi.org/10.1001/jama.2020.5394.
4. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020;382:2012–22, http://dx.doi.org/10.1056/NEJMoa2004500.
5. Hui DS, Chow BK, Lo T, Ng SS, Ko FW, Gin T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. Chest. 2015;147:1336–43, http://dx.doi.org/10.1378/chest.14-1934.
6. Cabrini L, Landoni G, Zangrillo A. Minimise nosocomial spread of 2019-nCoV when treating acute respiratory failure. Lancet. 2020;395:685, http://dx.doi.org/10.1016/S0140-6736(20)30359-7.
7. Tobin MJ. Basing Respiratory Management of COVID-19 on Physiological Principles. Am J Respir Crit Care Med. 2020;201:1319–20, http://dx.doi.org/10.1164/rccm.202004-1076ED.
8. Amirfarzan H, Shanahan JL, Schuman R, Leissner KB. Helmet CPAP: how an unfamiliar respiratory tool is moving into treatment options during COVID-19 in the US. Ther Adv Respir Dis. 2020;14, http://dx.doi.org/10.1177/1753466620951032, 1753466620951032.
9. Ferioli M, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. Eur Respir Rev. 2020;29, http://dx.doi.org/10.1183/16000617.0068-2020.
10. Vitacca M, Nava S, Santus P, Harari S. Early consensus management for non-ICU acute respiratory failure SARS-CoV-2 emergency in Italy: from ward to trenches. Eur Respir J. 2020;55(5), http://dx.doi.org/10.1183/13993003.00632-2020.
11. Radovanovic D, Rizzi M, Pini S, Saad M, Chiumello DA, Santus P. Helmet CPAP to Treat Acute Hypoxemic Respiratory Failure in Patients with COVID-19: A Management Strategy Proposal. J Clin Med. 2020;9(4), http://dx.doi.org/10.3390/jcm9041191.
12. Antonelli M, Conti G, Pelosi P, Gregoretti C, Pennisi MA, Costa R, et al. New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet–a pilot controlled trial. Crit Care Med. 2002;30:602–8, http://dx.doi.org/10.1097/00003246-200203000-00019.
13. Patroniti N, Verweij M, Kolobow T. Glottic-modulated lung ventilation during continuous transtracheal gas insufflation: an experimental study. Crit Care Med. 2003;31(5):1461–7, http://dx.doi.org/10.1097/01.CCM.0000065780.29668.72.
14. Retucci M, Aliberti S, Ceruti C, Santambrogio M, Tammaro S, Cuccarini F, et al. Prone and Lateral Positioning in Spontaneously Breathing Patients With COVID-19 Pneumonia Undergoing Noninvasive Helmet CPAP Treatment. Chest. 2020;158(6):2431–5, http://dx.doi.org/10.1016/j.chest.2020.07.006.
15. Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicenter, cohort study. Eur Respir J. 2020;56(4), http://dx.doi.org/10.1183/13993003.01935-2020, 2001935.
16. Tomashefski JF, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. Am J Pathol. 1983;112(1):112–26.
17. Lang M, Som A, Mendoza DP, Flores EJ, Reid N, Carey D, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis. 2020;20(12):1365–6, http://dx.doi.org/10.1016/S1473-3099(20)30367-4.
18. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, et al. Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations. Am J Respir Crit Care Med. 2020;202:690–9, http://dx.doi.org/10.1164/rccm.202004-1412OC.
19. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020;18:1738–42, http://dx.doi.org/10.1111/jth.14850.
20. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care. 2020;24(1):154, http://dx.doi.org/10.1186/s13054-020-02880-z.
21. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of ''happy'' hypoxemia in COVID-19. Respir Res. 2020;21(1):198, http://dx.doi.org/10.1186/s12931-020-01462-5.

22. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a ''Typical'' Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;201(10):1299–300, http://dx.doi.org/10.1164/rccm.202003-0817LE.
23. Camporota L, Vasques F, Sanderson B, Barrett NA, Gattinoni L. Identification of pathophysiological patterns for triage and respiratory support in COVID-19. Lancet Respir Med. 2020;8(8):752–4, http://dx.doi.org/10.1016/S2213-2600(20)30279-4.
24. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis. JAMA. 2020;324:57–67, http://dx.doi.org/10.1001/jama.2020.9524.
25. Cosentini R, Brambilla AM, Aliberti S, Bignamini A, Nava S, Maffei A, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. Chest. 2010;138:114–20, http://dx.doi.org/10.1378/chest.09-2290.
26. Principi T, Pantanetti S, Catani F, Elisei D, Gabbanelli V, Pelaia P, et al. Noninvasive continuous positive airway pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure. Intensive Care Med. 2004;30:147–50, http://dx.doi.org/10.1007/s00134-003-2056-9.
27. Navalesi P, Maggiore S, Tobin MJ. Chapter 10. Positive End-Expiratory Pressure. In: Principles and Practice of Mechanical Ventilation. 3rd ed McGraw-Hill; 2013.
28. Tobin, M.J., Ed.; McGraw Hill Medical: New York, NY, USA, 2013; pp. 253–302.) [LUOY Yonsei Med J. 2016;57:936-41].
29. Yoshida T, Uchiyama A, Fujino Y. The role of spontaneous effort during mechanical ventilation: normal lung versus injured lung. j intensive care. 2015;3(1):18, http://dx.doi.org/10.1186/s40560-015-0083-6.
30. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa ELV, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. Am J Respir Crit Care Med. 2013;188:1420–7, http://dx.doi.org/10.1164/rccm.201303-0539OC.
31. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med. 2017;195(4):438–42, http://dx.doi.org/10.1164/rccm.201605-1081CP.
32. Chiumello D, Pelosi P, Carlesso E, Severgnini P, Aspesi M, Gamberoni C, et al. Noninvasive positive pressure ventilation delivered by helmet vs. standard face mask. Intensive Care Med. 2003;29:1671–9, http://dx.doi.org/10.1007/s00134-003-1825-9.
33. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2016;315:2435–41, http://dx.doi.org/10.1001/jama.2016.6338.
34. Liu Q, Gao Y, Chen R, Cheng Z. Noninvasive ventilation with helmet versus control strategy in patients with acute respiratory failure: a systematic review and meta-analysis of controlled studies. Crit Care. 2016;20(1):265, http://dx.doi.org/10.1186/s13054-016-1449-4.
35. Longhini F, Bruni A, Garofalo E, Navalesi P, Grasselli G, Cosentini R, et al. Helmet continuous positive airway pressure and prone positioning: A proposal for an early management of COVID-19 patients. Pulmonology. 2020;26:186–91, http://dx.doi.org/10.1016/j.pulmoe.2020.04.014.
36. Sartini C, Tresoldi M, Scarpellini P, Tettamanti A, Carcò F, Landoni G, et al. Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit. JAMA. 2020;323:2338–40, http://dx.doi.org/10.1001/jama.2020.7861.
37. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19 related pneumonia. Eur Respir J. 2020;56(5):2002130, http://dx.doi.org/10.1183/13993003.02130-2020.
38. Gaulton TG, Bellani G, Foti G, Frazer MJ, Fuchs BD, Cereda M. Early Clinical Experience in Using Helmet Continuous Positive Airway Pressure and High-Flow Nasal Cannula in Overweight and Obese Patients With Acute Hypoxemic Respiratory Failure From Coronavirus Disease 2019. Critical Care Explorations. 2020;2(9):e0216, http://dx.doi.org/10.1097/CCE.0000000000000216.
39. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46:854–87, http://dx.doi.org/10.1007/s00134-020-06022-5.
40. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-august-6-2020.
41. Nava S, Navalesi P, Gregoretti C. Interfaces and humidification for noninvasive mechanical ventilation. Respir Care. 2009;54(1):71–84.
42. Taccone P, Hess D, Caironi P, Bigatello LM. Continuous positive airway pressure delivered with a ''helmet'': effects on carbon dioxide rebreathing. Crit Care Med. 2004;32(10):2090–6, http://dx.doi.org/10.1097/01.ccm.0000142577.63316.c0.
43. Isgrò S, Zanella A, Giani M, Abd El Aziz El Sayed Deab S, Pesenti A, Patroniti N. Performance of different PEEP valves and helmet outlets at increasing gas flow rates: a bench top study. Minerva Anestesiol. 2012;78(10):1095–100.
44. Patroniti N, Foti G, Manfio A, Coppo A, Bellani G, Pesenti A. Head helmet versus face mask for non-invasive continuous positive airway pressure: a physiological study. Intensive Care Med. 2003;29(10):1680–7, http://dx.doi.org/10.1007/s00134-003-1931-8. Epub 2003 Aug 28. PMID: 14564379.
45. Patroniti N, Saini M, Zanella A, Isgrò S, Pesenti A. Danger of helmet continuous positive airway pressure during failure of fresh gas source supply. Intensive Care Med. 2007;33(1):153–7, http://dx.doi.org/10.1007/s00134-006-0446-5.
46. Cortegiani A, Accurso G, Ball L, Ippolito M, Ingoglia G, Gregoretti C, et al. A New Configuration for Helmet Continuous Positive Airway Pressure Allowing Tidal Volume Monitoring. Am J Respir Crit Care Med. 2020;202:612–4, http://dx.doi.org/10.1164/rccm.202003-0550LE.
47. Racca F, Appendini L, Gregoretti C, Varese I, Berta G, Vittone F, et al. Helmet ventilation and carbon dioxide rebreathing: effects of adding a leak at the helmet ports. Intensive Care Med. 2008;34:1461–8, http://dx.doi.org/10.1007/s00134-008-1120-x.
48. Cortegiani A, Navalesi P, Accurso G, Sabella I, Misseri G, Ippolito M, et al. Tidal volume estimation during helmet noninvasive ventilation: an experimental feasibility study. Sci Rep. 2019;9:17324.
49. Esquinas Rodriguez AM, Scala R, Soroksky A, BaHammam A, de Klerk A, Valipour A, et al. Clinical review: humidifiers during non-invasive ventilation—key topics and practical implications. Crit Care. 2012;16:203, http://dx.doi.org/10.1186/cc10534.
50. Gross JL, Park GR. Humidification of inspired gases during mechanical ventilation. Minerva Anestesiol. 2012;78(4):496–502.
51. Chiumello D, Chierichetti M, Tallarini F, Cozzi P, Cressoni M, Polli F, et al. Effect of a heated humidifier during continuous positive airway pressure delivered by a helmet. Crit Care. 2008;12:R55, http://dx.doi.org/10.1186/cc6875.
52. Lucchini A, Elli S, Bambi S, De Felippis C, Vimercati S, Minotti D, et al. How different helmet fixing options could

affect patients' pain experience during helmet-continuous positive airway pressure. Nurs Crit Care. 2019;24:369–74, http://dx.doi.org/10.1111/nicc.12399.
53. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care. 2020;24(1):28, http://dx.doi.org/10.1186/s13054-020-2738-5.
54. Telias I, Katira BH, Brochard L. Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19? JAMA. 2020;323(22):2265–7, http://dx.doi.org/10.1001/jama.2020.8539.
55. Elharrar X, Trigui Y, Dols A-M, Touchon F, Martinez S, Prud'homme E, et al. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. JAMA. 2020;323:2336–8, http://dx.doi.org/10.1001/jama.2020.8255.
56. Scaravilli V, Grasselli G, Castagna L, Zanella A, Isgrò S, Lucchini A, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. J Crit Care. 2015;30:1390–4, http://dx.doi.org/10.1016/j.jcrc.2015.07.008.
57. Perier F, Tuffet S, Maraffi T, Alcala G, Victor M, Haudebourg A-F, et al. Effect of Positive End-Expiratory Pressure and Proning on Ventilation and Perfusion in COVID-19 Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;202:1713–7, http://dx.doi.org/10.1164/rccm.202008-3058LE.
58. Glenny RW, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. J Appl Physiol. 1991;71(2):620–9, http://dx.doi.org/10.1152/jappl.1991.71.2.620.
59. Coppo A, Bellani G, Winterton D, Di Pierro M, Soria A, Faverio P, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-COVID): a prospective cohort study. The Lancet Respir Med. 2020;8:765–74, http://dx.doi.org/10.1016/S2213-2600(20)30268-X.
60. Cavaliere F, Conti G, Costa R, Proietti R, Sciuto A, Masieri S. Noise exposure during noninvasive ventilation with a helmet, a nasal mask, and a facial mask. Intensive Care Med. 2004;30:1755–60, http://dx.doi.org/10.1007/s00134-004-2347-9.
61. Cavaliere F, Conti G, Costa R, Spinazzola G, Proietti R, Sciuto A, et al. Exposure to noise during continuous positive airway pressure: influence of interfaces and delivery systems. Acta Anaesthesiol Scand. 2008;52:52–6, http://dx.doi.org/10.1111/j.1399-6576.2007.01474.x.
62. Tegnestedt C, Günther A, Reichard A, Bjurström R, Alvarsson J, Martling C-R, et al. Levels and sources of sound in the intensive care unit - an observational study of three room types. Acta Anaesthesiol Scand. 2013;57:1041–50, http://dx.doi.org/10.1111/aas.12138.
63. Johansson L, Lindahl B, Knutsson S, Ögren M, Persson Waye K, Ringdal M. Evaluation of a sound environment intervention in an ICU: A feasibility study. Aust Crit Care. 2018;31:59–70, http://dx.doi.org/10.1016/j.aucc.2017.04.001.
64. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36(2):362–9, http://dx.doi.org/10.1183/09031936.00123509.
65. Gregoretti C, Decaroli D, Piacevoli Q, Mistretta A, Barzaghi N, Luxardo N, et al. Analgo-Sedation of Patients with Burns Outside the Operating Room. Drugs. 2008;68:2427–43, http://dx.doi.org/10.2165/0003495-200868170-00003.
66. Beltrame F, Lucangelo U, Gregori D, Gregoretti C. Noninvasive positive pressure ventilation in trauma patients with acute respiratory failure. Monaldi Arch Chest Dis. 1999;54(2):109–14. PMID: 10394822.
67. Gregoretti C, Foti G, Beltrame F, Giugiaro PM, Biolino P, Burbi L, et al. Pressure control ventilation and minitracheotomy in treating severe flail chest trauma. Intensive Care Med. 1995;21:1054–6, http://dx.doi.org/10.1007/BF01700674.
68. Winck JC, Ambrosino N. COVID-19 pandemic and non invasive respiratory management: Every Goliath needs a David. An evidence based evaluation of problems. Pulmonology. 2020;26:213–20, http://dx.doi.org/10.1016/j.pulmoe.2020.04.013.
69. Liu J, Duan J, Bai L, Zhou L. Noninvasive Ventilation Intolerance: Characteristics, Predictors, and Outcomes. Respir Care. 2016;61(3):277–84, http://dx.doi.org/10.4187/respcare.04220.
70. Racca F, Appendini L, Berta G, Barberis L, Vittone F, Gregoretti C, et al. Helmet ventilation for acute respiratory failure and nasal skin breakdown in neuromuscular disorders. Anesth Analg. 2009;109:164–7, http://dx.doi.org/10.1213/ane.0b013e3181a1f708.
71. Mistraletti G, Pelosi P, Mantovani ES, Berardino M, Gregoretti C. Delirium: clinical approach and prevention. Best Pract Res Clin Anaesthesiol. 2012;26(3):311–26, http://dx.doi.org/10.1016/j.bpa.2012.07.001.
72. Lucchini A, Bambi S, Mattiussi E, Elli S, Villa L, Bondi H, et al. Prone Position in Acute Respiratory Distress Syndrome Patients: A Retrospective Analysis of Complications. Dimens Crit Care Nurs. 2020;39:39–46, http://dx.doi.org/10.1097/DCC.0000000000000393.
73. Cabrini L, Antonelli M, Savoia G, Landriscina M. Non-invasive ventilation outside of the Intensive Care Unit: an Italian survey. Minerva Anestesiol. 2011;77(3):313–22.
74. Olivieri C, Costa R, Spinazzola G, Ferrone G, Longhini F, Cammarota G, et al. Bench comparative evaluation of a new generation and standard helmet for delivering noninvasive ventilation. Intensive Care Med. 2013;39:734–8, http://dx.doi.org/10.1007/s00134-012-2765-z.
75. Tobin MJ. Why Physiology Is Critical to the Practice of Medicine. Clinics in Chest Medicine. 2019;40(2):243–57, http://dx.doi.org/10.1016/j.ccm.2019.02.012.
76. Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, et al. Early Inspiratory Effort Assessment by Esophageal Manometry Predicts Noninvasive Ventilation Outcome in De Novo Respiratory Failure. A Pilot Study. Am J Respir Crit Care Med. 2020;202:558–67, http://dx.doi.org/10.1164/rccm.201912-2512OC.
77. Ing RJ, Bills C, Merritt G, Ragusa R, Bremner RM, Bellia F. Role of Helmet-Delivered Noninvasive Pressure Support Ventilation in COVID-19 Patients. J Cardiothorac Vasc Anesth. 2020;34(10):2575–9, http://dx.doi.org/10.1053/j.jvca.2020.04.060.
78. Ippolito M, Vitale F, Accurso G, Iozzo P, Gregoretti C, Giarratano A, et al. Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses. Pulmonology. 2020;26:204–12, http://dx.doi.org/10.1016/j.pulmoe.2020.04.009.
79. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: risk of bio-aerosol dispersion. Eur Respir J. 2020;56(4):2003136, http://dx.doi.org/10.1183/13993003.03136-2020.

Pulmonology 27 (2021) 438–447

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Practical considerations for spirometry during the COVID-19 outbreak: Literature review and insights

Claudia Crimi[a,*], Pietro Impellizzeri[b], Raffaele Campisi[a], Santi Nolasco[b], Antonio Spanevello[c], Nunzio Crimi[a,b]

[a] *Respiratory Medicine Unit, A.O.U. P̈oliclinico-Vittorio Emanuele¸ Via Santa Sofia, 78, Catania, Italy*
[b] *Department of Clinical and Experimental Medicine, Section of Respiratory Medicine, A.O.U. P̈oliclinico-Vittorio Emanuele¸ University of Catania, Via Santa Sofia, 78, Catania, Italy*
[c] *Istituti Clinici Scientifici Maugeri IRCCS, Via Crotto Roncaccio, 16, 21049 Tradate, VA, Italy*

Received 21 May 2020; accepted 17 July 2020

KEYWORDS
COVID-19;
SARS-CoV-2;
Pulmonary function test;
Spirometry;
Outpatient clinic;
Safety;
Guidelines.

Abstract
Background: As the Coronavirus disease 2019 (COVID-19) is spreading worldwide, countries are dealing with different phases of the pandemic. Lately, scientific evidence has been growing about the measures for reopening respiratory outpatient services during the COVID-19 pandemic. We aim to summarize the key differences and similarities among recommendations by different national and international organizations.
Methods: We searched on Google and Pubmed for recently published National and International Recommendations/Guidelines/Position Papers from professional organizations and societies, offering a guidance to physicians on how to safely perform pulmonary function testing during COVID-19 pandemic. We also searched for spirometry manufacturers' operational indications.
Results: Indications on spirometry were released by the Chinese Task force, the American Thoracic Society, the European Respiratory Society, the Thoracic Society of Australia and New Zealand, the Société de Pneumologie de Langue Française, the Spanish Societies (Sociedad Espanola de Neumologia y Cirugia Toracica, Sociedad Espanola de Alergologia e Inmunologia Clinica, Asociacion de Especialistas en Enfermeria del trabajo, Asociacion de Enfermeria Comunitaria), the Sociedade Portuguesa de Pneumologia, the British Thoracic Society/Association

Abbreviations: ACH, air changes per hour; ARTP, Association for Respiratory Technology and Physiology; BTS, British Thoracic Society; COVID-19, Coronavirus disease 2019; WHO, World Health Organization; ANZSRS, Australian and New Zealand Society of Respiratory Science Ltd; AET, Asociacion de Especialistas en Enfermeria del trabajo; AEC, Asociacion de Enfermeria Comunitaria; ATS, American Thoracic Society; CLEVELAND, Respiratory Institute Cleveland Clinic; COPD, Chronic obstructive pulmonary disease; ERS, European Respiratory Society; HCWs, health care workers; ITS, Irish Thoracic Society; IRS/SIP, Italian Respiratory Society/Società Italiana di Pneumologia; ITS/AIPO, Italian Thoracic Society/Associazione Italiana Pneumologi Ospedalieri; PFTs, pulmonary function tests; PPE, personal protective equipment; SEAIC, Sociedad Espanola de Alergologia e Inmunologia Clinica; SEPAR, Sociedad Espanola de Neumologia y Cirugia Toracica; SPLF, Société de Pneumologie de Langue Française; SPP, Sociedade Portuguesa de Pneumologia; SUNEUMO, Sociedad Uruguaya de Neumologia; TSANZ, Thoracic Society of Australia and New Zealand; UV, ultraviolet.

* Corresponding author.
E-mail addresses: dott.claudiacrimi@gmail.com (C. Crimi), pietroimpellizzeri2018@gmail.com (P. Impellizzeri), raffaelemd@hotmail.it (R. Campisi), nolascos@hotmail.it (S. Nolasco), antonio.spanevello@icsmaugeri.it (A. Spanevello), crimi@unict.it (N. Crimi).

https://doi.org/10.1016/j.pulmoe.2020.07.011

for Respiratory Technology & Physiology, the Irish Thoracic Society, the Sociedad Uruguaya de Neumologia, the Italian Thoracic Society and the Italian Respiratory Society, Cleveland Clinic and Nebraska Medical Center. Detailed technical recommendations were found on manufacturers' websites. We found several similarities across available guidelines for safely resuming pulmonary function services, as well as differences in criteria for selecting eligible patients for which spirometry is deemed essential and advice which was not homogenous on room ventilation precautions.

Conclusions: This study shows a synthesis of national/international guidelines allowing practicing physicians to adapt and shape the way to organize their outpatient services locally. There is generally good agreement on the importance of limiting pulmonary function testing to selected cases only. However, significant differences concerning the subsets of candidate patients, as well as on the management of adequate room ventilation, were observed.

Introduction

Coronavirus disease 2019 (COVID-19) has spread worldwide, becoming a public health emergency of international concern,[1] officially designated as a pandemic by World Health Organization (WHO) on March 11.[2] COVID-19 has had a high impact on the health care system, necessitating unprecedented measures for containing the infection, shutting down all the outpatient activities and providing treatment only for emergency cases.[3]

The infection is mainly transmitted by respiratory droplets[4] and close contacts, so both pulmonologists and their patients are at high risk of COVID-19 transmission during the outpatient visit and the pulmonary function testing procedures. Therefore, in the early phases of the pandemic some International Societies such as the Chinese expert consensus,[5] the American Thoracic Society (ATS),[6] the Thoracic Society of Australia and New Zealand (TSANZ/ANZSRS),[7] the Sociedade Portuguesa de Pneumologia (SPP),[8] the Société de Pneumologie de Langue Française (SPLF),[9] the Spanish Societies [Sociedad Espanola de Neumologia y Cirugia Toracica (SEPAR), Asociacion de Enfermeria Comunitaria (AEC), Asociacion de Especialistas en Enfermeria del trabajo (AET), Sociedad Espanola de Alergologia e Inmunologia Clinica (SEAIC)][10] and the Irish Thoracic Society (ITS),[11] recommended stopping or postponing pulmonary visits and pulmonary function tests (PFTs) during the pandemic surge unless deemed clinically essential.[5–8,11,12]

Nevertheless, PFTs cannot be delayed for a long time in some patients' groups. Moreover, a respiratory follow-up of patients who recovered from COVID-19 pneumonia is crucial in the monitoring of a possible fibrotic complication of the disease which could lead to a reduction of the pulmonary function.[1,5] Entering the second phase of the COVID-19 pandemic, we need to consider that the infection will remain endemic and we have to coexist with the disease, which will become a part of the routine practice. Therefore, hospitals have to be prepared to safely bring back regular ambulatory services and PFT labs, especially to assess patients suffering from pre-existing chronic respiratory diseases, to prevent their risk of mortality and disability.

To date, several official Recommendations/Guidelines from National and International Societies, hospitals or professional organizations have been released on this topic with operational indications during the COVID-19 surge.[5–11,13] Some Organizations updated their own documents,[14–16] and other Societies, such as the European Respiratory Society (ERS),[17] the British Thoracic Society/Association for Respiratory Technology & Physiology (BTS/ARTP),[12] the Sociedad Uruguaya de Neumologia (SUNEUMO),[18] the Italian Thoracic Society (ITS/AIPO),[19] and the Italian Respiratory Society (IRS/SIP),[20] as well as renowned medical centers such as Cleveland Clinic,[21] recently published statements.

We aim to summarize the available official recommendations on the use of spirometry in the context of COVID-19 infection and to compare them, reviewing in detail the most important aspects, such as eligible patients, health-care workers' and patients' protection, equipment, and environmental management to prevent COVID-19 transmission. These results will help practicing physicians make decisions on how to safely reshape and reopen ambulatory services, tailoring measures to the specific context of their needs, and organizational issues.[22]

Methods

We searched and reviewed all recent Guidelines, Consensus documents, Statements, and Position Papers from National and International Societies or local policies of medical centers on how to perform spirometry during COVID-19, published on official websites in four languages: English, Italian, French and Spanish.

To increase the search strategy's sensitivity, we also searched on Google the websites of the spirometer manufacturers using the following terms: COVID-19, Sar-Cov-2, spirometry, pulmonary function test.

Results

We considered the challenging issues related to performing spirometry and the solutions that may be adopted, as

Table 1 Issues related to safely performing pulmonary function test and proposed solutions by National/International Organizations.

Issue	Proposed solutions													
	CHINESE TASK FORCE[5] 04/03/2020	SPLF[9] 17/03/2020	ATS[6] 20/03/2020	SPP[9,16] 23/03/2020	SEPAR/ AEC/ AET/ SEAIC[10] 25/03/2020	ANZSRS/ TSANZ[7,14] 25/03/2020	ITS[11] 30/03/2020	NEBRASKA 01/04/2020	CLEVELAND[21] 13/04/2020	SUNEUMO[18] 13/04/2020	BTS/ ARTP[12] 27/04/2020	ERS[17] 09/05/2020	ITS/ AIPO[19] 09/05/2020	IRS/ SIP[20] 12/05/2020
Eligible patients	U/ ET tests for Dx of current illness COPD/ Asthma: postpone or use PFM	U tests for: - PRE-OP - CA - clinical decision	U/ ET tests for immediate treatment	U tests for: - PRE-OP - CA - Dx - therapies	Avoid PFT in patients with respiratory Sx unless necessary	Afebrile Asymptomatic	U tests for: - RALC O/ P - CF I/ P - PRE-OP - ID	ET tests for: - LTP - PRE-OP - CF Pts - IST - Asymptomatic	ET tests for: - LTP - CTX surveillance - Surgery - ILD - PAH	ET tests for: - PRE-OP for LR, CS, OS - ILD Dx - PneumoTox Dx - ID (tested first)	ET tests for: - LTC - CA I/ P - PRE-OP for US - ID (tested first)	U/ ET tests for immediate Dx	U/ ET tests for: - PRE-OP TAS - immediate Dx COPD/ Asthma: postpone or use PFM	ET tests for: - PRE-OP TAS - LTPs - COPD Dx - Asthma Dx - ILD (Dx, F/ U, drug Rx) - ID (tested first)
Post-COVID-19 pneumonia	- Normal BT > 3d - Sx improvement - Imaging improvement —2 consecutive negative swabs										12-wks after discharge	30d post-infection	30d post-infection dedicated PFT lab	Pts with Sx
Social Distancing/ Prevention	Pts wear mask	Pts wear mask Hand hygiene		Pts wear mask Pts alone/ one caregiver	Hand hygiene Pts wear mask if have Sx Pts sit >1 m Pts alone/ one caregiver		Pts remain in the car RP phone to pts to come for PFT Pts sit >2 m Hand sanitizer	Pts wear mask			Pts sit >2 m	Pts wear mask Pts sit >2 m Hand hygiene Use gloves Pts alone/ one caregiver	Pts wear mask and gloves Pts alone/ one caregiver	Pts wear mask Hand hygiene Pts alone/ one caregiver
Trace suspicious cases	Risk assessment questionnaire BT detection			Risk assessment questionnaire BT detection		BT detection	Risk assessment questionnaire	Risk assessment questionnaire 48—72 h before and the day of the test	Risk assessment questionnaire	Risk assessment questionnaire BT detection	Hand sanitizer BT detection	Risk assessment questionnaire BT detection	Risk assessment questionnaire Evaluate swab 48—72 h before	Risk assessment questionnaire BT detection Evaluate swab 48—72 h before
HCWs protection	PPE: - mask - eye protection - gloves Hand hygiene before/ after gloves use Attention to medical staff health	PPE: - surgical mask - eye protection - gloves - gown	PPE Hand hygiene	PPE: - N95/ FFP2 (change q4h-q6h or if wet) - eye protection - nitrile gloves - gown - shoe protector	PPE: - FFP2/ FFP3 - gloves - eye protection - gowns	PPE	PPE: - FFP2	PPE: - N95 mask - eye protection - gowns - gloves Hand hygiene	PPE: - surgical mask - eye protection - gloves If aerosolization: - gown - gloves - eye protection - N95 - powered air purifying	PPE: - N95/ FFP-mask - gloves - eye protection - cap and hair up - eye protection - gowns	PPE: - FFP3 - eye protection Hand hygiene	PPE: - FFP2/ FFP3 - gloves - eye protection Hand hygiene	PPE: - FFP3/ FFP2 - eye protection - gloves	PPE: - FFP2 - eye protection - gowns - gloves

Table 1 (*Continued*)

Issue	Proposed solutions													
	CHINESE TASK FORCE[5] 04/03/2020	SPLF[9] 17/03/2020	ATS[6] 20/03/2020	SPP[9,16] 23/03/2020	SEPAR/ AEC/ AET/ SEAIC[10] 25/03/2020	ANZSRS/ TSANZ[7,14] 25/03/2020	ITS[11] 30/03/2020	NEBRASKA 01/04/2020	CLEVELAND[21] 13/04/2020	SUNEUMO[18] 13/04/2020	BTS/ ARTP[12] 27/04/2020	ERS[17] 09/05/2020	ITS/ AIPO[19] 09/05/2020	IRS/ SIP[20] 12/05/2020
Testing and equipment	1 exam at time Disposable BVF BVF total resistance <1.5 cmH20 at a flow rate of 14 $L{\cdot}s^{-1}$ Technician sit in the same directionof pts Separate test/ admin area Edu program/ Telematic report	Perform the exam inside a plethysmography booth Recalibrate the equipment after decontamination		Disposable BVF BD test: disposable expansion chambers	Separate test/ administrative area Disposable BVF Disposable nose-clips Technician sit in the same direction of pts Informational posters	Disposable BVF BD test: pts' salbutamol inhaler or a single-use inhaler Portable individual patient dedicated spirometers			Disposable BVF		Disposable BVF	Disposable BVF with minimum efficiency for high expiratory flow of 600–700 L/ min Single use consumables Telemedicine for high-risk O/ P Recalibrate the equipment after decontamination Separate test/ admin area	1 exam at a time Disposable BVF Total resistance of BVF and tube of spirometer should <1.5 $cmH_2O{\cdot}L^{-1}{\cdot}s^{-1}$ Disposable nose-clips Technician sit in the same direction of pts Recalibrate the equipment after decontamination Edu program Separate test/ admin area	Disposable BVF > 99% efficiency for HEF of 600–700 L/ min Disposable nose-clips BD test: pts' salbutamol inhaler or a single-use inhaler or aerochamber® Separate test/ admin area
Room ventilation	160 L/ s for each pt for hour if natural ventilation 12 ACH for hour if negative room Turn off the A/ C	15 min open windows closed doors		Ventilated rooms to avoid recirculation	Ventilated rooms to avoid recirculation			Room closed for 1 h after the procedure			30 min for isolation room with 10–12 ACH 60 min for side room with 6 ACH	15 min open windows closed doors Negative pressure room for high-risk pts NO HEPA filters	15 min open windows closed doors	
Environment/ surfaces cleaning	Clean external instruments twice with 75% ethanol for 3min Sanitize the environment BID UV light room decontamination for >30 min	Clean equipment/ surfaces	Wiping down surfaces with appropriate cleaners	Clean equipment/ surfaces	Minimal furniture Clean equipment/ surfaces Cleaning solutions: Alcohol 60–70 °, 0.5% hydrogen peroxide or disposable wipes, hypochlorite 0.1%	Minimal furniture Clean equipment/ surfaces	Clean contact parts with appropriate wipes		Super Sani-Cloth germicidal disposable wipes (PDI, Woodcliff Lake,NJ) for hard surfaces Sani-Cloth AF3 for glass and other clear surfaces		Clean contact parts with appropriate wipes (alcohol/ Clinell wipes) Cleaning solutions: - ethanol >70% - sodium hypochlorite at least 0.21%	Regular equipment cleaning protocols UV light or ozone room decontamination at intervals	Clean equipment/ surfaces UV light or ozone room decontamination at intervals Sanitize the environment BID	Clean equipment/ surfaces Sanitize according to ecdc indications UV light, ozone/ hydrogen room decontamination
Wait time between patients				60 min			30 min	60 min			30–60 min	30–60 min		

List of Abbreviations: 30d: 30 days; A/C: air conditioning; ACH: air changes per hour; Admin: administrative; AET: Asociacion de Especialistas en Enfermeria del trabajo; AEC: Asociacion de Enfermeria Comunitaria; AS: Asymptomatic; ARTP: Association for Respiratory Technology and Physiology; ATS: American Thoracic Society; ANZSRS: Australian and New Zealand Society of Respiratory Science Ltd; ANZSRS: Australian and New Zealand Society of Respiratory Science Ltd; BD-Test: Post Bronchodilator test; BID: twice a day; BT: Body Temperature; BTS: British Thoracic Society; BVF: Bacterial/viral filter; CA: Cancer Patients; CF: Cystic fibrosis; CLEVELAND: Respiratory Institute Cleveland Clinic; COPD: Chronic Obstructive Pulmonary Disease; CS: Cardiac Surgery; CTX: chemotherapy; Dx: diagnosis; ecdc: European Centre for Disease Prevention and Control; Edu program: Educational program; ERS: European Respiratory Society; ET: essential; FFP: filtering face piece; F/U: follow up; HCWs: Health Care Workers; HEF: High Expiratory Flow; HEPA: High Efficiency Particulate Air filter; I/P: inpatients; ID: Immunocompromised patients; ILD: Interstitial Lung Diseases; IRS/SIP: Italian Respiratory Society/Società Italiana di Pneumologia; IST: Immunosuppressive Therapies; ITS: Irish Thoracic Society; ITS/AIPO: Italian Thoracic Society/Associazione Italiana Pneumologi Ospedalieri; LR: Lung Resection; LTC: long-term conditions; LTP: Lung Transplant Patients; Min: minutes; O/P: outpatients; OS: Oncological Surgery; PAH: Pulmonary Arterial Hypertension; PFM: Peak Flow Meter; PFTs: Pulmonary Function Tests; PneumoTox: Pneumotoxicity; PPE: personal protective equipment; PRE-OP: Preoperative patients; Pt/Pts: patient/patients; q4h: every 4 h; q6h: every 6 h; RALC: Rapid Access Lung Cancer Patients; RP: Respiratory Physiologist; SEIAC: Spanish Society of Allergy and Clinical Immunology; SEPAR: Spanish Society of Pneumology and Thoracic Surgery; Sx: symptoms; SPLF: Société de Pneumologie de Langue Française; SPP: Sociedade Portuguesa de Pneumologia; SUNEUMO: Sociedad Uruguaya de Neumologia; TAS: Thoraco-Abdominal Surgery; TR: Telematic Reports; TSANZ: Thoracic Society of Australia and New Zealand; U: urgent; US: Urgent Surgery; UV: ultraviolet; Wks: weeks.

suggested by official Recommendations. Table 1 summarizes Societies' Recommendations on performing PFTs.

Eligible patients

There was an overall good agreement among Guidelines on limiting PFTs to patients really needed them, weighing the benefits of ongoing care and clinical evaluation with ''exposure risk'' to COVID-19 for individuals coming to the hospital. Nevertheless, we found heterogeneous indications on the subgroup of patients considered a priority.

The ATS[6] and ERS[17] Recommendations generically advise performance of PFTs when they are essential for immediate treatment decisions of the current illness. At the same time, SPP,[16] SPLF[9] and BTS/ARTP guidelines[12] strongly encourage performing essential procedures only in cancer patients or in cases of pre-operative assessments for urgent surgery. In contrast, the recent update of the Australian Guidelines[14] suggests that asymptomatic patients might undergo PFTs, especially in cases of a pre-operative evaluation for elective surgery. The ITS[11] Guidelines recommend performing PFTs in patients with cystic fibrosis and rapid access lung cancer and in those needing a pre-operative assessment for emergency surgery. Furthermore, they recommend spirometry in immunocompromised patients for urgent treatment (e.g. bone marrow transplant, lung transplants, pre-chemotherapy treatments), suggesting testing them first on the day. Conversely, the Chinese expert Recommendations[5] limit PFTs only to patients needing them; moreover, they specify that in patients with asthma and chronic obstructive pulmonary disease (COPD), the test might be suspended unless urgently needed for diagnosis and treatment, suggesting the use of a peak flow meter for self-monitoring the lung function. Similar indications come from the Position Paper of the ITS/AIPO Italian Society,[19] which also prioritizes patients needing thoraco-abdominal surgery. The latest released IRS/SIP Recommendations,[20] provide more broad indications, including the diagnosis of COPD and asthma and interstitial lung diseases, the follow-up and the antifibrotic drugs prescription. Cleveland[21] is the only Organization that also mentions patients with pulmonary hypertension, while SUNEUMO[18] also takes into account patients with pneumoconiosis and respiratory drug toxicity. Finally, the SEPAR/AEC/AET/SEAIC[10] Recommendations suggest performing PFTs in negative rooms and postponing them unless urgently needed.

As regards patients recovered from COVID-19 experiencing persistent or evolving respiratory complications, BTS/ARTP[12] Guidelines propose a detailed follow-up: all patients recovered from a severe (hospitalized in Intensive Care Unit/High Dependency Unit, or necessitating protracted dependency on a high fraction of inspired oxygen or noninvasive ventilation during the hospital stay, or discharged with oxygen or with significant ongoing respiratory symptoms) or a mild to moderate pneumonia, or clinically improved patients with persistent changes in the chest X-ray 12 weeks post-discharge, should undergo PFTs. Patients with a previous COVID-19 pneumonia are also mentioned by the ERS[17] Guidelines that only specify that these patients must not be tested for a minimum of 30 days post-infection. The ITS/AIPO[19] Position Paper recommends a documented negative swab test 48—72 h before PFTs or arranging dedicated post-COVID PFTs lab facilities, while IRS/SIP[20] Guidelines state that these patients need to be tested without specifying any strategy. No specific indications for PFTs in COVID-19 recovered patients are mentioned by the other Guidelines.

Patient management: measures to ensure social distancing

To safely restart PFTs services, it is mandatory to appropriately assess each outpatient, considering everyone as a potential symptomatic or asymptomatic COVID-19, avoiding at the same time denying access to many patients. All Guidelines are generally encouraging similar strategies to guarantee health safety, are implementing measures to warrant social distancing and to identify suspected patients for limiting the transmission of the infection, are ensuring the safety of health-care workers (HCWs) with adequate personal protective equipment (PPE), because subclinical patients may still transmit the virus.

Patient visit

Chinese,[5] ITS/AIPO,[19] IRS/SIP,[20] and Irish Recommendations particularly emphasize that patients should be scheduled for a visit at a specific date and time, in order to avoid early arrival of the patient and crowded waiting rooms. The Irish Thoracic Society specifies that patients booked for a visit should wait in their own car, entering the department for testing only after a phone call by the administrative team.[11] No mention of scheduled visits was formulated by ATS,[6] BTS/ARTP,[12] TSANZ/ANZSRS,[14] SSP,[8] SUNEUMO,[18] SPLF,[9] SEPAR/AEC/AET/SEAIC[10] Societies.

Waiting rooms

The Recommendations generally encourage patients to come to the visit alone, without accompanying persons, when possible, or limited to one caregiver if they need support. Maintaining a minimum of 2 m distance between sitting patients is recommended by Irish,[11] Chinese,[5] ITS/AIPO,[19] ERS,[17] and BTS/ARTP[12] Societies, while SEPAR/AEC/AET/SEAIC limit the distance to at least 1 m.

Furthermore, the Chinese task force,[5] and ITS/AIPO[19] Position Paper suggest making a demonstration video focused on the maneuvers for correctly performing spirometry and to project it in the waiting area, enabling patients to be prepared before the visit, while SEPAR/AEC/AET/SEAIC[10] Societies recommend to use educational posters.

Patient entrance

ERS[17] and ITS/AIPO,[19] IRS/SIP,[20] Portuguese,[16] SPLF[9] and Nebraska medical center[15] Guidelines specify that patients coming to their visit should wear a mask, stressing that patients without a mask will not be allowed to enter the outpatient facility. SEPAR/AEC/AET/SEAIC[10] Societies suggest wearing a mask only if patients have respiratory symptoms.

Screening

All the Guidelines besides ATS,[6] TSANZ/ANZSRS[14] and BTS/ARTP[12] recommend administering a symptoms screening questionnaire to patient on arrival and checking body

temperature, in order to verify if they are likely to have a COVID-19 infection. A sample screening questionnaire is provide by ERS,[17] ITS/AIPO[19] and IRS/SIP[20] documents. ITS/AIPO,[19] IRS/SIP,[20] Irish[11] and Chinese task force[5] specify that the questionnaire, when possible, might also be administered by telephone (tele-screening) 48—72 hours before the visit. Body temperature detection alone is recommended only by TSANZ/ANZSRS[14] Guidelines: if the temperature is greater than 37.3 °C, the visit will be suspended. No information on PPE to be used by the personnel during the triage is provided by any Guidelines. ITS/AIPO[19] and IRS/SIP[20] Guidelines strongly recommend a documented negative swab test 48—72 h before PFTs for suspected cases, while ITS/AIPO[19] Guidelines encourage physicians to arrange dedicated post-COVID-19 PFTs lab facilities.

Patient preparation
After this screening phase, the patient will perform careful hand hygiene and enter the PFTs operative room; ITS/AIPO[19] Guidelines specify that patients need to wear gloves too.

HCWs protection

There is a lack of evidence about whether the PFTs should be considered aerosol-generating procedures. Nevertheless, HCWs assigned to PFTs lab should adopt all the precautionary measures suggested by WHO, since the procedure needs close contact with the patient and can induce coughing, similar to that induced by collecting diagnostic respiratory samples (e.g. nasopharyngeal swab). All Societies cautiously recommend PPE use for HCWs performing PFTs, specifying that HCWs should wear filtering facepiece respirators FFP3 or, when not available, FFP2 and eye protection. Only SPLF[9] Guidelines state that HCWs can use a simple surgical mask. Changing disposable gloves between patients is highly recommended and rigorous hand hygiene is essential. BTS/ARTP[12] Guidelines further specify that HCWs also need to wear a fluid-resistant gown and a disposable plastic apron, while IRS/SIP,[20] SPLF[9] and SEPAR/AEC/AET/SEAIC[10] Guidelines mention only the gown. However, the Chinese task force[5] and Portuguese[8] Guidelines recommend the use of overshoes and surgical hats and replacing masks, gloves, and protective glasses if contaminated with saliva, sputum, and other secretions. Furthermore, Chinese task force,[5] SEPAR/AEC/AET/SEAIC[10] and ITS/AIPO Position Paper[19] for an additional level of safety consider it appropriate that the chair direction of the PFTs operator should sit beside the patient, facing the same way, and recommend avoiding sitting face to face.

Equipment management

Spirometry systems are not designed to be sterile. There are three main potential sources of cross-contamination when performing the test: skin contact, aerosolized particles and saliva/body fluids; therefore, hygiene measures to protect users are crucial.

Filter
The ERS,[17] BTS/ARTP,[12] SEPAR/AEC/AET/SEAIC[10] and ITS/AIPO[19] Guidelines specify that in-line bacterial/viral filters should be used to protect the whole circuit from contamination with exhaled microorganisms, and the patient from inhaling particles from the circuit, while ATS,[6] ITS[11] and TSANZ/ANZSRS[14] Guidelines do not specify any precaution in this regard.

To ensure the protective effect, BTS/ARTP [12] Guidelines recommend using in-line filters with a high-quality filtration performance against viruses but with proven evidence of not altering function measurements. Similarly, ITS/AIPO [19] and the Chinese Task force [5] state that verification of the total resistance of the filter and lung respiratory tube function instrument should be < 1.5 cmH_2O at a flow rate of 14 $L \cdot s^{-1}$, in order to not affect the results of the lung function test. At the same time, ERS [17] Guidelines suggest selecting a filter with a minimum proven efficiency for a high expiratory flow of 600–700 L/min.

Interestingly, only the SPLF[9] Guidelines recommend performing PFTs in a plethysmography boot with a shut door.

Bronchodilator
As far as bronchodilator challenge is concerned, TSANZ/ANZSRS[14] Societies suggest using the patient's own salbutamol inhaler or a single-use inhaler, while ITS[11] Guidelines recommend considering the use of Turbohaler® or an aerosol holding chamber (spacer) device (i.e. aerochamber®), the latter also endorsed by the Portuguese Society.[16]

Equipment cleaning
The use of in-line filters does not preclude the necessity for thorough cleaning of the equipment. After each use, equipment cleaning with 75 % ethanol for 3 min twice is recommended by the Chinese task force.[17] SEPAR/AEC/AET/SEAIC[10] and BTS/ARTP Guidelines[12] also describe in detail the type of disinfectant solution, as shown in Table 1. A general statement regarding regular equipment cleaning protocol following local policies is advised by IRS/SIP.[20]

Nose-clip
The use of disposable nose clips is strongly recommended by ERS,[17] BTS/ARTP,[12] ITS/AIPO,[19] IRS/SIP[20] and SEPAR/AEC/AET/SEAIC[10] Guidelines.

Environment management

Ventilation
Airborne transmission occurs through the dissemination of droplets from infectious patients; the motion of droplets significantly depends on gravity, direction and strength of local airflow, temperature, and relative humidity. It is crucial, therefore, to perform the spirometry in a properly ventilated room, in order to control any possible cross-infection. Ventilation is defined as the supply/distribution or removal of air from a space by mechanical or natural procedures. The clearance rate of aerosols in a closed space is dependent on the extent of any mechanical or natural ventilation; therefore, the greater the ventilation rate, expressed as the number of air changes per hour (ACH), the sooner any aerosol will be cleared.[23] A single air change is estimated to remove 63% of airborne contaminants:

after 5 air changes, less than 1% of airborne contamination is thought to remain.[24] A minimum of 20 min, that is 2 air changes, in hospital settings, where most of these procedures occurs, is considered pragmatic.[25]Nevertheless, the issue of adequate ventilation was considered only by ERS,[17] ITS/AIPO,[19] BTS/ARTP,[12] Chinese task force,[5] SUNEUMO[18] and Nebraska Medical Center[15] Recommendations. SEPAR/AEC/AET/SEAIC[10] and Portuguese[8] Guidelines generally suggest avoidance of air recycling.

In particular, adequate room ventilation, i.e. at least 15 min to ventilate the room (open windows, closed doors), is recommended by SPLF,[9] ERS[17] and ITS/AIPO[19] Guidelines. Negative isolation rooms with 6–12 ACH or side rooms with 6 ACH are encouraged by BTS/ARTP[12] Guidelines.

The Nebraska Medical Center[15] states that the procedure room should remain closed for an hour after the PFTs. The Chinese task force[5] recommend maintaining the ventilation of the lung function examination room, ensuring 12 ACH if operating in a negative isolation room or an air flow of at least 160 L / s per patient or hourly in a naturally ventilated room, as well as opening windows as much as possible for natural ventilation.

Chinese,[5] SEPAR/AEC/AET/SEAIC[10] and ITS/AIPO Guidelines[19] proposed separating the test area from the administrative area of the room.

Room and surfaces cleaning and infection control

All the reviewed Guidelines agreed on the importance of cleaning equipment and surfaces; SEPAR/AEC/AET/SEAIC,[10] BTS/ARTP[12] and Chinese[5] Guidelines also recommend the type of cleaning solution to be used, Table 1.

Disposable cleaning wipes were strongly recommended by SEPAR/AEC/AET/SEAIC[10] BTS/ARTP,[12] ITS,[11] and Cleveland Clinic[21] Guidelines, but only TSANZ/ANZSRS[14] and SEPAR/AEC/AET/SEAIC[10] Guidelines expressly recommend the presence of minimal furnishings that can be easily cleaned and disinfected.[14]

As regards PFTs operating room cleaning, ERS[17] ITS/AIPO[19] and IRS/SIP[20] Guidelines suggest the use of UV light or ozone room decontamination at intervals, compliant with local infection policies, while more detailed precautions are provided by the Chinese task force.[5]

The Chinese task force also recommend switching off the central air conditioner, sanitizing the room at least twice a day, using UV light for at least 30 min a day to clean the air and medical air purification devices for air disinfection during lung function tests.

Waiting time between patients

The suggested time required between visits by ERS,[17] BTS/ARTP[12] Guidelines is 30 min for a regular side room and 60 min for a negative isolation room. The Portuguese Society[16] recommends a period time of 60 min between visits and the Nebraska medical center[15] specifies that the operating room must be closed for 1 h after the visit.

Interesting suggestions come from ITS/AIPO[19] and SPLF[9] Guidelines that recommend a new calibration of the spirometer after the cleaning procedures, and from ERS,[17] the only Society that takes into account high-risk patients, that suggest performing a remote test with live video instructions in these subgroups of patients.

A plan to manage the respiratory issues of people with acute respiratory symptoms, pre-existing chronic lung diseases or conditions that need adequate pulmonary function assessment to be appropriately diagnosed and treated, is essential to prevent an inevitably indirect effect of COVID-19 on frail patients that could be devastating, increasing death and disability.

Manufacturers' policies

Manufacturers' policies[26–29] are summarized in Table 2.

Discussion

The COVID-19 pandemic completely changed the routine of providing health-care services, shifting from elective to essential/acute management and limiting several diagnostic resources for chronic respiratory patients such as pulmonary function labs and sleep labs.[30] We analyzed Society-specific clinical practice Guidelines on how to safely perform PFTs and the recommendation level of consensus for each clinically relevant problem; we found similarities but also several differences. In particular, the Societies' Guidelines on spirometry during the COVID-19 outbreak differ greatly in relation to the subgroup of patients that need to be prioritized for testing.

The Guidelines agreed about prioritizing patients with urgent need to initiate treatment and pre-operative assessment, except Cleveland,[21] which takes into account also pulmonary hypertension patients, IRS/SIP,[20] which also considered patients with a diagnosis of pulmonary fibrosis and follow-up and for therapy prescription, as well as patients with a diagnosis of asthma and COPD, and Uruguayans[18] Guidelines, providing indications also for pneumoconiosis and drug toxicity.

We identified a recommendation level of consensus on patient screening, on HCWs protection, and on the use of in-line filters for spirometry, but a little reference to adequate ventilation policies. No details on PPE that should be worn by the triage personnel were found, as well as no indications on how to safely perform spirometry using point of care portable spirometers with turbines in any National and International Guideline. ERS[17] and BTS/ARTP[12] Guidelines provided detailed information on when to perform PFTs in patients with a previous COVID-19 pneumonia, while IRS/SIP[20] and ITS/AIPO[19] Guidelines strongly recommend nasopharyngeal swab testing before the visit, probably taking into account only in-patients. The Chinese task force[5] and ITS/AIPO[19] Guidelines, interestingly, recommend providing an educational video on how to perform PFTs in the waiting rooms. ERS[17] is the only Society that suggests the possibility of remote testing in very severely ill patients, ''untethering'' them from physical sites, promoting decentralized medical services. Manufacturers concentrate on in-detail technical issues, such as the type of in-line filters to be used or the cleaning procedures for the equipment of each product.

Table 2 Issues related to safely performing pulmonary function test: spirometry manufacturers' proposed solutions.

Issue	Proposed solutions			
	Vitalograph26	Morgan Scientific[28]	ndd[27]	Vyaire[29]
Cleaning and infection control	New BVF for each pt Clean the exterior surface with a 70% isopropyl alcohol solution The interior of the patient circuit requires no decontamination between tests If internal contamination is suspected, follow appropriate protocol	New BVF for each pt Clean the exterior surface with a 70% isopropyl alcohol solution The interior of the patient circuit requires no decontamination between tests Equipment cleaning and disinfection required after use on infected subjects or prior to use on ID	The ndd hygiene solution, which uses the inserts spirette, FlowTube and bamette, requires no cleaning of internal tubing or sensor Surface cleaning is required Separate test / administrative area Risk assessment questionnaire	Use MicroGard II BVF Minimize contamination performing PFTs Use an enzyme cleaner with neutral pH (pH 6–8) Do not use temperatures above 130 °F
HCWs protection			PPE: - surgical mask - disposable gloves	
Minimum wait time between patients		5 minutes		
Ventilation			Air ventilation and sterilization	
Critical issue			Measurements are influenced by the filter's resistance	

List of Abbreviations: BVF: Bacterial Viral Filter; HCWs: health-care workers; ID: Immunocompromised patients; PFTs: Pulmonary Function Tests; PPE: personal protective equipment; Pt: patient.

This review provides a summary of clinical practice Guidelines/Recommendations/Position Papers on practical problems that might arise worldwide during the safe reopening of respiratory outpatient services during COVID-19 pandemic, with a special focus on spirometry, but does not represent a Guideline itself. The main strength of this research is that all the reviewed Guidelines were published in the restricted time period of the COVID-19 outbreak, with publication dates ranging from 4, March 2020 to 12, May 2020. Therefore, the scientific evidence available when they were developed was almost the same for them all.

Differences in national healthcare systems, resource availability and different times of epidemic evolution might explain any dissimilarity in terms of consensus. However, the lack of specific COVID-19-related evidence could be another reason for heterogeneity of the Guidelines, mainly based on experts' opinions rather than evidence-based recommendations. Furthermore, national and international recommendations may overlap due to the contribution of national representatives who possibly served also as the international experts in the Societies' statement. Finally, although we have searched for national guidelines on spirometry resumption in four common languages (English, Spanish, French and Italian) we might have failed to detect recommendations of some Societies due to language restrictions.

Conclusion

The review of Guidelines/Recommendations/Position Papers indicate a good agreement in the need to prioritize patients for PFTs, patients screening, HCWs protection, and in the use of in-line filters for spirometry but poor consensus on the subgroup of patients considered a priority, and few indications on the measures to implement for adequate ventilation. We believe that this summary of the available literature may be a useful guide helping HCWs to select appropriate measures, tailored to the highly specific context in which they will be used, to meet the needs of intended users.

Authors' contribution

CC conceived the content, drafted the manuscript and approved the final version to be submitted. PI drafted the manuscript, approved the final version to be submitted. RC, SN, helped in writing the manuscript and approved the final version to be submitted. AS helped in writing the manuscript, revised it critically for important intellectual content and approved the final version to be submitted. NC conceived the content, revised it critically for important intellectual content and approved the final version to be submitted.

Funding

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

Competing interests

All authors declare no competing interests.

Acknowledgment

The authors thank Dr. Pietro Zucchi, medical writer, for improving the use of English in the manuscript.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;10223:470–3, http://dx.doi.org/10.1016/S0140-6736(20)30185-9.
2. WHO. Coronavirus disease (COVID-2019) Situation Report; 2020. Date last updated: 4 May 2020. Date last accessed: 17 May 2020; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen.
3. WHO. Critical preparedness, readiness and response actions for COVID-19: interim guidance. Date last updated: 22 March 2020. Date last accessed: 17 May 2020; Available from: https://apps.who.int/iris/handle/10665/331511.
4. Anfinrud P, Stadnytskyi V, Bax CE, Bax A. Visualizing Speech-Generated Oral Fluid Droplets with Laser Light Scattering. N Engl J Med. 2020;382:2061–3, http://dx.doi.org/10.1056/NEJMc2007800.
5. Task Force of Pulmonary Function Testing, Clinical Respiratory Physiology, Chinese Association of Chest Physicians, Pulmonary Function Testing Group, Respiratory Therapeutics Group and Chinese Thoracic Society. [Expert consensus on Pulmonary Function Testing during the epidemic of Coronavirus disease 2019]. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43:302–7, http://dx.doi.org/10.3760/cma.j.cn112147-20200225-00175.
6. American Thoracic Society. Pulmonary Function Laboratories: Advice Regarding COVID-19; 2020. Date last updated: 31 March, 2020. Date last accessed: 17 May, 2020; Available from: https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/pulmonary-function-laboratories.php.
7. TSANZ/ANZSRS. Peak Respiratory Bodies recommend suspension of lung function testing; 2020. Date last updated. Date last accessed; Available from: https://www.anzsrs.org.au/images/anzsrs/peak_respiratory_bodies_recommend_suspension_of_lung_function_testing_002.pdf.
8. Sociedade Portuguesa de Pneumologia. Recomendaço˜es da SPP para a realizaça˜o de provas funcionais respiratórias durante o surto COVID-19; 2020. Date last updated: 23 March 2020. Date last accessed: 17 May 2020; Available from: https://www.sppneumologia.pt/uploads/subcanais_conteudos_ficheiros/adenda-pfr-covid19.pdf.
9. SPLF. Position du groupe Fonction de la SPLF concernant la pratique des Explorations Fonctionnelles Respiratoires pendant la période d'épidémie COVID-19; 2020. Date last updated: 17 March 2020. Date last accessed: 12 July 2020; Available from: http://splf.fr/wp-content/uploads/2020/03/COVID_position-groupe-fonction_v6.pdf.
10. SEPAR/AEC/AET/SEAIC. Recomendaciones de prevención de infección por coronavirus en las unidades de función pulmonar de los diferentes ámbitos asistenciales; 2020. Date last updated: 26 March 2020. Date last accessed: 12 July 2020; Available from: https://www.separ.es/node/1773.
11. Irish Thoracic Society. Guidance on Lung Function Testing: SARS COVID-19; 2020. Date last updated: 24 March 2020. Date last accessed: 17 May 2020; Available from: https://irishthoracicsociety.com/wp-content/uploads/2020/03/ITS-Guideline-on-lung-function-testing-24.03-FINAL.pdf.
12. BTS/ARTP. COVID19 Guidelines; 2020. Date last updated: 18 March 2020. Date last accessed: 17 May 2020; Available from: https://www.artp.org.uk/News/artp-covid19-update-18th-march-2020.
13. UNMC Nebraska Medicine. SBAR for Performing Pulmonary Function Test in PFT lab; 2020. Date last updated: 1 April 2020. Date last accessed: 17 May 2020; Available from: https://www.nebraskamed.com/sites/default/files/documents/covid-19/Guidance-regarding-pulmonary-function-testing-(PFT).pdf?date=04012020.
14. TSANZ/ANZSRS. Update on suspension of lung function testing; 2020. Date last updated: 30 April 2020. Date last accessed: 17 May 2020; Available from: https://www.anzsrs.org.au/images/Updated_Lung_Function_Testing_Guidelines_-_30th_April_2020.pdf.
15. UNMC Nebraska Medicine. Recommendations on Performing Pulmonary Function Test (PFT) in PFT lab; 2020. Date last updated: 10 May 2020. Date last accessed: 17 May 2020; Available from: https://www.nebraskamed.com/sites/default/files/documents/covid-19/Guidance-regarding-pulmonary-function-testing-(PFT).pdf?date=05122020.
16. Sociedade Portuguesa de Pneumologia (SPP). Reabertura de Laboratórios de funça˜o Pulmonar; 2020. Date last updated. Date last accessed: 17 May 2020; Available from: https://www.sppneumologia.pt/uploads/subcanais_conteudos_ficheiros/adenda-pfr-covid19.pdf.
17. Recommendation from ERS Group 9.1 (Respiratory function technologists /Scientists) Lung function testing during COVID-19 pandemic and beyond. 2020. Date last updated: 09 May 2020. Date last accessed: 17 May 2020; Available from: https://ers.app.box.com/s/zs1uu88wy51monr0ewd990itoz4tsn2h.
18. Sociedad Uruguaya de Neumología. Recomendaciones para realizar Estudios Funcionales Respiratorios durante la epidemia causada por el coronavirus SARS–CoV–2 (COVID19); 2020. Date last updated: 13 April 2020. Date last accessed: 17 May 2020; Available from: https://suneumo.org/descargar/adjunto/32-grl8hr-coronavirus-2020-15mar-reco1.pdf.
19. ITS/AIPO. Le prove di funzionalità respiratoria nell'era della pandemia da COVID-19 - Position Paper; 2020. Date last updated: 9 May 2020. Date last accessed: 17 May 2020; Available from: http://www.aiponet.it/news/speciale-covid-19/2471-le-prove-di-funzionalita-respiratoria-nell-era-della-pandemia-da-covid-19-position-paper-aipo-its.html.
20. IRS/SIP. Esami di funzionalità respiratoria nel contesto COVID-19 Position Paper; 2020. Date last updated: 12 May 2020. Date last accessed: 17 May 2020; Available from: https://irn.sipirs.it/storage/61/Documento-EsamiFunzionalitàRes-Covid_Vers.1_12.05.2020.pdf.
21. Ramos JA. Pulmonary function testing precautions in a time of COVID-19 Cleve. Clin J Med. 2020 [Epub ahead of print]. https://doi.org/10.3949/ccjm.87a.ccc006.
22. Crimi C, Impellizzeri P, Campisi R, Spicuzza L, Vancheri C, Crimi N. Resumption of Respiratory Outpatient Services in the COVID-19 era: experience from Southern Italy. Am J Infect Control. 2020;20:30633–7, http://dx.doi.org/10.1016/j.ajic.2020.06.210.
23. WHO. Natural Ventilation for Infection Control in Health-Care Settings; 2010. Date last updated: 5 March 2010. Date last

accessed: 17 May 2020; Available from: https://www.who.int/water_sanitation_health/publications/natural_ventilation.pdf.
24. Coia JE, Ritchie L, Adisesh A, Makison Booth C, Bradley C, Bunyan D, et al. Healthcare Infection Society Working Group on R and Facial P. Guidance on the use of respiratory and facial protection equipment. J Hosp Infect. 2013;3:170–82, http://dx.doi.org/10.1016/j.jhin.2013.06.020.
25. NHS. COVID-19: infection prevention and control guidance; 2020. Date last updated: 27 April 2020. Date last accessed: 17 May 2020; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/881489/COVID-19_Infection_prevention_and_control_guidance_complete.pdf.
26. Vitalograph. Recommended Cleaning Instructions for your Spirometry device; 2020. Date last updated: 12 May 2020. Date last accessed: 17 May 2020; Available from: https://vitalograph.com/news/1117/recommended-cleaning-instructions-for-your-spirometry-device.
27. ndd. Statement about the use of ndd devices regarding COVID-19; 2020. Date last updated: 1 April 2020. Date last accessed: 17 May 2020; Available from: https://www.ndd.ch/en/ndd/about/news-stories/statement-about-the-use-of-ndd-devices-regarding-covid-19.html.
28. Morgan Scientific. COVID-19 Updates; 2020. Date last updated: 24 Aprile 2020. Date last accessed: 17 May 2020; Available from: https://www.morgansci.com/covid-19/.
29. vyaire. Information on Respiratory Diagnostics Products in context of COVID-19; 2020. Date last updated: 23 March 2020. Date last accessed: 17 May 2020; Available from: https://intl.vyaire.com/sites/default/files/2020-05/vyr-gbl-2000116-ib_rdx_covid-19-recommendations-final-v0.3.pdf.
30. Drummond M. Sleep labs, lung function tests and COVID-19 pandemic - Only emergencies allowed! Pulmonology. 2020;4:244–5, http://dx.doi.org/10.1016/j.pulmoe.2020.04.002.

Pulmonology 27 (2021) 448–473

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Ventilator configuration in children on long term home ventilation during the COVID19 pandemic

Introduction

On March 11th, the World Health Organization (WHO) declared the novel coronavirus disease (COVID-19) a pandemic.[1] Paediatric patients with COVID-19 are underrepresented in this epidemic so that management strategies and standards of care are poorly defined especially in patients with chronic respiratory diseases. Technologically dependent children on a ventilator represent a subgroup with medical complexity that accounts for about 1/3 of economic health resources.[2,3] It is important to remember that these patients are mainly affected by chronic ''respiratory pump failure'' conditions which can aggravate their clinical condition in cases of respiratory tract infections.[4] In most of the cases, children are ventilated, either using non-invasive ventilation (NIV), with an single-limb intentional leak circuit, where typically the leak is within the interface, or a single-limb non-intentional leak circuit with an active exhalation valve inserted into the mask. For tracheostomy ventilation (TIPPV) a single-limb non-intentional leak circuit with an active exhalation valve is normally used, however, some patients are managed with single-limb intentional leak circuit or a double limb circuit.[5]

Paediatric ventilator-dependent patients are reluctant to change their ventilation modes, settings and interface.[6,7]

However, during this pandemic, when the patients are admitted to the hospital for an exacerbation of their underlying disease, or with suspected, or positive infection for SARS-COV2 several of the healthcare providers and parents may be in close contact with the children. Where precautions are not taken the risk of transmission of virus due to the ventilator being an aerosol generating procedure (AGP) is high. This is because, expired air aerosolization from ventilators and interfaces[8] as well as from plain tracheostomy tube[9] may be the cause of contamination of environment and infection in health care workers. It has been demonstrated, in an adult population, that physiotherapy and NIV delivered with vented mask generated large droplets close to the patient but, the fall out of these decreases significantly at 1 m from the patient. NIV using non vented mask and filtered exhalate can reduce the amount of aerosolization.[8] In addition, full face or total face masks have a built in ''anti-asphyxia valve'' that opens when the ventilator does not work properly. The exhaled air from this ''anti-asphyxia valve'' is also bound to contaminate the environment with the virus.[10] Although hospitalization of these patients needs maximum attention in terms of personal protection equipment (PPE) for health care workers and parents the ventilators as well interfaces should be also upgraded to reduce aerosolization of exhaled air see Figs. 2, 4 to 6.

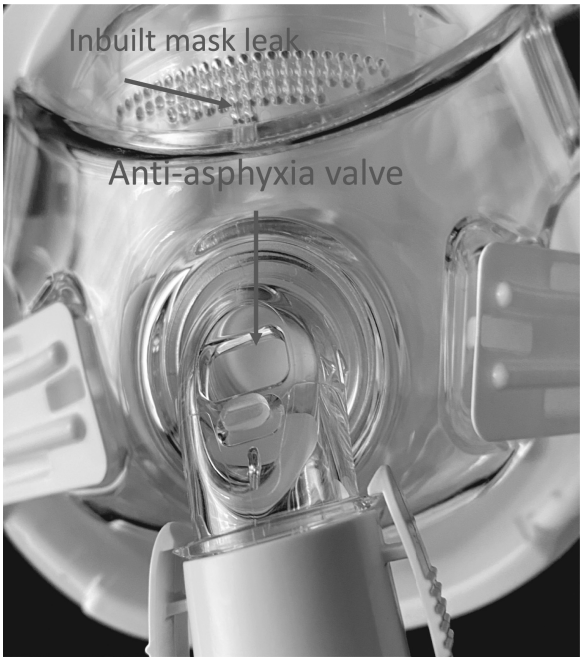


Figure 1 Shows an example of a mask with an inbuilt leak and anti-asphyxia valve.

However changing to a non-vented mask has the potential to cause problems. One potential issue is leaving out the expiratory intentional leak. Training and education need to occur in the hospital to prevent adverse events. This can be done by showing a picture of the circuit above the bed. This can also include a reminder to change the heat and moisture exchanger (HME) daily otherwise this will lose the filtration properties required. Another potential risk is a waterlogged filter. This can affect triggering and cause problems with the alarms. These filters need to be checked regularly. Changing from a nasal mask also has the potential to increase the risk of abdominal distention. This can be alleviated by venting the gastrostomy or the feeding tube. Likewise enteral feeding may need to be commenced if ventilator time has increased. The insertion of a nasogastric tube may cause mask leak and this needs to be minimized.

We therefore provide practical recommendations for how to optimize home ventilators circuits and interface configu-

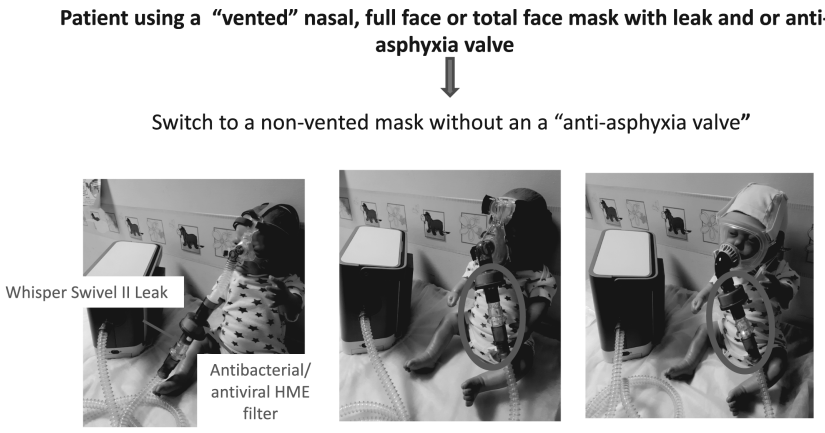


Figure 2 Shows suggestions for switching from a vented mask to a non-vented mask attached to an antibacterial/antiviral heat moisture exchanger (HME) filter, then attached to a controlled leak (Whisper swivel II (Philips, Murraysville, USA). Left picture shows a child mannequin wearing a non–vented nasal mask. Centre picture a full face mask and right picture a total face mask. Note the position of the HME and Whisper Swivel controlled leak (labelled and circled).

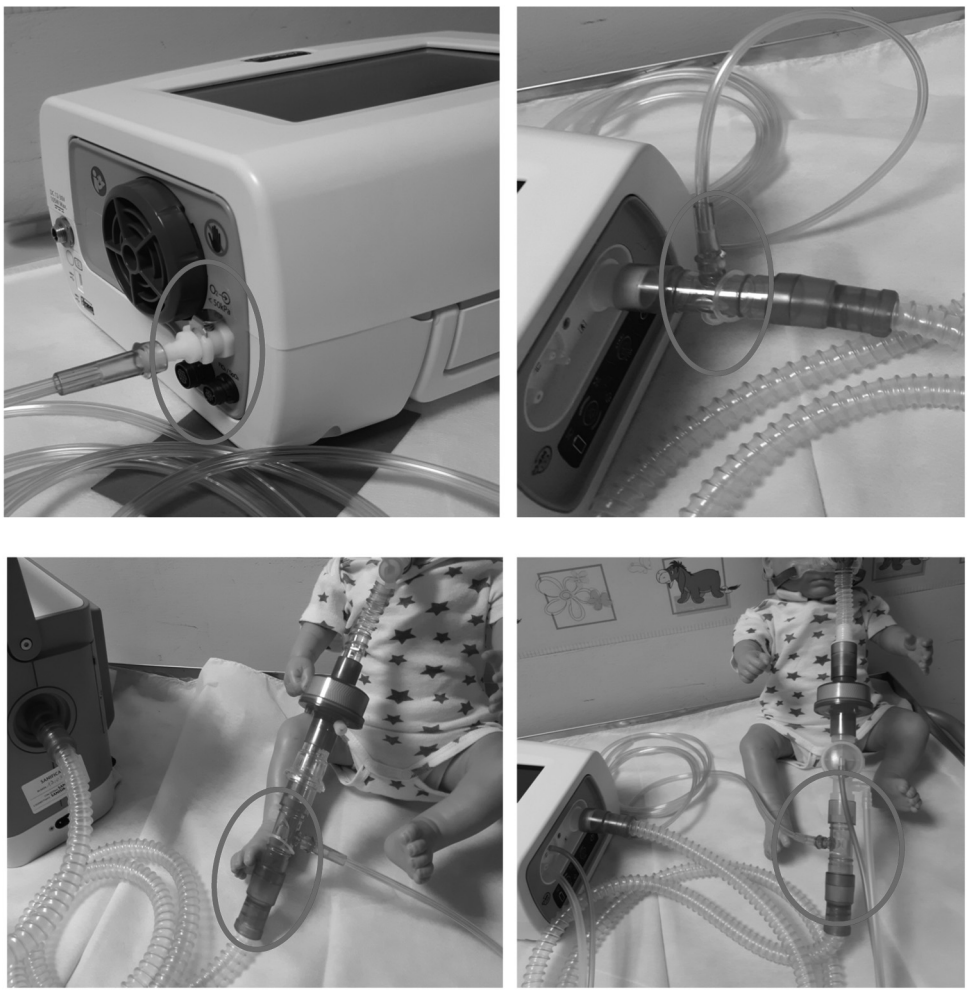


Figure 3 Top left hand photograph demonstrated that oxygen should be entrained using a dedicated connector where possible (circled). If this is not possible the top right hand photograph illustrates the position of an oxygen connector attached to the ventilator tubing (circled). It can also be placed on, before intentional leak (bottom left photograph) or before the ''active valve'', bottom right photograph.

ration in different case scenarios to avoid airborne spread and cross infection, in hospital admissions.

Recommendations for children using a ''vented'' nasal, full face or total face mask

Box 1

1) Switch to a non-vented mask without an a ''anti-asphyxia valve'', (Fig. 1)
2) Attach a antibacterial/antiviral low resistance heat and moisture exchanger (HME)(*) into the mask or after the catheter (for tracheostomy ventilation), (Fig. 2)
3) Next attach an intentional leak for example a whisper swivel II (Phillips Respironics, Murrysville, PA, USA), (Fig. 2)
4) Ensure any wet humidification is removed.
5) Evaluate for an increase in resistance by checking for a possible reduction in the estimated tidal volume when using a time or flow cycled pressure controlled mode without any tidal volume or alveolar ventilation target mode.[8] Or in volume controlled mode check for an increase in maximal peak pressure. Perform a measurement of CO_2 to assess carbon dioxide level (**)
6) For patients who require oxygen, entrain oxygen at the back of the ventilator (Fig. 3). Or insert oxygen before the controlled leak or active valve with a dedicated connector. (Fig. 3)

Recommendations for children using a non-vented nasal or full face mask with an active valve circuit

Box 2

1) Remove an a ''anti-asphyxia valve'' if present
2) Attach the low resistance antibacterial/antiviral HME (*) before the expiratory valve (Fig. 4)
3) Ensure wet humidification is removed
4) Evaluate for an increase in resistance by checking for a possible reduction in the estimated tidal volume when using a time or flow cycled pressure controlled mode without any tidal volume or alveolar ventilation target mode.[8] Or in volume controlled mode check for an increase in maximal peak pressure.
5) Perform a measurement of CO_2 to assess carbon dioxide level (**)
6) For patients who require oxygen, entrain oxygen at the back of the ventilator (Fig. 3). Or insert oxygen before the controlled leak or active valve with a dedicated connector. (Fig. 3)

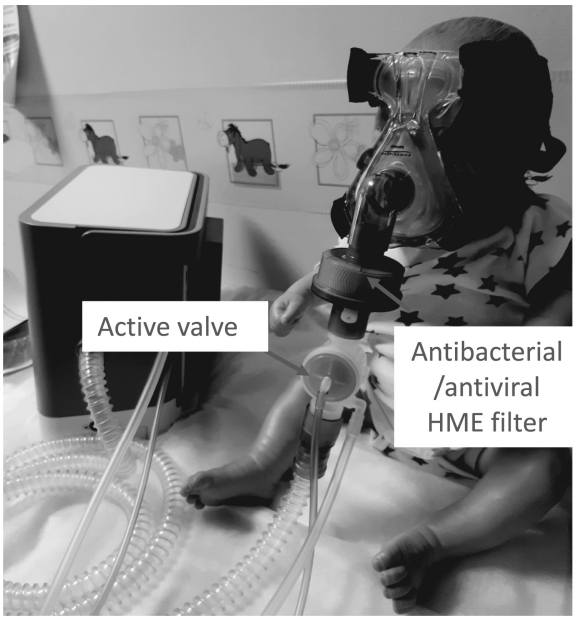


Figure 4 Picture shows a child mannequin wearing a non–vented nasal mask with the active valve circuit set up. Note the position of the HME and active valve in the circuit. The same set-up can be used for a face mask or a total face mask.

Tracheostomised patients

Box 3

1) Where possible replace a cuff-less tracheostomy tube to a cuffed tube
2) Remove heated humidification
3) Insert a low resistance antibacterial/antiviral HME (*) between the catheter mount and the circuit (see Fig. 5 for circuit set up)
4) Evaluate for an increase in resistance by checking for a possible reduction in the estimated tidal volume when using a time or flow cycled pressure controlled mode without any tidal volume or alveolar ventilation target mode.[8] Or in volume controlled mode check for an increase in maximal peak pressure.
5) Take measurement of CO_2 to assess carbon dioxide level (**)
6) In patients who require oxygen, entrain oxygen at the back of the ventilator (Fig. 3). Or insert oxygen before the active valve with a dedicated connector. (Fig. 3)

(*)The addition of a HME will increase the dead space of the circuit. This can cause a drop in the delivered IPAP. If this occurs increasing inspiratory pressure by 1—2 cmH2O solves the problem. The HME will also cause a small increase in the resistance to the circuit. Changing the device triggers sensitivity to be more sensitive which will help to overcome this problem. If triggering remains a problem, switching from a

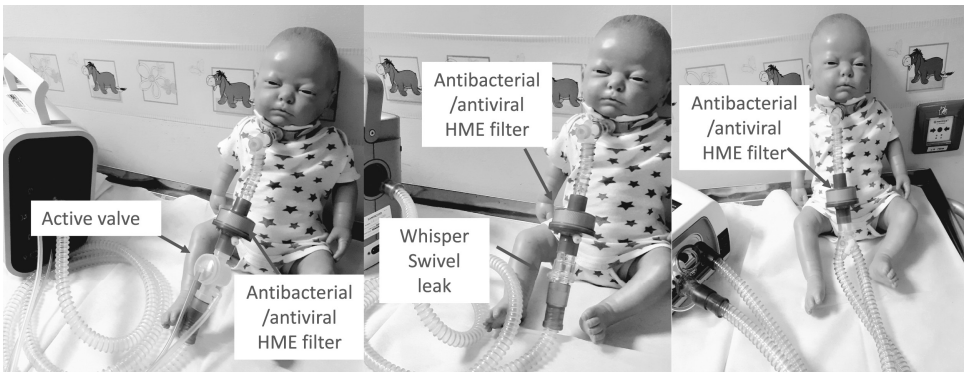


Figure 5 The three photographs show a child mannequin with a tracheostomy. The left picture shows a active valve circuit. The centre picture a controlled leak circuit and the right picture a double limb circuit.

pressure support mode to pressure control with an appropriate back up rate (near to patient's rate)

(**) We recommend in the first instance continuous transcutaneous CO_2 ($TcCO_2$) with pulse oximetry monitoring for the first 24 h to ensure optimal ventilation and no adverse increase in $PaCO_2$ levels as a result of the change in the circuit. If $TcCO_2$ monitoring is unavailable, then this should be replaced with end tidal CO2 ($EtCO_2$) with pulse oximetry monitoring. Where non-invasive monitoring is unavailable percutaneous capillary measurements should be carried out 3 h after changing the mask. If the CO_2 levels are satisfactory we then recommend repeating the following morning unless the patient's SpO_2 deteriorates.

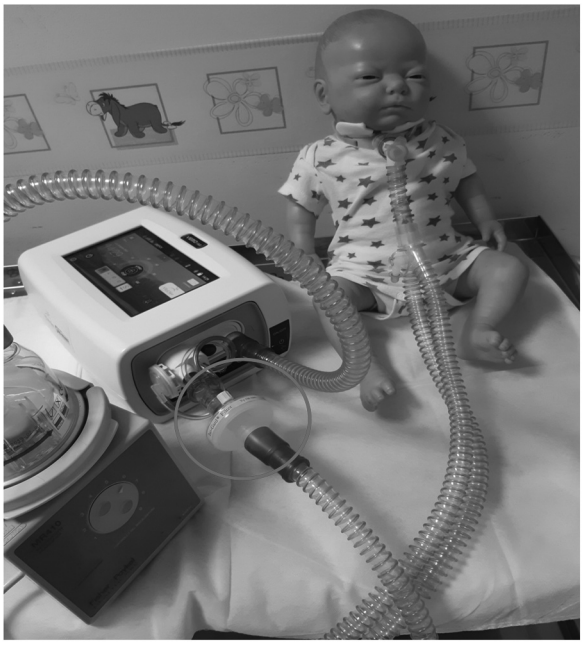


Figure 6 This picture shows the set-up of heated humidification if required in a child with a tracheostomy. Note the position of the filter on the expiratory limb to protect the ventilator and the environment.

Additional scenarios

Secretion retention

If secretions are a problem remove the HME and insert heated humidification with a double limb circuit (see Fig. 6). The expiratory limb should be protected by a hydrophobic antibacterial (HEPA) filter.

It should always remembered when ventilation is required:

- Mask on
- Ventilator on
- Check for nonintentional leaks
- Add oxygen if required.
- Stop ventilation, oxygen off, ventilator off, mask off

Conclusion

Children receiving any respiratory support should be cared for in airborne isolation rooms at negative pressure whenever possible.

Non-vented face or total face masks should be used as the first choice. A non-vented nasal mask[11] should be used as the second choice when the children cannot tolerate the oronasal mask or for inability to ventilate the children. Use of pacifiers should be stimulated and mouth-piece ventilation should be avoided.

Staff should adopt full contact, droplet, and airborne isolation precautions whether the patient is positive or suspected of having a COVID-19 infection.

In particular, appropriate type of masks/filtering facepiece respirators (FFR) should be selected according to risk of aerosolization.[12–14] If present (as in case of NIV), healthcare personnel should always wear FFR ensuring both droplets and airborne protection (e.g. FFP2, KN95, N95, FFP3).[12]

Providers and parents should be aware that theoretically, coronaviruses can remain infectious on inanimate surfaces like metal, glass or plastic for up to 9 days.[14] Surfaces and equipment like ventilators used for SARS-2- CoV-infected children should be carefully disinfected with appropriate solutions (ie about 62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 min of cleaning).[15]

Finally, regardless of their respiratory support patients who are admitted to hospital from home with suspicion of having COVID-19–associated respiratory failure, should be closely monitored for deterioration. An emergency care pathway including an escalation plan and ceiling of care should be discussed and documented on arrival.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33, http://dx.doi.org/10.1056/NEJMoa2001017.
2. Cohen E, Kuo DZ, Agrawal R, Berry JG, Bhagat SKM, Simon TD, et al. Children with medical complexity: an emerging population for clinical and research initiatives. Pediatrics. 2011;127:529–38, http://dx.doi.org/10.1542/peds.2010-0910.
3. Srivastava R, Downie J, Hall J, Reynolds G. Costs of children with medical complexity in Australian public hospitals. J Paediatr Child Health. 2016;52:566–71, http://dx.doi.org/10.1111/jpc.13152.
4. Poponick JM, Jacobs I, Supinski G, DiMarco AF. Effect of upper respiratory tract infection in patients with neuromuscular disease. Am J Respir Crit Care Med. 1997;156:659–64, http://dx.doi.org/10.1164/ajrccm.156.2.9611029.
5. Gregoretti C, Navalesi P, Ghannadian S, Carlucci A, Pelosi P. Choosing a ventilator for home mechanical ventilation. Breathe. 2013;9:394–409, http://dx.doi.org/10.1183/20734735.042312. European Respiratory Society.
6. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax. 2012;67 Suppl 1:i1–40, http://dx.doi.org/10.1136/thoraxjnl-2012-201964.
7. Gregoretti C, Pelosi P, Chidini G, Bignamini E, Calderini E. Noninvasive ventilation in pediatric intensive care. Minerva Pediatr. 2010;62:437–58.
8. Hui DS, Chow BK, Lo T, Ng SS, Ko FW, Gin T, et al. Exhaled air dispersion during noninvasive ventilation via helmets and a total facemask. Chest. 2015;147:1336–43, http://dx.doi.org/10.1378/chest.14-1934.
9. Gregoretti C, Foti G, Beltrame F, Giugiaro PM, Biolino P, Burbi L, et al. Pressure control ventilation and minitracheotomy in treating severe flail chest trauma. Intensive Care Med. 1995;21:1054–6, http://dx.doi.org/10.1007/BF01700674.
10. Simonds AK, Hanak A, Chatwin M, Morrell M, Hall A, Parker KH, et al. Evaluation of droplet dispersion during noninvasive ventilation, oxygen therapy, nebuliser treatment and chest physiotherapy in clinical practice: implications for management of pandemic influenza and other airborne infections. Health Technol Assess. 2010;14:131–72, http://dx.doi.org/10.3310/hta14460-02.
11. Conti G, Spinazzola G, Gregoretti C, Ferrone G, Cortegiani A, Festa O, et al. Comparative bench study evaluation of different infant interfaces for non-invasive ventilation. BMC Pulm Med. 2018;18:57, http://dx.doi.org/10.1186/s12890-018-0620-x.
12. Ippolito M, Vitale F, Accurso G, Iozzo P, Gregoretti C, Giarratano A, et al. Medical masks and Respirators for the Protection of Healthcare Workers from SARS-CoV-2 and other viruses. Pulmonology. 2020, http://dx.doi.org/10.1016/j.pulmoe.2020.04.009.
13. Ippolito M, Gregoretti C, Cortegiani A, Iozzo P. Counterfeit filtering facepiece respirators are posing an additional risk to health care workers during COVID-19 pandemic. Am J Infect Control. 2020, http://dx.doi.org/10.1016/j.ajic.2020.04.020.
14. Ippolito M, Iozzo P, Gregoretti C, Grasselli G, Cortegiani A. Facepiece filtering respirators with exhalation valve should not be used in the community to limit SARS-CoV-2 diffusion. Infect Control Hosp Epidemiol. 2020:1–2, http://dx.doi.org/10.1017/ice.2020.244.
15. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104:246–51, http://dx.doi.org/10.1016/j.jhin.2020.01.022.

I. Esposito[a], M. Chatwin[b], G. Accurso[c,*], A. Cortegiani[c], C. Gregoretti[c], E. Bignamini[a]

[a] *AOU Città della Salute e della Scienza di Torino SC Pneumologia Presidio Regina Margherita, Turin, Italy*
[b] *Clinical and Academic Unit of Sleep & Breathing, Royal Brompton & Harefield NHS Foundation Trust, London, UK*
[c] *Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.), Section of Anaesthesia, Analgesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, University of Palermo, Italy*

* Corresponding author.
E-mail addresses: espirene75@gmail.com (I. Esposito), m.chatwin@rbht.nhs.uk (M. Chatwin), giuseppe.accurso86@gmail.com (G. Accurso), andrea.cortegiani@unipa.it (A. Cortegiani), cesare.gregoretti@unipa.it (C. Gregoretti), elisabetta.bignamini@gmail.com (E. Bignamini).

9 May 2020
Available online 16 July 2020

https://doi.org/10.1016/j.pulmoe.2020.06.010

Functional impairment during post-acute COVID-19 phase: Preliminary finding in 56 patients

Dear Editor,

Rehabilitation in a bedded setting is estimated to be needed in 4% of 2019 novel Coronavirus (COVID-19) patients discharged from hospital, especially from Intensive Care Unit (ICU).[1]

Functional impairment of patients surviving the COVID-19 acute phase has been poorly described, and the only available information is provided by experts[2] or inferred from patients with other clinical conditions (e.g., Acute Respiratory Failure-ARF).[3] Two recent studies suggested that early, post-hospitalization rehabilitative interventions would be recommended.[4,5]

Aim of this study is to assess the clinical and functional presentation of post-acute COVID-19 patients at admission for inpatient rehabilitation. All consecutive COVID-19 patients admitted to undergo inpatient rehabilitation at Isti-

tuti Clinici Scientifici (ICS) Maugeri, Tradate, Italy between April 1st and July 31st were evaluated. The study was approved by the Central Ethical Committee of ICS Maugeri (CEC2279; March 12th, 2020) and patients signed the consent form. Healthcare operators were trained in personal protection measures.[6] The following evaluations were performed: clinical examination (including vital signs and blood gas analysis) and anthropometric assessment. Dyspnoea and perceived health state were measured by Barthel Dyspnea Index (Bd) (total scores range from 0-best- to 100-worst-), and Euro Quality of Life (EuroQoL-VAS), respectively (total scores range from 0-worst- to 100-best-), whereas disability with Barthel Index (Bi) (total scores range from 0-worst- to 100-best-), and Short Physical Performance Battery (SPPB) (total score results from the sum of three scores: standing balance, walking, and standing from sitting position, with disability if <9—1/2: severe; 3/8 moderate-).[7] Functional assessment with Medical Research Council Muscle (MRCm) strength test for quadriceps and biceps (≥4 normal) and respiratory muscles fatigue with Single Breath Counting (SBC) were also evaluated.

Exercise capacity was assessed with the 6-min walk test (6MWT) or One Minute Sit to Stand (1STS)[8] (reference value of repetitions: 30–37/min in men and 27–34/min in women, aged 60–79 years). Data accounted for length of stay (LoS) before admission for pulmonary rehabilitation, previous treatment for ARF (Invasive Mechanical Ventilation (IMV), Non-Invasive mechanical Ventilation (NIV), and oxygen), comorbidities (Cumulative Illness Rating Scale (CIRS)) gender and age.

Table 1 Baseline characteristics of 56 patients surviving the acute COVID-19 phase.

	All	IMV (n = 24)	NIV (n = 11)	Oxygen (n = 21)	p-Value
Males, n (%)	39 (69.6)	19 (79.2)	7 (63.6)	13 (61.9)	0.40
Age, years	69.4 (9.9)	64.5 (8.7)	71.6 (7.6)	73.8 (10.2)	0.004[b]
LoS, days	48.0 (17.4)	57.9 (14.2)	42.5 (15.5)	39.4 (16.4)	0.0004[c]
BMI, kg/m^2	25.3 (23.2–27.4)	24.9 (23.2–28.9)	23.9 (20.4–30.1)	25.6 (23.9–27.3)	0.67
FiO_2	0.21 (0.21–0.24)	0.21 (0.21–0.21)	0.21 (0.21–0.28)	0.21 (0.21–0.21)	0.24
PaO_2, mmHg	82.4 (73.3–95.4)	83.3 (74.2–100.5)	79 (67–92.9)	84.4 (76.5–93.4)	0.73
$PaCO_2$, mmHg	34.1 (32.4–38.3)	32.8 (31.6–35.1)	33.4 (32.3–38.4)	34.7 (33.4–39.6	0.05
pH	7.44 (7.42–7.45)	7.431 (7.42–7.456)	7.44 (7.40–7.46)	7.439 (7.406–7.447)	0.61
CIRS CI	1.7 (0.3)	1.6 (0.2)	1.7 (0.3)	1.7 (0.3)	0.81
CIRS SI	3.4 (1.5)	3.3 (1.2)	3.6 (1.5)	3.6 (1.8)	0.74
Bi	68.7 (28.0)	62.6 (26.3)	74.3 (25.9)	74.7 (30.9)	0.39
Bd	20 (11–40)	26.5 (12.5–46.5)	22 (17–34)	13 (9–27)	0.21
SBC	20.4 (10.6)	20.5 (10.7)	17 (8.4)	22.9 (11.9)	0.46
SPPB total score	0.5 (0–6)	0 (0–5)	0 (0–6)	2 (0–8)	0.34
SPPB balance testing	1.6 (1.8)	1.5 (1.8)	1.7 (2.0)	1.5 (1.6)	0.94
SPPB walk	0 (0–3)	0 (0–2)	0 (0–3)	1 (0–3)	0.55
SPPB stands	0 (0–1)	0 (0–1)	0 (0–1)	0 (0—1)	0.55
MRC Quadriceps	3.9 (0.9)	3.9 (0.9)	4.3 (0.8)	3.7 (0.8)	0.34
MRC Biceps	4.1 (0.8)	4.2 (0.8)	4.2 (1.0)	3.9 (0.8)	0.53
1STS, number of stands	0 (0—10)	0 (0—0)	0 (0—9)	9 (0—17)	0.006[d]
6MWT, meters	0 (0—0)	0 (0—0)	0 (0—0)	0 (0—0)	0.84
EuroQoL-VAS	60.6 (19.1)	54.8 (17.6)	68.6 (21.5)	63.0 (18.2)	0.10
Deviation from normal value[a]					
σ SPPB total score (n = 50)	9 (4—9)	9 (5—9)	9 (4—9)	8 (5—9)	0.81
σ 1STS, number of stands	33 (23.5—35.0)	35 (34–35)	33(26–35)	25 (16–35)	0.002[e]
σ 6MWT, meters	482 (419—539)	515.5 (464.5–568.5)	483 (383–537)	457 (369–481)	0.004[f]
σ SBC (n = 21)	7.9 (5.3)	7.3 (5.8)	8.7 (4.8)	7.8 (5.7)	0.90
σ MRCm Quadriceps (n = 15)	1	1	1	1	–
σ MRCm Biceps	1	1	1	1	–

Value are expressed as number, mean or median SD or IQR.

Legend: IMV: Invasive Mechanical Ventilation; NIV: Non Invasive Mechanical Ventilation; LoS: length of stay; BMI: body mass index; FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; CIRS: Cumulative Illness Rating Scale including the comorbidity index (CI) and the severity index (SI); Bi: Barthel of activity of daily life; Bd: Bathel dyspnoea; SBC: Single Breath Counting; SPPB: Short Physical Performance Battery; MRCm: Medical Research Council Muscular; 1STS: One Minute Sit to Stand; 6MWT: six minute walk test; EuroQoL-VAS: Euro Quality of Life with visual analogue scale. Sidak and Bonferroni multiple comparison tests were performed.

[a] Estimation of variability of the outcome in relation to reference values.

[b] IMV VS. Oxygen p-value = 0.004.

[c] IMV VS. Oxygen p-value = 0.02; IMV VS. Oxygen p-value = 0.001.

[d] IMV VS. Oxygen p-value = 0.002.

[e] IMV VS. Oxygen p-value = 0.0008.

[f] MV VS. Oxygen p-value = 0.004.

Table 2 Correlations between LoS, age, CIRS and impairment outcomes.

	LoS Rho (p-value)	Age Rho (p-value)	CIRS CI Rho (p-value)	CIRS SI Rho (p-value)
Bi	−0.47 (0.002)	−0.21 (0.19)	−0.10 (0.53)	−0.08 (0.60)
Bd	0.37 (0.008)	0.14 (0.32)	0.12 (0.41)	0.11 (0.42)
SBC	−0.38 (0.03)	−0.13 (0.45)	0.05 (0.81)	0.04 (0.83)
SPPB TOT	−0.12 (0.38)	−0.02 (0.91)	0.05 (0.74)	0.03 (0.82)
MRCm Quadriceps	0.25 (0.15)	−0.46 (0.004)	−0.14 (0.42)	−0.16 (0.35)
MRCm Biceps	0.28 (0.10)	−0.21 (0.20)	−0.05 (0.76)	−0.12 (0.48)
1STS	−0.34 (0.18)	−0.04 (0.86)	0.06 (0.81)	−0.05 (0.83)
6MWT	–	−0.74 (0.47)	0.92 (0.26)	0.95 (0.20)
EuroQoL-VAS	−0.31 (0.04)	0.05 (0.75)	0.11 (0.46)	0.02 (0.89)

Legend: LoS: length of stay; CIRS: Cumulative Illness Rating Scale including the comorbidity index (CI) and the severity index (SI); Bi: Barthel of activity of daily life; Bd: Bathel dyspnoea; SBC: Single Breath Counting; SPPB: Short Physical Performance Battery; MRCm: Medical Research Council Muscular; 1STS: One Minute Sit to Stand; 6MWT: six minute walk test; EuroQoL-VAS: Euro Quality of Life with visual analogue scale.

Qualitative and quantitative variables were described with absolute and relative (percentage) frequencies and means (standard deviations, SD) or medians (interquartile ranges, IQR), depending on their normal or non-normal distribution, respectively. Demographic, epidemiological, and clinical variables were compared, stratifying by ICU stay and gender. Chi-squared or Fisher exact test was used for qualitative variables; analysis of variance or Kruskall–Wallis was computed for quantitative variables with a normal or non-normal distribution, respectively. CIRS and LoS were correlated with key clinical variables (Spearman's correlation) and were ranked according to the Chan's classification. A p-value <0.05 was considered statistically significant.

All 56 patients showed a reduced Bi and EuroQoL-VAS and increased Bd (Table 1). Overall 27/56 (48.2%) patients had a total SPPB score of 0, 22/56 (39.3%) between 1 and 8, and 7/56 (12,5%) ≥9. The SPBB 'standing balance' was less than 4 in 40 (71.4%) patients. Only 19/56 (33.9%) completed the 1STS test with a median (IQR) number of 14 (9.3–19.8) repetitions. The majority (53, 94.6%) could not perform the 6MWT and 5.4% covered a mean (SD) distance of 423.7 (34.8) m, around 70% of the Enright predicted value.

No statistically significant differences were found for clinical and functional data between males and females.

Patients previously treated with IMV were younger (p-value: 0.004), experienced a longer LoS (p-value: 0.0004), and had worse 1STS (p-value: 0.006) when compared with patients previously treated with oxygen (Table 2).

Furthermore, a statistically significant fair correlation was found between LoS and Bi, Bd, SBC and EuroQoL-VAS and between age and MRC quadriceps oriented to a worse functional and symptomatic status.

The results of the present study show that COVID-19 survivors can have an impairment of functional and muscular performance, dyspnoea, as well as impaired perceived health state. Patients who underwent IMV were younger, had a longer LoS and could not perform any exercise test.

Our patients, without acute respiratory failure, showed more clinical complications (*i.e.*, reduced ability to carry out daily living activities and moderate dyspnoea, even at rest) when compared with another cohort, which included respiratory failure survivors with an average SPBB < 4.[9]

Our findings are consistent with those of recent studies,[4,5] where post-acute COVID-19 patients suffer from dyspnoeaand severe disability. Although information about fatigue is missing in our study; a recent review underlined this as an important outcome in pulmonary rehabilitation.[10] These data support the rationale for pulmonary rehabilitation, being effective in reducing dyspnea and fatigue, improving exercise capacity and quality of life.

In conclusion, our preliminary data suggest indication for previously hospitalized COVID-19 patients to undergo a comprehensive clinical and functional assessment to identify those who are likely to benefit from rehabilitation. However, future studies in this field are also needed about potential effects of pulmonary rehabilitation.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors wish to thank all staff (nurses, physiotherapists, physicians) of the Pulmonary Rehabilitation department Istituti Clinici Scientifici Maugeri, Tradate, who make this study possible.

References

1. Murray A, Gerada C, Morris J, https://www.hsj.co.uk/commissioning/we-need-a-nightingale-model-for-rehab-after-covid-19-/7027335.article. [Accessed 21 August 2020] We need a Nightingale model for rehab after covid-19; 2020.
2. Vitacca M, Lazzeri M, Guffanti E, Frigerio P, D'Abrosca F, Gianola S, et al. Italian suggestions for pulmonary

rehabilitation in COVID-19 patients recovering from acute respiratory failure: results of a Delphi process. Monaldi Arch Chest Dis. 2020;90(2):385–93, http://dx.doi.org/10.4081/monaldi.2020.1444.
3. Choon-Huat Koh G, Hoenig H. How should the rehabilitation community prepare for 2019-nCoV? Arch Phys Med Rehabil. 2020;101(6):1068–71, http://dx.doi.org/10.1016/j.apmr.2020.03.003.
4. Belli S, Balbi B, Prince I, Cattaneo D, Masocco F, Zaccaria S, et al. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived hospitalisation. Eur Respir J. 2020;56(4):2002096, http://dx.doi.org/10.1183/13993003.02096-2020.
5. Curci C, Pisano F, Bonacci E, Camozzi DM, Ceravolo C, Bergonzi R, et al. Early rehabilitation in post acute COVID-19 patients: data from an Italian COVID-19 rehabilitation unit and proposal of a treatment protocol. A cross-sectional study. Eur J Phys Rehabil Med. 2020;56(5):633–41, http://dx.doi.org/10.23736/S1973-9087.20.06339-X.6.
6. Ippolito M, Vitale F, Accurso G, Iozzo P, Gregoretti C, Giarratano A, et al. Medical masks and respirators for the protection of Healthcare Workers from SARS-CoV-2 and other viruses. Pulmonology. 2020;26(4):204–12, http://dx.doi.org/10.1016/j.pulmoe.2020.04.009.
7. Bernabeu-Mora R, Medina-Mirapeix F, Llamazares-Herrán E, García-Guillamón G, Giménez Giménez LM, Sánchez-Nieto JM. The short physical performance battery is a discriminative tool for identifying patients with COPD at risk of disability. Int J Chron Obstruct Pulmon Dis. 2015;10:2619–26, http://dx.doi.org/10.2147/COPD.S94377.
8. Bui KL, Nyberg A, Maltais F, Saey D. Functional tests in chronic obstructive pulmonary disease, part 2: measurement properties. Ann Am Thorac Soc. 2017;14(May (5)):785–94, http://dx.doi.org/10.1513/AnnalsATS.201609-734AS.
9. Gandotra S, Lovato J, Case D, Bakhru RN, Gibbs K, Berry M, et al. Physical function trajectories in survivors of acute respiratory failure. Ann Am Thorac Soc. 2019;16(4):471–7, http://dx.doi.org/10.1513/AnnalsATS.201806-375OC.
10. Paneroni M, Vitacca M, Venturelli M, Simonelli C, Bertacchini L, Scalvini S, et al. The impact of exercise training on fatigue in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Pulmonology. 2020;26(5):304–13, http://dx.doi.org/10.1016/j.pulmoe.2020.02.004.

E. Zampogna[a,*], G.B. Migliori[b], R. Centis[b], F. Cherubino[a], C. Facchetti[a], D. Feci[c], G. Palmiotto[c], P. Pignatti[d], L. Saderi[e], G. Sotgiu[e], A. Spanevello[a,c], M. Zappa[c], D. Visca[a,c]

[a] *Respiratory Rehabilitation of the Institute of Tradate, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy*
[b] *Respiratory Diseases Clinical Epidemiology Unit, Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy*
[c] *Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, Varese-Como, Italy*
[d] *Allergy and Immunology Unit, Istituti Clinici Scientifici Maugeri, IRCCS, Pavia, Italy*
[e] *Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy*

* Corresponding author at: Istituti Clinici Scientifici Maugeri IRCCS, Via Maugeri 4, 27100 Pavia, Italy.
E-mail address: elisabetta.zampogna@icsmaugeri.it (E. Zampogna).

29 October 2020
Available online 6 January 2021

https://doi.org/10.1016/j.pulmoe.2020.12.008

Non-invasive ventilation through a nasal interface during transoesophageal echocardiogram in a high-risk chronic patient

Dear Editor,

Non-invasive ventilation (NIV) has been an efficient strategy for ventilatory support and sedation related respiratory failure prevention during endoscopic procedures in high-risk patients. However, there is not enough evidence concerning the ideal pressure setting and choice of interface, mainly in home mechanical ventilated patients that have different interface options.[1]

We report the use of NIV in a high-risk chronic patient undergoing transoesophageal echocardiography (TEE) under sedation using her own home care vented nasal interface with intentional leaks (Mirage FX™, ResMed, Australia).

The patient was a 31-year-old woman, 45 kg weight, with a previous medical history of cystic fibrosis, chronic respiratory failure and end-stage kidney disease. She was on home mechanical ventilation with high ventilatory dependency (>18 h/day) in spontaneous/timed (ST) bi-level pressure cycled mode [inspiratory positive airway pressure (IPAP) of 17 cmH_2O; expiratory positive airway pressure (EPAP) of 4 cmH_2O; backup respiratory rate (RR) of 16 cpm], alternating between oro-nasal and nasal interface during sleep and daytime, respectively, continuous oxygen (O_2) therapy (2 L/min) and haemodialysis through a catheter placed in the right atrium.

She was hospital admitted due to fluid overload and fever of unknown origin. Aetiological investigation isolated a *Methicillin-susceptible Staphylococcus aureus* in blood cultures without evidence of respiratory or urinary tract infection. Transthoracic echocardiogram showed a mass in the right atrium in relation to the catheter, requiring TEE characterisation.

Monitoring during TEE included non-invasive blood pressure and pulse oximetry (SpO_2). NIV was applied with ST bi-level pressure cycled mode using an acute hospital ventilator with an O_2 blender permitting a fraction of inspired oxygen (FiO_2) of 100% (*Trilogy 202™, Philips Respironics, Pennsylvania, United States*). The interface was patient's home care vented nasal mask. Sedation was performed with intravenous midazolam — intended sedation level of -3 in the Richmond Agitation Sedation Scale (RASS).

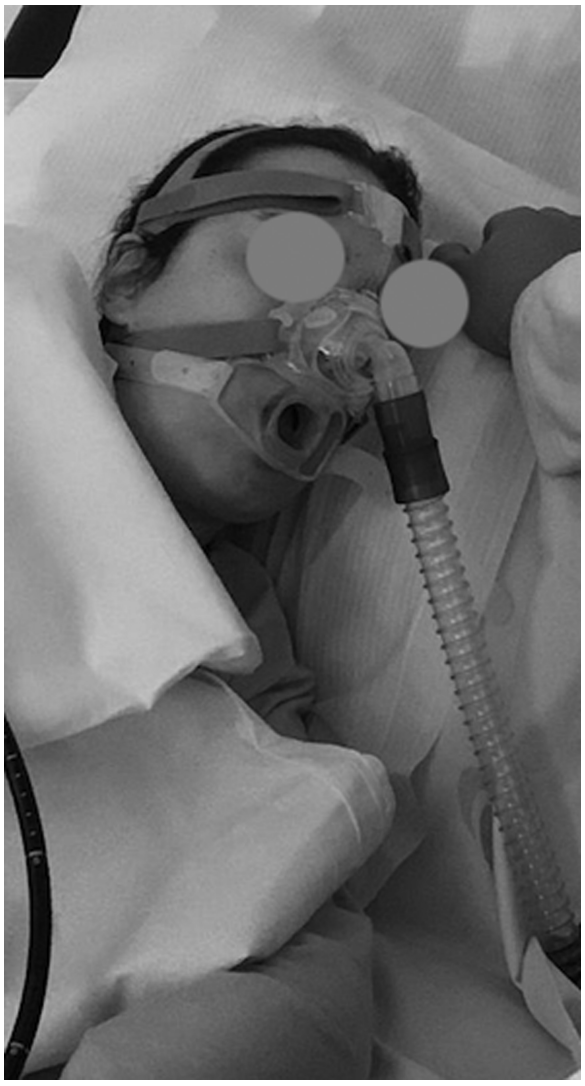


Figure 1 Mouthpiece placement for transoesophageal echocardiography probe insertion during non-invasive ventilation trough nasal mask.

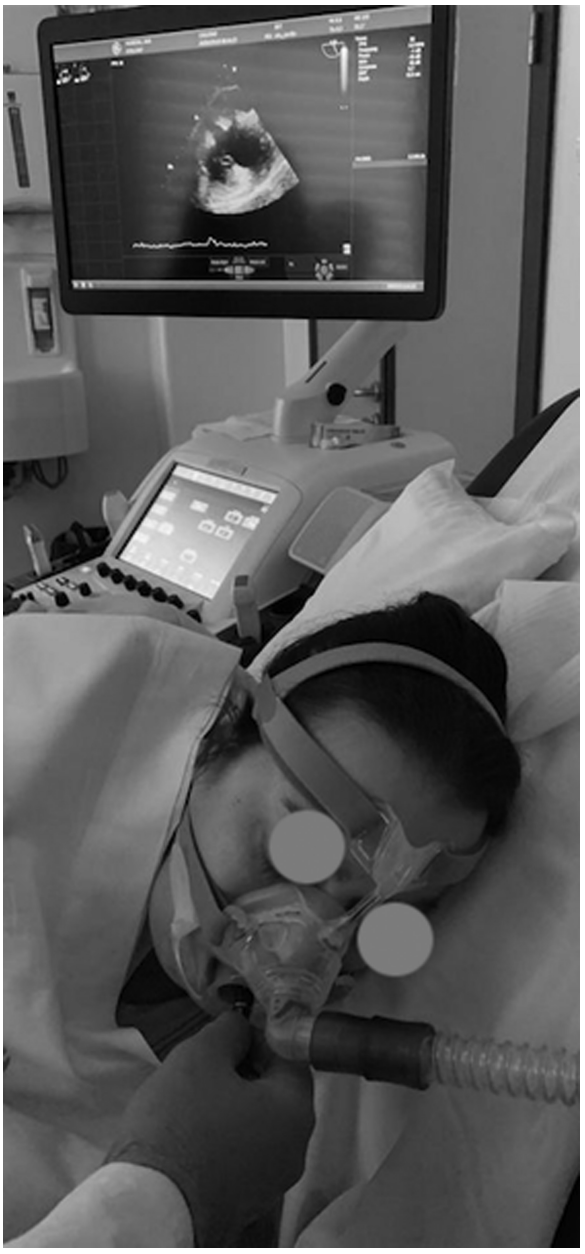


Figure 2 Transoesophageal echocardiogram performance during non-invasive ventilation trough nasal mask.

Patient was positioned in lateral decubitus and a mouthpiece was placed for TEE probe insertion (Fig. 1). Initial ventilator settings were set at 22 cmH_2O IPAP, 6 cmH_2O EPAP and 40% FiO_2 to achieve normal RR and SpO_2 > 95%. Ventilator settings and FiO_2 were adjusted in every episode of SpO_2 < 95%.

Incremental doses of 2 mg of midazolam (total 4 mg) were administered to achieve the depth of sedation. Few minutes after initiating the TEE, patient's SpO_2 decreased to 88% and a significant increase of mouth leak (>60 L) was observed. IPAP was incremented to 24 cmH_2O and FiO_2 was set first at 80% and then 100%, resulting in a SpO_2 of 100% and chest excursion throughout, even with persistent mouth leaks. TEE lasted 11 min and operators did not mention any technical difficulty. Patient remained RASS score-3 all procedure, was alert ten minutes post-procedure and tolerated it well with nasal NIV without complaints or complications. TEE revealed a thrombus in the right atrium.

Intravenous sedation is an effective way of achieving patient compliance during TTE. However, it is widely recognized that its use is associated with respiratory depression, desaturation and sometimes with respiratory failure, especially with increased sedative doses[2,3] and in chronic respiratory failure patients.[3] We describe the use of a home care nasal mask to deliver NIV during TEE in a high-risk patient and proved its effectiveness in preventing sedation induced respiratory failure. No similar report has been found in the English literature.

Air leaks through the mouthpiece were high during the procedure, which in association with the respiratory depression caused by sedation, were responsible for the desaturation episode. Nevertheless, they were effectively compensated with increment of pressure support, resulting in a SpO_2 of 100% and chest excursion throughout. When using a single tubing system and with such a large leak, the

use of tidal volume (V_{te}) for ventilatory monitoring may be misleading, since real V_{te} quantification in this situation is not possible.

The use of NIV as an adjunct to TEE has already been shown to be effective in preventing respiratory failure due to sedation. However, all reports described the use of oronasal or total-face masks.[4–6] In those cases, the endoscopic probe had to overcome a mask port before reaching the mouth. The main difficulties reported were in introducing TEE's probe due to suboptimal gliding through the mask port and excessive image attrition due to difficulties in moving the probe.[6] The use of a nasal mask had no interference in TEE probe insertion and handling (Fig. 2). Moreover, the novelty of using the patient's home care mask is considered to contribute to increased tolerance and cooperation, as she was already trained in its use.

In conclusion, we find two advantages for this approach. First, it is effective in delivering efficient ventilatory support in high-risk patients during TEE avoiding the risk of respiratory failure. Second, the choice of a home care vented nasal mask did not interfere with TEE technique. Monitoring of SpO_2 and qualitative clinical signs, such as chest excursion, can be useful for NIV optimization during the procedure.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Mineiro MA, Guimarães MJ, Winck JC. Organization of home mechanical ventilation in Portugal: characterization of current centers and a pathway to uniformization. Pulmonology. 2020;26(2):84–9, http://dx.doi.org/10.1016/j.pulmoe.2019.05.006.
2. Sutaria N, Northridge D, Denvir M. A survey of sedation and monitoring practices during transoesophageal echocardiography in the UK: are recommended guidelines being followed? Heart. 2000;84 Supple 2:ii19, http://dx.doi.org/10.1136/heart.84.suppl_2.ii19.
3. Nordt SP, Clark RF. Midazolam: a review of therapeutic uses and toxicity. J Emerg Med. 1997;15(3):357–65, http://dx.doi.org/10.1016/S0736-4679(97)00022-X.
4. Guarracino F, Cabrini L, Baldassarri R, Cariello C, Covello RD, Landoni G, et al. Non-invasive ventilation-aided transoesophageal echocardiography in high-risk patients: a pilot study. Eur J Echocardiogr. 2010;11(6):554–6, http://dx.doi.org/10.1093/ejechocard/jeq019.
5. Pieri M, Landoni G, Cabrini L. Noninvasive ventilation during endoscopic procedures: rationale, clinical use, and devices. J Cardiothorac Vasc Anesth. 2018;32(2):928–34, http://dx.doi.org/10.1053/j.jvca.2017.09.038.
6. Zangrillo A, Mazzone P, Votta CD, Villari N, Della Bella P, Monaco F. Prolonged transesophageal echocardiography during percutaneous closure of the left atrial appendage without general anesthesia: the utility of the Janus mask. Can J Anesth. 2016;63(8):962–5, http://dx.doi.org/10.1007/s12630-016-0659-1.

R.E. Gomes[a,*], M.T. Redondo[b], M.R. Gonçalves[b,c]

[a] *Serviço de Pneumologia, Hospital Garcia de Orta, Almada, Portugal*
[b] *Unidade de Fisiopatologia Respiratória e Ventilação Não Invasiva, Serviço de Pneumologia, Centro Hospitalar e Universitário São João, Portugal*
[c] *Faculdade de Medicina, Universidade do Porto, UNiC — Unidade de Investigação Cardiovascular, Portugal*

* Corresponding author at: Pulmonology Department, Hospital Garcia de Orta, Av. Torrado da Silva, 2805-267 Almada, Portugal.
E-mail addresses: ricardo.gomes@hgo.min-saude.pt, ricardoegomes@gmail.com (R.E. Gomes), margarida.tredondo@gmail.com (M.T. Redondo), goncalvesmr@gmail.com (M.R. Gonçalves).

30 September 2020
Available online 28 March 2021

https://doi.org/10.1016/j.pulmoe.2021.03.001

High-flow nasal oxygen in re-expansion pulmonary oedema

Dear editor,

Re-expansion pulmonary edema (RPE) is a rare clinical condition with a low incidence rate, which normally occurs with the rapid expansion of the collapsed lung after drainage of the pleural cavity. It often manifests with acute respiratory failure, in some cases making invasive mechanical ventilation (IMV) necessary.

The authors report a case of a 49-year-old male, smoker of 20 packs per year, who went to the emergency department with fever, dyspnea, cough, purulent sputum, and right posterior pleuritic chest pain with 4 days of evolution. Physical examination revealed cachexia (BMI of 14.8 kg/m2), tachycardia, tachypnea, and decreased breath sounds in the lower half of the right lung field. Blood gas revealed type 1 respiratory failure (paO2/FiO2 223) and analyses identified leukocytosis with neutrophilia and increased inflammatory parameters (C-reactive protein 39 mg/dL, normal < 0.5 mg/dL). The chest radiograph revealed pulmonary homogenous opacification of the right lung, with obliteration of right costophrenic angle and superior concavity, compatible with pleural effusion (Fig. 1A). The thoracic computed tomography (CT) evidenced a large loculated right pleural effusion with pleural thickening, compatible with empyema (Fig. 1B), and extensive centrilobular and paraseptal emphysema with bullous dystrophy of apical predominance (Fig. 1C). For infection focus control, a 24 Fr chest tube was placed, with drainage of 2000 mL of purulent pleural fluid. The analysis of this liquid revealed leukocytes 28868/mm3, glucose < 5 mg/dL, LDH > 3100 IU/L, pH 6.0. The chest radiograph (Fig. 2A) after drainage, showed

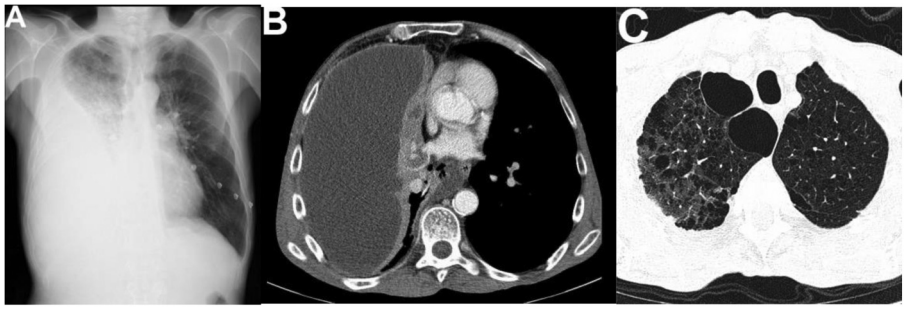


Figure 1 Imaging exams on admission.
A) Posteroanterior chest radiograph: pulmonary homogenous opacification of the lower two thirds of the right lung, with obliteration of right costophrenic angle and superior concavity, compatible with pleural effusion.
B) Thoracic computed tomography: large loculated right pleural effusion (200 × 74 mm in the axial plane) with pleural thickening, compatible with empyema.
C) Thoracic computed tomography: extensive centrilobular and paraseptal emphysema with bullous dystrophy of apical predominance.

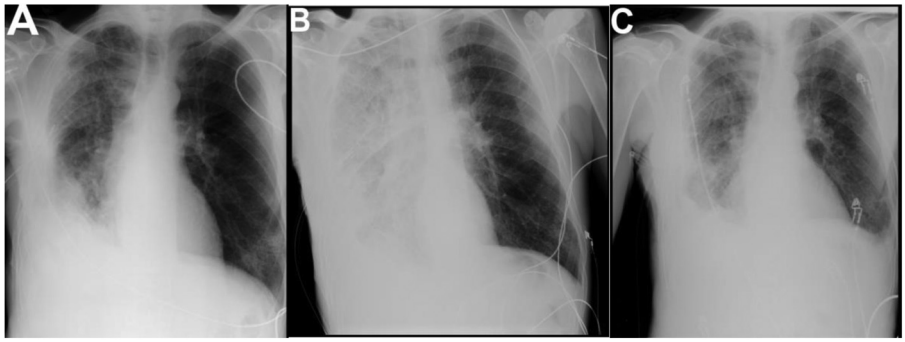


Figure 2 Imaging evolution during ICU stay.
A) Reduction of pleural effusion after placement of chest tube.
B) Apicocaudal opacification at the right pulmonary field, compatible with reexpansion pulmonary edema.
C) Improvement of right lung field opacification at discharge from the ICU.

improvement of the pleural effusion. At the same time, empirical antibiotic therapy (ceftriaxone and clindamycin) was started.

One hour after the placement of the chest tube, the patient presented marked dyspnea with sudden worsening of the respiratory failure (paO2/FiO2 120). The radiograph was repeated (Fig. 2B) and revealed an opacification of the entire right lung field compatible with RPE. Due to the worsening of respiratory failure, he was admitted to the Intensive Care Unit (ICU). Because of the low BMI, the sarcopenia, and the extensive pulmonary emphysema with bullous dystrophy, IMV and non-invasive ventilation (NIV) were delayed and High-Flow Nasal Oxygen (HFNO) was initiated with the following parameters: gas flow 60 L/min; FiO2 70%. Concomitantly, diuretic therapy was started, as the administration of diuretics can diminish the occurrence of pulmonary edema by raising the osmotic pressure and decreasing pulmonary blood flow.[1] The patient showed progressive recovery under HFNO over the 72 h after admission. He was discharged from the ICU on the 4th day of hospitalization, under oxygen mask (FiO2 31%) and improvement of the respiratory failure (paO2/FiO2 319). The chest radiograph (Fig. 2C) at discharge from the ICU reveals an almost complete resolution of pulmonary edema.

RPE is an uncommon condition, with an incidence rate between 0 and 1% after rapid pulmonary re-expansion of a collapsed lung.[2] It presents a sudden clinical installation, which can cause severe hypoxemia and mortality rates that can reach 20%.[3,4] It is usually unilateral, occurring after the active drainage of a large amount of air or liquid from the pleural cavity and risk factors for its occurrence are young age, prolonged pulmonary collapse (usually greater than 72 h), and rapid pulmonary re-expansion.[4,5]

The pathophysiological mechanism of RPE is multifactorial and is not fully understood. At its base is the increase in vascular permeability secondary to damage to capillaries and alveolar membrane, as well as the decrease in surfactant production, airway obstruction, changes in pulmonary artery pressure, and the production of inflammatory mediators (IL-8 and Leukotriene B4).[6,7]

In the case presented, the patient had decreased BMI, pulmonary emphysema, and extensive bullous dystrophy and was being a poor candidate for IMV and NIV due to the risk of barotrauma. Therefore, and taking into account the severe respiratory failure (paO2/FiO2 120), HFNO was implemented.

HFNO is a high-flow oxygen system that allows the administration of up to 60 L/min of heated and humidified gas

with a variable FiO2 (21%-100%). Studies have shown that, compared to conventional oxygen therapy, HFNO allows for better oxygenation and greater comfort, which is justified by its physiological effects: generation of positive pressure at the end of expiration (PEEP), improvement of the inspired oxygen fraction, wash-out and reduction of pharyngeal dead space, reduction of respiratory work and improvement of mucociliary clearance.[8]

HFNO provides spontaneous breathing, maintaining positive pressure in alveoli and stable supply of a high concentration of oxygen.[9] It is a simpler and more comfortable application than NIV and avoids complications associated with the latter therapy such as abdominal distention, aspiration of gastric content, facial injuries, and barotrauma.

Frat et al.[10] demonstrated a decrease in mortality at 90 days (without increasing the rate of intubation) in patients with type 1 respiratory failure and paO2/FiO2 ratio < 200 treated with HNFO compared to patients treated with NIV.

In exacerbated COPD patients, HFNO has been used as an alternative to NIV. In these patients, work of breathing is reduced with HFNO by a similar extent to NIV, while keeping similar PaCO2 values. HFNO has the advantage of being more comfortable than NIV because it does not require a ¨trueïinteraction or synchrony between the system and the patient.[11]

In comparison with IMV, it reduces the period of treatment and hospitalization in the ICU since ventilatory weaning is not necessary, as well as reducing the incidence of ventilator-associated pneumonia and barotrauma.

In the case described, the patient's particular symptoms made him a poor candidate for mechanical ventilation, with HFNO providing the necessary respiratory support and allowing a complete recovery from the RPE episode.

In conclusion, RPE is a rare and potentially fatal clinical condition and timely diagnosis is essential to ensure proper treatment. The therapeutic is based on organ support, with a special focus on pulmonary support, and mechanical ventilation is the cornerstone of this approach. The results obtained with HFNO in this[9] and other cases of type 1 respiratory failure seem promising, however, more studies are needed to establish HFNO as a safe approach to RPE.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Sohara Y. Reexpansion pulmonary edema. Am Thorac Cardiovasc Surg. 2008;14(4):205–9.
2. Echevarria C, Twomey D, Dunning J, Chanda B. Does re-expansion pulmonary oedema exist? Interact Cardiovasc Thorac Surg. 2008;7(3):485–9, http://dx.doi.org/10.1510/icvts.2008.178087.
3. Carlson RI, Classen KL, Gollan G, Gobbel Jr WG, Sherman DE, Christensen RO. Pulmonary edema following the rapid re-expansion of a totally collapsed lung due to a pneumothorax: a clinical and experimental study. Surg Forum. 1958;9:367–71.
4. Matsuura Y, Nomimura T, Murakami H, Matsushima T, Kakehashi M, Kajihara H. Clinical analysis of re-expansion pulmonary edema. Chest. 1991;100(6):1562–6, http://dx.doi.org/10.1378/chest.100.6.1562.
5. Mahfood S, Hix WR, Aaron BL, Blaes P, Watson DC. Re-expansion pulmonary edema. Ann Thorac Surg. 1988;45(3):340–5, http://dx.doi.org/10.1016/s0003-4975(10)62480-0.
6. Chakraborty PP, Chakraborty S. Re-expansion pulmonary edema. Indian J Surg. 2012;74(2):174–6, http://dx.doi.org/10.1007/s12262-011-0258-x.
7. Komatsu T, Shibata S, Seo R, Tomii K, Ishihara K, Hayashi T, et al. Unilateral re-expansion pulmonary edema following treatment of pneumothorax with exceptionally massive sputum production followed by circulatory collapse. Can Respiratory J. 2010;17(2):53–5, http://dx.doi.org/10.1155/2010/259195.
8. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. Chest. 2015;148(1):253–61, http://dx.doi.org/10.1378/chest.14-2871.
9. Lee SK, Son BS, Son J, Lee SE, Yeo HJ, Kim DH. High-flow oxygen therapy for treating re-expansion pulmonary edema. Ann Transl Med. 2019;7(12):272, http://dx.doi.org/10.21037/atm.2019.05.08.
10. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372(23):2185–96, http://dx.doi.org/10.1056/NEJMoa1503326.
11. Pisani L, Astuto M, Prediletto I, Longhini F. High flow through nasal cannula in exacerbated COPD patients: a systematic review. Pulmonology. 2019;25(6):348–54, http://dx.doi.org/10.1016/j.pulmoe.2019.08.001.

A. Fontoura[a,*], F.R. Fernandes[b,c], M. Oliveira[b], P. Santos[a], L.P. Trindade e Silva[a,c]

[a] *Department of Intensive Medicine, Unidade Local de Saúde da Guarda E.P.E. – Hospital Sousa Martins, Portugal*
[b] *Department of Pulmonology, Unidade Local de Saúde da Guarda E.P.E. – Hospital Sousa Martins, Portugal*
[c] *Faculdade de Ciências da Saúde, Universidade da Beira Interior, Portugal*

[*] Corresponding author at: Hospital Sousa Martins – Unidade Local de Saúde da Guarda - Avenida Rainha Dona Amélia, 6301-857 Guarda, Portugal.
E-mail addresses: alexandreptfontoura@gmail.com (A. Fontoura), filipasrfernandes@gmail.com (F.R. Fernandes), marcosandre.oliveira90@gmail.com (M. Oliveira), pedro.santos@ulsguarda.min-saude.pt (P. Santos), luis.paulo@sapo.pt (L.P. Trindade e Silva).

16 December 2020
Available online 13 May 2021

https://doi.org/10.1016/j.pulmoe.2021.01.011
2531-0437/

Reversed halo sign in radiation induced organizing pneumonia: natural course of the underlying pathophysiology

The reversed halo sign (RHS) refers to a focal rounded area of ground-glass opacity surrounded by a more or less complete ring of consolidation.[1] It was initially described by Voloudaki et al.[2] in two patients with cryptogenic organizing pneumonia (COP). Zompatori et al. used the term atoll sign,[3] while the term RHS was first introduced by Kim et al.[4] Initially, it was considered to be relatively specific to COP. Subsequently, the RHS has been reported in a wide variety of pulmonary diseases including infectious, neoplastic and non infectious/non neoplastic, thus losing its specificity.

Despite the fact that the RHS is quite extensively studied in terms of radiology,[5] data on corresponding pathology are actually scarce. In the initial report by Voloudaki et al.,[2] histology from the periphery of the lesions showed the presence of buds of granulation-fibromyxoid tissue in the lumen of alveolar ducts and alveoli, while the central area of the ground glass attenuation showed less granulation tissue and more alveolar septal inflammation. These findings were confirmed in a much larger cohort of 43 patients, where the ''ring'' of the RHS corresponded pathologically to intraluminal organizing fibrosis in distal air spaces.[6] The RHS has no specificity as it can be observed in a wide variety of diseases. Furthermore, it can appear in different phases of disease progression. The pathology remains vague as to what this image implies. In order to delineate the pathology correlation, it is essential to specify the actual timeframe at which the RHS appears. We present a representative case of radiation induced organizing pneumonia (RIOP) in which the temporal evolution of imaging findings sheds light on the pathological and clinical significance of the RHS.

A 68-year-old female was diagnosed with right breast cancer. She was managed with breast conserving surgery (lumpectomy) followed by radiotherapy. The patient presented with progressive dyspnea and fatigue 16 weeks after completion of radiotherapy. CT revealed areas of consolidation in the right upper and right middle lobe (Fig. 1a,b), ipsilateral to the irradiated side. A presumptive diagnosis of radiation pneumonitis was made at an outside facility and the patient was started on corticosteroids with gradual tapering. A subsequent CT after 4 months showed a complete resolution of the lung opacities in the right upper lobe but appearance of a new consolidative area in the right lower lobe (Fig. 1c,d). Corticosteroid therapy continued and after 3 months all opacities completely resolved (Fig. 1e,f). After 5 months from corticosteroid discontinuation, the patient complained again of fatigue. At that time, she was referred to our interstitial lung disease unit. A new HRCT exhibited several areas of ring consolidation surrounding a central area of ground glass opacity in the right upper and right lower lobe (Fig. 2). Based on history, clinical examination and imaging findings, a diagnosis of relapsing RIOP was established.[7] This time, azithromycin was administered to the patient at a dose of 250 mg three times weekly. After 2 months of treatment, the patient reported resolution of her symptoms. A chest radiograph showed an almost complete resolution of the abnormal imaging findings as well (Fig. 3).The patient reports no symptoms and has a normal chest radiograph and laboratory work-up, at 1 year. It is worth noting that the administration of steroids in the context of RIOP is related to a higher rate of relapse.[8]

The incidence of organizing pneumonia (OP) following breast radiotherapy is 1–3% and the interval period between completion of radiotherapy and onset of symptoms is 2.3–47 weeks (usually 4–24 weeks).[7–14] Increasing age ($\geq$50 years),[9,15] concurrent endocrine therapy,[9] smoking,[15] increasing lung volume within the radiation field[16] and increasing central lung distance[13,16] have been associated with the development of RIOP. Usually, the initial imaging findings are unilateral (ipsilateral to the irradiated side), however, bilateral involvement can also be seen at presentation.[7,8,10] In patients with migratory infiltrates and relapsing disease, it is more likely to have bilateral involvement.[10] The exact pathogenesis and pathology of RIOP has not been clarified. Proposed mechanisms are radiation induced injury of alveolar epithelial cells (DNA double-strand breaks) and mutations in the ATM (ataxia telangiectasia mutated) gene.[17] The ATM gene plays a key role in the repair of DNA double-strand breaks.[18] However, it is important to highlight that radiation in the lung causes endothelial damage and impairs the stability of the alveolar-capillary membrane.[19] The increased permeability of the latter leads to the exudation of plasma protein, intra-alveolar clotting, deposition of fibrin, and finally colonization by matrix-producing fibroblasts resulting in the formation of intraluminal bus of connective tissue.

In order to understand the radiology-pathology correlation, reviewing diseases in which the RHS is the initial radiological manifestation of the healing response can provide significant insight. Such characteristic paradigms are pulmonary infarction, mucormycosis and pulmonary radiofrequency ablation. The study of underlying pathology in these cases reveals a common pathology and response to injury.

The RHS has been described in cases of pulmonary infarcts, consisting of a thick consolidative ''ring'' surrounding a central ground glass area. Pathologically, the external rim of consolidation corresponds to organizing granulation tissue associated with the presence of histiocytes, foamy macrophages, hemosiderin-laden macrophages, and activated fibroblasts. The central area corresponds to coagulative necrosis associated with hemorrhage. Necrosis often assumes a geographic pattern, crisscrossing the parenchyma and traversing interlobular septa.[20] Fluorodeoxyglucose-positron emission tomography computed tomography (FDG-PET/CT) provides valuable information delineating the metabolic pathophysiology of the RHS in the context of pulmonary infarction. Specifically, in cancer patients with pulmonary infarction, the ''rim sign'' has been described.[21] It corresponds to slight FDG uptake strictly along the periphery of the infarct, while the central area shows no uptake. This finding has a strong correlation with the pathological features of pulmonary infarction as the increased peripheral uptake is due to the increased metabolic activity of the activated fibroblasts and macrophages that are located in this area.

The RHS seems to be consistent in cases of pulmonary infarction regardless of the cause of interrupted blood flow. In the clinical setting of immunosuppression (especially neu-

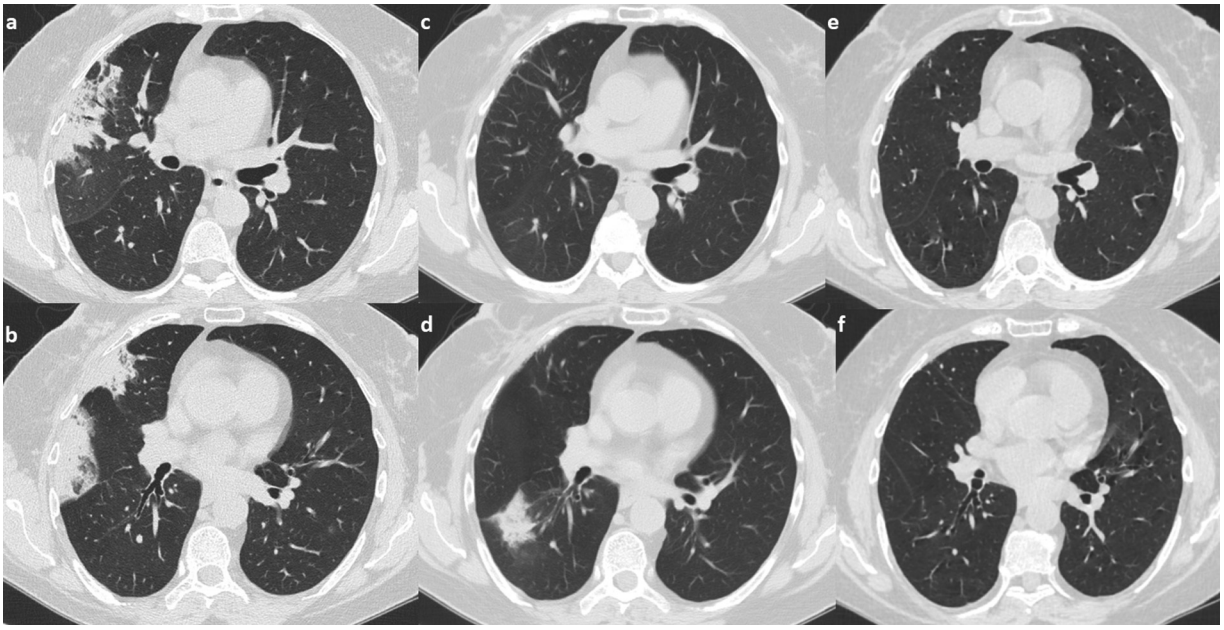


Figure 1 Areas of consolidation in the right upper and middle lobe. The consolidative area in the right middle lobe has a ''bird nest'' appearance (panel a, b). After 4 months under steroid treatment there is clearance of the infiltrates in the right upper and middle lobe. There is a new area of consolidation in the right lower lobe consistent with a migratory pattern (panel c, d). After 6 months under steroid treatment there is a complete resolution of the imaging findings (panel e, f).

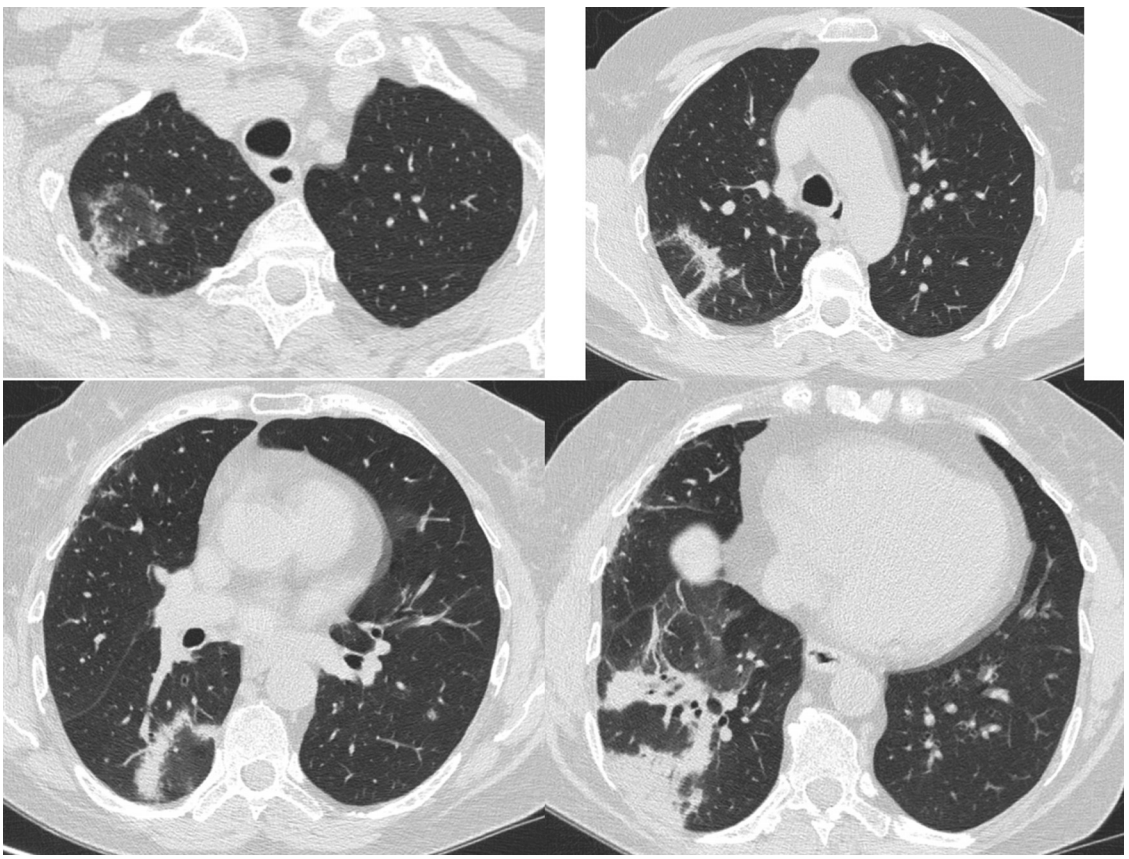


Figure 2 Same patient as Figure 1. Five months after treatment cessation. In the right upper and lower lobe there are areas consisting of an external rim of consolidation surrounding a central area of ground glass attenuation (reverse halo sign).

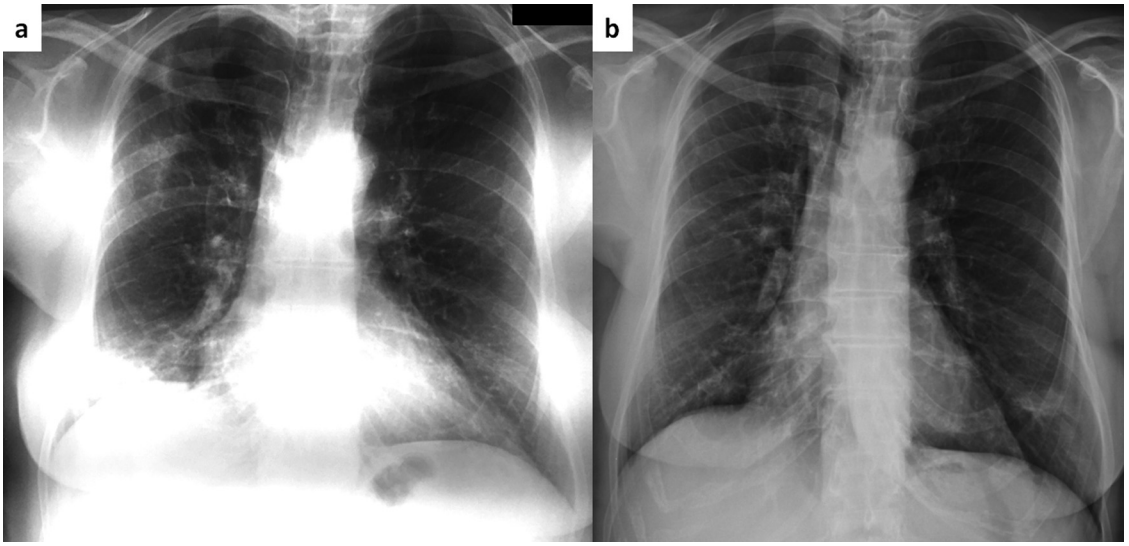


Figure 3 Same patient as Figure 1. Chest roentgenogram 5 months after cessation of steroids with areas of consolidation in the right upper and lower lung zone (panel a). After two months of treatment with azithromycin (250 mg thrice weekly), there is a complete resolution of abnormal findings (panel b).

tropenic patients with hematologic malignancies receiving chemotherapy or bone marrow transplantation), the RHS is considered highly suggestive of underlying fungal infection, especially pulmonary mucormycosis.[22,23] It is worth emphasizing that Mucorales infections are more angioinvasive than aspergillus infections,[23] resulting in vessel thrombosis, thus infarction of infected tissues is a hallmark of the disease. The lesions are mainly peripheral in distribution.[24] When the RHS is present in mucormycosis, the central ground glass area corresponds pathologically to coagulative necrosis, while the outer rim of consolidation to organization.[25] From an imaging point of view, the RHS presents different morphological characteristics when present in OP and invasive fungal infections. The presence of reticulation within the central area, increased thickness of the outer rim exceeding 1 cm (and the presence of pleural effusion), favors the diagnosis of the latter.[26]

Radiofrequency ablation (RFA) has been used for the management of selected patients with Non-Small Cell Lung Cancer (NSCLC) unable to undergo curative surgical resection, selected patients with pulmonary metastases or those with recurrences after surgery, chemotherapy, or radiation treatment.[27] RFA leads to coagulative necrosis and, as expected based on the previous observations, it is a cause of the RHS with a ''bird nest'' morphology.[28]

In our case of RIOP, it is important to note that when relapse occurred, the patient sought medical advice almost immediately, thus imaging findings correspond to the initial phase of the healing process. Based on the paradigms of pulmonary infarction, angioinvasive mucormycosis and RFA, it seems that when the RHS is observed at the initial stages, it corresponds pathologically to activated fibroblasts encircling certain areas of lung injury. In the above mentioned entities, the initial lung injury results in coagulative necrosis. The actual nature of injury in cases of RIOP remains unknown. Intriguingly, radiation induced necrosis is also coagulative.

This type of response follows a specific course which is typically depicted by the resolution of a pulmonary infarction. Specifically, the resolution follows a centripetal course from the periphery to the center of the infracted area, which preserves its initial shape. On the other hand, there are cases where the clearance of an infiltrate starts from the center and expands centrifugally, creating an image consistent with the RHS.[29,30] However, in such cases the RHS is not the initial radiological manifestation, it is observed during the healing phase and it does not have the pathophysiological significance as described above. Interestingly, Covid-19 represents an example where the RHS is observed at later stages of the disease, when consolidation develops around GGO or when the absorption of infiltrates starts from the center as mentioned before.[31,32]

From a pathological point of view, the presence of the RHS depends on a variety of parameters. The presence of low dense tissue in the central part (when necrosis, and/or edema is present) with dense (granulation) tissue in the surrounding area can manifest the RHS. Also, as mentioned earlier, there are cases when the healing process of OP starts from the central part. Finally, the presence of inflammatory aspects in the central area (NSIP like pattern, alveolar macrophages etc.) surrounded by a rim of granulation tissue can give the appearance of a lobular pattern or reversed halo sign.[33,34]

Given the wide range of clinical entities that can present with the RHS, it is important to determine the actual timeframe at which it occurs, i.e. at the beginning or during the response of the lung to injury. This can increase the clinical significance of the RHS by narrowing differential diagnosis. Treatment for OP is based on steroids. The recommended doses are significantly high[35,36] and one of the main problems in the management of OP is not the disease itself but the management of steroid induced complications (e.g., obesity, osteoporosis, diabetes, depression, and immunosuppression). Based on the above observations, the RHS reflects the initial step of a successful response to lung

injury. The type of injury is coagulative necrosis, regardless of the actual cause of reduced blood flow (e.g., thrombi in pulmonary embolism, fungal angioinvasion in mucormycosis, and thermal injury in case of RFA). In cases of RIOP, the RHS also seems to represent an initial response to injury. The actual cause of injury (parenchymal or vascular) is unknown. It is intriguing that radiation causes coagulative necrosis and impairs the permeability of the basement membrane leading to intra-alveolar clotting, deposition of fibrin, and finally colonization by matrix-producing fibroblasts resulting in the organizing pneumonia pattern. Equally intriguing is the fact that steroid treatment increases the recurrence of RIOP after breast-conserving therapy, thus prolonging disease duration.[8] Given the fact that the RHS represents the initial phase of a successful healing response, it would be important to clarify the natural history of these cases without the administration of drugs. In conclusion, phenotyping cases of OP based on clinical and imaging characteristics, can lead to more specific management, avoiding unnecessary adverse events.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697–722.
2. Voloudaki AE, Bouros DE, Froudarakis ME, Datseris GE, Apostolaki EG, Gourtsoyiannis NC. Crescentic and ring-shaped opacities. CT features in two cases of bronchiolitis obliterans organizing pneumonia (BOOP). Acta Radiol. 1996;37(6):889–92.
3. Zompatori M, Poletti V, Battista G, Diegoli M. Bronchiolitis obliterans with organizing pneumonia (BOOP), presenting as a ring-shaped opacity at HRCT (the atoll sign). A case report. La Radiol Med. 1999;97(4):308–10.
4. Kim SJ, Lee KS, Ryu YH, Yoon YC, Choe KO, Kim TS, et al. Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: diagnostic implications. Am J Roentgenol. 2003;180(5):1251–4.
5. Marchiori E, Zanetti G, Hochhegger B, Irion KL, Carvalho AC, Godoy MC. Reversed halo sign on computed tomography: state-of-the-art review. Lung. 2012;190(4):389–94.
6. Zhan X, Zhang L, Wang Z, Jin M, Liu M, Tong Z. Reversed halo sign: presents in different pulmonary diseases. PloS one. 2015;10(6):e0128153.
7. Crestani B, Valeyre D, Roden S, Wallaert B, Dalphin JC, Cordier JF. Bronchiolitis obliterans organizing pneumonia syndrome primed by radiation therapy to the breast. The Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERMÖP). Am J Respir Crit Care Med. 1998;158(6):1929–35.
8. Otani K, Nishiyama K, Ito Y, Kawaguchi Y, Inaji H. Steroid treatment increases the recurrence of radiation-induced organizing pneumonia after breast-conserving therapy. Cancer Med. 2014;3(4):947–53.
9. Katayama N, Sato S, Katsui K, Takemoto M, Tsuda T, Yoshida A, et al. Analysis of factors associated with radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy. Int J Radiat Oncol Biol Phys. 2009;73(4):1049–54.
10. Ogo E, Komaki R, Fujimoto K, Uchida M, Abe T, Nakamura K, et al. A survey of radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy in Japan. Int J Radiat Oncol Biol Phys. 2008;71(1):123–31.
11. Miwa S, Morita S, Suda T, Suzuki K, Hayakawa H, Chida K, et al. The incidence and clinical characteristics of bronchiolitis obliterans organizing pneumonia syndrome after radiation therapy for breast cancer. Sarcoidosis Vasculitis Diffuse Lung Dis. 2004;21(3):212–8.
12. Epler GR, Kelly EM. Post-breast cancer radiotherapy bronchiolitis obliterans organizing pneumonia. Respir Care. 2020;65(5):686–92.
13. Sato H, Ebi J, Tamaki T, Yukawa A, Nakajima M, Ohtake T, et al. Incidence of organizing pneumonia after whole-breast radiotherapy for breast cancer, and risk factor analysis. J Radiat Res. 2018;59(3):298–302.
14. Epler GR, Kelly EM. Systematic review of postradiotherapy bronchiolitis obliterans organizing pneumonia in women with breast cancer. Oncolog. 2014;19(12):1216–26.
15. Murofushi KN, Oguchi M, Gosho M, Kozuka T, Sakurai H. Radiation-induced bronchiolitis obliterans organizing pneumonia (BOOP) syndrome in breast cancer patients is associated with age. Radiat Oncol. 2015;10:103.
16. Kubo A, Osaki K, Kawanaka T, Furutani S, Ikushima H, Nishitani H. Risk factors for radiation pneumonitis caused by whole breast irradiation following breast-conserving surgery. J Med Invest. 2009;56(3-4):99–110.
17. Cordier JF, Cottin V, Lazor R, Stoppa-Lyonnet D. Monoallelic germline ATM mutation and organising pneumonia induced by radiation therapy to the breast. Eur Respir J. 2016;47(3):997–1000.
18. Lee JH, Paull TT. Activation and regulation of ATM kinase activity in response to DNA double-strand breaks. Oncogene. 2007;26(56):7741–8.
19. Hanania AN, Mainwaring W, Ghebre YT, Hanania AN, Ludwig M. Radiation-induced lung injury: assessment and management. Chest. 2019;156(1):150–62.
20. Yousem SA. The surgical pathology of pulmonary infarcts: diagnostic confusion with granulomatous disease, vasculitis, and neoplasia. Modern Pathol. 2009;22(5):679–85.
21. Soussan M, Rust E, Pop G, Morere JF, Brillet PY, Eder V. The rim sign: FDG-PET/CT pattern of pulmonary infarction. Insights Into Imaging. 2012;3(6):629–33.
22. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis. 2011;52(9):1144–55.
23. Legouge C, Caillot D, Chretien ML, Lafon I, Ferrant E, Audia S, et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia? Clin Infect Dis. 2014;58(5):672–8.
24. Hammer MM, Madan R, Hatabu H. Pulmonary mucormycosis: radiologic features at presentation and over time. Am J Roentgenol. 2018;210(4):742–7.
25. Okubo Y, Ishiwatari T, Izumi H, Sato F, Aki K, Sasai D, et al. Pathophysiological implication of reversed CT halo sign in invasive pulmonary mucormycosis: a rare case report. Diag Pathol. 2013;8:82.
26. Marchiori E, Marom EM, Zanetti G, Hochhegger B, Irion KL, Godoy MCB. Reversed halo sign in invasive fungal infections: criteria for differentiation from organizing pneumonia. Chest. 2012;142(6):1469–73.
27. Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node-negative nonsmall cell lung carcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys. 1996;36:607.
28. Mango VL, Naidich DP, Godoy MCB. Reversed Halo Sign After Radiofrequency Ablation of a Lung Nodule. J Thorac Imaging. 2011;26(4).

29. Zhan X, Zhang L, Wang Z, Jin M, Liu M, Tong Z. Reversed halo sign: presents in different pulmonary diseases. PloS one. 2015;10(6):e0128153-e.
30. Tzilas V, Bastas A, Provata A, Koti A, Tzouda V, Tsoukalas G. The ïreversed haloŝign in pneumonococcal pneumonia: a review with a case report. Eur Rev Med Pharmacol Sci. 2010;14(5): 481–6.
31. Ye Z, Zhang Y, Wang Y, Huang Z, Song B. Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. 2020:1–9.
32. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): relationship to duration of infection. Radiology. 2020;295(3):200463.
33. Ujita M, Renzoni EA, Veeraraghavan S, Wells AU, Hansell DM. Organizing pneumonia: perilobular pattern at thin-section CT. Radiology. 2004;232(3):757–61.
34. Papiris SA, Manali ED, Kolilekas L, Kagouridis K, Maniati M, Borie R, et al. Investigation of lung involvement in connective tissue disorders. Respiration. 2015;90(1): 2–24.
35. Epler GR, Colby TV, McLoud TC, Carrington CB, Gaensler EA. Bronchiolitis obliterans organizing pneumonia. N Engl J Med. 1985;312(3):152–8.
36. Cordier JF. Cryptogenic organising pneumonia. Eur Respir J. 2006;28(2):422.

V. Tzilas[a], V. Poletti[b,c], D. Bouros[a,d,*]

[a] *Interstital Lung Disease Unit, Athens Medical Center, Athens, Greece*
[b] *Department of Diseases of the Thorax, Azienda USL Romagna, GB Morgagni Hospital, Forlì, Italy*
[c] *Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark*
[d] *First Academic Department of Pneumonology, Hospital for Diseases of the Chest, ''Sotiria'', Medical School, National and Kapodistrian University of Athens, Greece*

* Corresponding author at: First Academic Department of Pneumonology, Hospital for Diseases of the Chest, ''Sotiria'', Medical School, National and Kapodistrian University of Athens, L. Kifissias 58, Maroussi, 15125, Athens, Greece.
E-mail address: dbouros@med.uoa.gr (D. Bouros).

28 December 2020
Available online 11 April 2021

https://doi.org/10.1016/j.pulmoe.2020.12.015

Hypersensitivity pneumonitis in a patient with pulmonary alveolar proteinosis — A case report

Dear Editor,

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the alveolar accumulation of surfactant due to a deficient macrophage activity, resulting in impaired gas exchange.[1]

PAP can be classified into different types. Autoimmune PAP is the most common (90–95%), and results from autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF).[1,2] Secondary PAP is related with an underlying condition.[1] Additional forms of PAP, such as Congenital, are associated with genetic abnormalities.[1,3]

The diagnosis of auto-immune PAP is based on three findings: crazy paving pattern on high resolution chest tomography (HRCT) as a consequence of intra and interlobular septal thickening superimposed on patchy ground-glass opacities; positive GM-CSF autoantibody; and bronchoalveolar lavage (BAL) with milky appearance and finding of lipid-rich proteinaceous material, positive to periodic acid-Schiff stain. Lung biopsy may be required if the previous findings are indefinite.[1]

Therapeutic decisions are made in accordance with PAP classification and disease severity.[1] Whole-lung lavage (WLL) has been the cornerstone therapy,[1] but treatment with inhaled GM-CSF has shown improvement in measures of pulmonary gas transfer, functional health status and pathologic features, when compared to placebo.[2] Corticosteroid therapy suggested more damage than gain.[1]

Hypersensitivity pneumonitis (HP) is an immunologically mediated interstitial lung disease, caused by repeated exposure to inducing environmental agents in a genetically predisposed individual. Its diagnosis relied on a multidisciplinary discussion focused on typical chest CT scan, histological findings and high lymphocytosis in BAL.[4] Although HP may be triggered by a comprehensive number of antigens, the antigen responsible is often not identified, and chronic forms of HP can even be indistinguishable from idiopathic pulmonary fibrosis.[5,6]

The authors present the case of a 43-year-old Caucasian male, former smoker (10 pack-year), volunteer firefighter, and with medical history of peptic ulcer, that presented in 2011 a 12-month history of progressive exertional dyspnoea and cough. Symptoms initiated after exposure to smoke. He denied fever, weight loss, arthralgia, haemoptysis or chest pain. No history of infections, malignancy or previous respiratory lung disease. Physical examination was unremarkable.

He was diagnosed as having PAP based on chest HRCT findings (Fig. 1A), BAL (significant amount of periodic Acid-Schiff material, namely with various cell bodies) and positive anti-GM-CSF antibodies. Lung function tests showed a mild defect in carbon monoxide transfer factor (TLCO).

In 2013 he presented symptomatic, functional (PaO2 74 mmHg; shunt fraction 20.8%) and radiological deterioration; therefore, therapeutic WLL was carried out, resulting in symptom and gas exchange improvement.

Five years later, despite clinical and functional stability, chest HRCT (Fig. 1B) revealed a shift in its pattern, characterized by peripheral and peribronchovascular reticulation, and traction bronchiectasis. New flexible bronchoscopy with BAL analysis was performed, revealing intense lymphocyto-

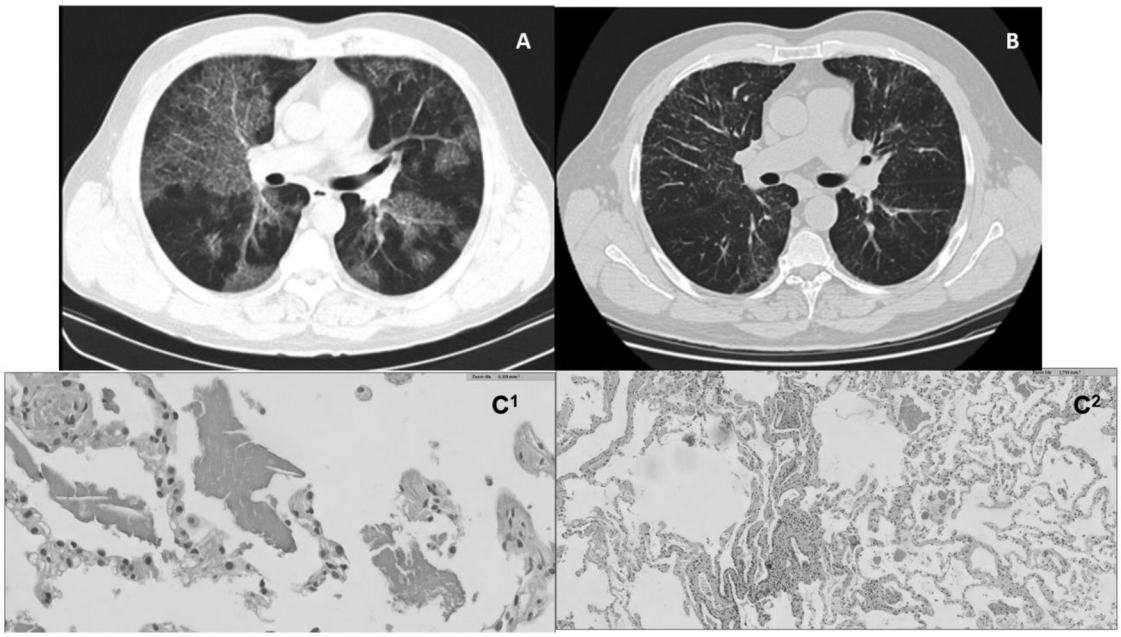


Figure 1 A and B – High resolution computed tomography images (axial lung window). On the left, image from 2011, illustrating bilateral ground glass alveolar infiltrates and interlobular septal thickening consistent with a 'crazy paving' pattern (A); On the right, image from 2018, with reticular opacity in a manly peripheral distribution, and traction bronchiectasis in the bases (B). C^1 and C^2 – histology images. On the left, HE 10X – pulmonary alveolar proteinosis (PAP) shows alveolar filling by a proteinaceous material (C^1); On the right, HE 10X – cellular interstitial pneumonia airway-centered and peribronchiolar metaplasia; multinucleated giant cell (C^2).

sis (56,4%), with cd4/cd8 ratio of 1,7. BAL was translucent and negative for periodic Acid-Schiff (PAS) granules.

New occupational and environmental exposure to organic antigens were pursued; serum specific IgG antibodies (avian and fungus) as well as autoimmune screening were repeated; all were found to be negative.

After multidisciplinary discussion, a transbronchial lung cryobiopsy was performed; histology revealed features of alveolar proteinosis consisting of intra-alveolar eosinophilic material and coexisting features consistent with hypersensitivity pneumonitis (Fig. 1 – C^1 and C^2).

PAP and HP are known interstitial lung diseases, however completely different entities with distinct clinical features. An overlap phenotype between HP and PAP has already been described in a published article reviewing five cases, where patients show concurrent radiological and histopathological features of both diseases.[7] Nonetheless, to the best of our knowledge, this is the first case presenting this sequence of events – PAP initially, with HP appearing later on.

We hypothesized that the patient always presented positive GM-CSF antibodies and the exposure to smoke or silica extinguisher powder acted as a trigger to develop PAP; it is known that inhalation of toxic dusts and fumes is a major risk factor for developing secondary PAP.[8] Many patients with autoimmune PAP have a history of exposure (23%), and positive autoimmunity may be present in some secondary PAP cases.[9] At least two recognized cases reporting PAP secondary to extinguisher particle's exposure, are described in the literature.[10,11]

Curiously, our patient developed HP later on, once PAP was under control. We postulate that the development of HP might be explained by the capability of PAP itself to predispose to a secondary pathology, causing a lung hypersensitivity reaction.[7] It is possible that alveolar epithelial damage following PAP might induce susceptibility to environmental triggers, especially if there is an underlying immune dysregulation. Our patient had positive GM-CSF antibodies and some studies demonstrate that GM-CSF antibodies have an important role in reducing lung injury after insult.[12] High values of GM-CSF antibodies were found in patients with HP and sarcoidosis who also presented various features allusive of autoimmune PAP. This finding suggests that measurement of GM-CSF antibodies could help in identifying concomitant early-onset autoimmune PAP.[13]

Another hypothesis is that leakage of PAS positive material from damaged alveoli/bronchus led to a pulmonary response similar to HP.

In conclusion, PAP is a rare entity, with still much to clarify regarding its evolution. We reported the first case of HP after PAP. It is unclear if this association occurred by chance or if PAP predisposed the HP. Longitudinal records and registries may be a helpful tool to better understand the natural history of PAP.

Ethical disclosure

I, Margarida Costa e Silva, hereby state that this study was conducted in accordance with Helsinki Declaration, revised in 2013, and approved by the ethical committee of Centro Hospitalar de Vila Nova de Gaia/Espinho.

Authorisation for publishing clinical data was obtained from the patient. Nevertheless, personal data was anonymized.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. Lancet Respir Med. 2018;6(7):554–65, http://dx.doi.org/10.1016/S2213-2600(18)30043-2.
2. Trapnell BC, Inoue Y, Bonella F, Morgan C, Jouneau S, Bendstrup E, et al. Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. New N Engl J Med. 2020;383(17):1635–44, http://dx.doi.org/10.1056/NEJMoa1913590.
3. China N, Gurioli C, Maitan S, Poletti V. rs1573858 GATA-2 homozygote variant associated with pulmonary alveolar proteinosis, cytopenia and neurologic dysfunction. Pulmonology. 2020;26(3):178–80, http://dx.doi.org/10.1016/j.pulmoe.2019.09.008.
4. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of hypersensitivity pneumonitis in adults. An official ATS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2020;202(3):e36–69, http://dx.doi.org/10.1164/rccm.202005-2032ST.
5. Santos V, Martins N, Sousa C, Jacob M, Padrão E, Melo N, et al. Hypersensitivity pneumonitis: main features characterization in a Portuguese cohort. Pulmonology. 2020;26(3):130–7, http://dx.doi.org/10.1016/j.pulmoe.2019.09.004.
6. Alberti ML, Malet Ruiz JM, Fernández ME, Fassola L, Caro F, Roldán IB, et al. Comparative survival analysis between idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis. Pulmonology. 2020;26(1):3–9, http://dx.doi.org/10.1016/j.pulmoe.2019.08.007.
7. Verma H, Nicholson AG, Kerr KM, Dempsey OJ, Gibbs AR, Campbell I, et al. Alveolar proteinosis with hypersensitivity pneumonitis: a new clinical phenotype. Respirology. 2010;15(8):1197–202, http://dx.doi.org/10.1111/j.1440-1843.2010.01848.x.
8. Li M, Alowami S, Schell M, Davis C, Naqvi A. Pulmonary alveolar proteinosis in setting of inhaled toxin exposure and chronic substance abuse. Case Rep Pulmonol. 2018;2018:5202173, http://dx.doi.org/10.1155/2018/5202173.
9. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, et al. Pulmonary alveolar proteinosis. Eur Respir Rev. 2011;20(120):98–107, http://dx.doi.org/10.1183/09059180.00001311.
10. Yorozuya T, Ikeda K, Chiba H, Saito A, Kuronuma K, Nishikiori H, et al. Autoimmune pulmonary alveolar proteinosis diagnosed after exposure to a fire extinguisher containing silica powder. Intern Med. 2019;58(14):2067–72, http://dx.doi.org/10.2169/internalmedicine.1557-18.
11. Kim Y, Shin J, Kang S, Kyung S, Park JW, Lee S, et al. Pulmonary alveolar proteinosis induced by hydrofluoric acid exposure during fire extinguisher testing. J Occup Med Toxicol. 2015;10:6, http://dx.doi.org/10.1186/s12995-015-0048-7.
12. Moore BB, Coffey MJ, Christensen P, Sitterding S, Ngan R, Wilke CA, et al. GM-CSF regulates bleomycin-induced pulmonary fibrosis via a prostaglandin-dependent mechanism. J Immunol. 2000;165(7):4032–9, http://dx.doi.org/10.4049/jimmunol.165.7.4032.
13. Katayama K, Hirose M, Arai T, Hatsuda K, Tachibana K, Sugawara R, et al. Clinical significance of serum anti-granulocyte-macrophage colony-stimulating factor autoantibodies in patients with sarcoidosis and hypersensitivity pneumonitis. Orphanet J Rare Dis. 2020;15(1):272, http://dx.doi.org/10.1186/s13023-020-01546-x.

M. Costa e Silva[a,*], S. Campainha[a], C. Souto Moura[b], I. Marques[c], S. Neves[a]

[a] *Department of Pulmonology, Centro Hospitalar Vila Nova de Gaia, Espinho, Portugal*
[b] *Department of Pathology, Centro Hospitalar São João, Portugal*
[c] *Department of Radiology, Centro Hospitalar Vila Nova de Gaia, Espinho, Portugal*

* Corresponding author.
E-mail address: mm.costasilva@gmail.com (M. Costa e Silva).

27 December 2020
Available online 5 February 2021

https://doi.org/10.1016/j.pulmoe.2021.01.001

Airway stents in malignant central airway obstruction

Dear editor,

Central airway obstruction develops in a significant proportion of lung cancer patients and many other cancers through metastasis.[1] Tumors that cause obstruction of the trachea and the main bronchi are often inoperable.[2] Airway stenting is a therapeutic option for malignant central airway obstructions (MCAO) and is indicated for both intraluminal and extraluminal obstructions.[3,4] There are several types of stents available and there is a progressive and improved experience of professionals regarding their management.[3] Stenting is associated with immediate symptom relief and improved quality of life.[5] Palliative and therapeutic benefits are well established, however, complications related to several types of metal and silicone stents are also reported. We report 5 years' experience with stent placement in patients with MCAO, using rigid bronchoscopy (RB), between January 2015 and December 2019, at Centro Hospitalar Universitário São João.

Fifty-six stents were placed in patients with MCAO, 57.1% for lung cancer, regional extension by other malignancies including esophageal cancer (30.4%), head and neck (3.6%) and lung metastases (3 colorectal, 1 tongue sarcomaand 1 unknown primary). Baseline characteristics of the popula-

Table 1 Baseline characteristics.

	MCAO, n = 56
Age (years), mean ± SD	59.5 ± 12
Male sex, n (%)	45 (80.4)
Primary site of malignancy	
Local extension, n (%)	
Esophageal cancer, n (%)	17 (30.4)
Head and neck cancer, n (%)	2 (3.6)
Tracheal and lung, n (%)	32 (57.1)
Metastatic disease	
Colorectal cancer, n (%)	3 (5.4)
Tongue, n (%)	1 (1.8)
Occult, n (%)	1 (1.8)
Site of lesion	
Single lesion	
Trachea, n (%)	19 (33.9)
Right main bronchus, n (%)	5 (8.9)
Right bronchus intermedius, n (%)	3 (5.4)
Left main bronchus, n (%)	10 (17.9)
Extended lesion	
Trachea and ≥1 bronchus, n (%)	19 (33.9)
Type of obstruction	
Intraluminal lesion, n (%)	11 (19.6)
Extrinsic compression, n (%)	14 (25.0)
Mixed lesion, n (%)	31 (55.4)
Grade of obstruction (Myer and Cotton classification)[a]	
I, n (%)	2 (3.6)
II, n (%)	13 (23.2)
III, n (%)	39 (69.6)
IV, n (%)	2 (3.6)
Tracheoesophageal fistula, n (%)	10 (17.9)
Time interval from diagnosis of MCOA to stent inserted (days), median (IQR)	76.5 (382)
Adjuvant interventions	
None, n (%)	28 (50)
Mechanical debulking, n (%)	21 (37.5)
Mechanical dilatation, n (%)	6 (10.7)
Laser therapy, n (%)	13 (23.1)
Type of stent	
Silicon stent (Dumon), n (%)	28 (50)
Y stent, n	2
Metallic stent, n (%)	28 (50)
Y stent, n	10
Time until first complication (days), median (IQR)	39 (80)
No complications, n (%)	35 (62.5)
Complications found	
Mucostasis, n (%)	18 (32.1)
Granulation tissue, n (%)	9 (16.1)
Migration, n (%)	3 (5.4)
Halitosis, n (%)	4 (7.1)
Tumor in-growth, n (%), n (%)	15 (26.8)
Death, n (%)	52 (92.9%)
Survival (days), median (IQR)	68 (32−247)

Data are presented as frequency (n) and percentage (%) or median and interquartile range (IQR).
MACO: malignant central airways obstructions; SD: standard deviation.
[a] Classification based on the percentage of reduction in airway cross-sectional aera grade I ≤50% obstruction, grade II 51%–70% obstruction, grade III 71–99%, grade IV no detectable lumen.

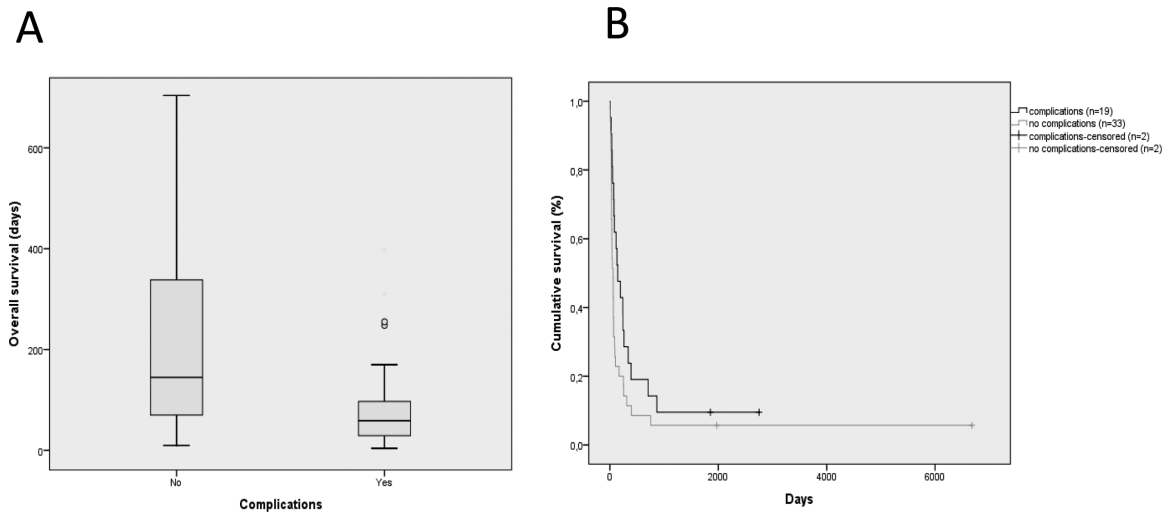


Figure 1 (A) Box plot demonstrating survival difference (days of survival) in MCAO patients with stent-related complications versus patients without complications. (B) Kaplan–Meier curve for overall survival after stent placement in relation to the occurrence of stent-related complications (black) and the absence of stent-related complications (gray): + indicates censoring cases.

tion and the characteristics of the obstruction observed by bronchoscopy are summarized in Table 1. Most patients had a single lesion, trachea (33.9%), right main bronchus (8.9%), bronchus intermedius (5.4%), left main bronchus (17.9%) and 33.9% of patients had an extended lesion. The severity of airway obstruction was determined using the Myer-Cotton grading system and forty-one patients (73.2%) had $\geq$ 71% airway lumen obstruction (Grade III or IV). In 10 cases tracheoesophageal fistula was detected.

An equal number of silicone (n = 28) and metallic (n = 28) stents were placed. In addition to stent insertion, in half of the cases, another bronchoscopy modality was performed, including mechanical dilation, tumor mechanical debulking and laser therapy.

Twenty-one (37.5%) of all stents placed were associated with $\geq$1 complication, such as mucostasis (in 12 patients, secretions were easily removable by flexible bronchoscopy while in 6 patients RB was needed), migration (n = 3), tumor in-growth (n = 15), granulation tissue (n = 9) and halitosis (n = 4) (Table 1). The median time until first complication was 39 (16–96) days.

The occurrence of complications was independent of the type of stent placed (p = 0.78), localization of obstruction (p = 0.43), type of obstruction (p = 0.69), origin of the malignancy (p = 0.78), tracheoesophageal fistula (p=0.48) and the extent of the obstruction (p = 0.08). However, there was a statistically significant difference between the number of complications and the presence of $\geq$71% airway lumen obstruction ($p < 0.05$) and in patients with a y-stent ($p < 0.05$).

Overall, the median survival was 68 (32—247) days. The Kaplan-Meier method was used to estimate the overall survival after stent placement in relation to the origin of the neoplasia (pulmonary vs non-pulmonary), type of obstruction and occurrence of complications. According to the analysis (Fig. 1), the median time until death was 145 (70–338) days for patients with stent-related complications and 59 (28–103) days for patients without complications, this difference was the only statistically significant one ($p < 0.05$).

Discussion

In patients with MCAO, bronchoscopic interventions can provide significant palliation of symptoms and quality of life.[5] We report the experience of our bronchology department in the placement of stents in cases with MCAO. Stent placement requires a careful selection of patients and the type of stent, as well as knowledge and experience regarding the technique, follow-up and management of complications. Although several types of stents are available, the ideal type of stent for each situation is still a matter of debate.[3] The main indications for stenting in MCAO are obstruction by extrinsic compression, endobronchial tumor with residual obstruction/malacia after bronchoscopic resection and malignant tracheoesophageal fistula.[2] Prior to stent placement, it is important that the obstructive lesion is dilated and removed to facilitate stent deployment and obtain the best possible benefit, which is maintaining long-term airway patency.[3]

Stent-related complications are not uncommon[3–5] and appear to be related to the median time of stenting.[6] Mucostasis, tumor in-growth and granulation tissue were the most common stent-related complications in our patients. The median survival found in our study was 68 days, which is close to that estimated in other series,[7,8] and the patients with longer survival after stent placement may be more likely to have $\geq$1 complication.

In conclusion, although this treatment potentially improves patients' symptoms and quality of life, we highlight the importance of regular and close monitoring to promptly diagnose complications in long cancer survivors.

References

1. Mudambi L, Miller R, Eapen GA. Malignant central airway obstruction. J Thor Dis. 2017;9 suppl 10:S1087–110.
2. Oberg C, Folch E, Santacruz JF. Management of malignant airway obstruction. AMJ. 2018;3:115, http://dx.doi.org/10.21037/amj.2018.11.06.
3. Mitchell PD, Kennedy MP. Bronchoscopic management of malignant airway obstruction. Adv Ther. 2014;31:512–38, http://dx.doi.org/10.1007/s12325-014-0122-z.
4. Kniese CM, Musani AI. Bronchoscopic treatment of inoperable nonsmall cell lung cancer. ERR. 2020;29:200035, http://dx.doi.org/10.1183/16000617.0035-2020.
5. Kim BG, Shin B, Chang B, Kim H, Jeong BH. Prognostic factors for survival after brochoscopic intervention in patients with airway obstruction due to primary pulmonary malignancy. BMC Pulm Med. 2020;20:54, http://dx.doi.org/10.1186/s12890-020-1095-0.
6. Freitas C, Martins N, Novais-Bastos H, Morais A, Fernandes G, Magalhães A, et al. The role of interventional bronchoscopy in the management of post-intubation tracheal stenosis: a 20-year experience. Pulmonology. 2019, http://dx.doi.org/10.1016/j.pulmoe.2019.12.004, 2531-0437.
7. Breitenbücher A, Chhajed PN, Brutsche MH, Mordasini C, Schilter D, Tamm M. Long-term follow-up and survival after UltraflexTM stent insertion in the management of complex malignant airway stenoses. Respiration. 2008;75:443–9, http://dx.doi.org/10.1159/000119053.
8. Vonk-Noordegraaf A, Postmus PE, Sutedja TG. Tracheobronchial stenting in the terminal care of cancer patients with central airways obstruction. Chest. 2001;120:1811–4, http://dx.doi.org/10.1378/chest.120.6.1811.

M. Serino[a,*], C. Freitas[a,e], S. Saleiro[b], B. Cabrita[c], M. Conde[d], M.G.O. Fernandes[a,e], A. Magalhães[a]

[a] *Pulmonology Department, Centro Hospitalar Universitário São João, Porto, Portugal*
[b] *Pulmonology Department, Instituto Português de Oncologia do Porto, Porto, Portugal*
[c] *Pulmonology Department, Hospital Pedro Hispano, Matosinhos, Portugal*
[d] *Pulmonology Department, Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal*
[e] *Faculty of Medicine, University of Porto, Portugal*

* Corresponding author.
E-mail address: mariana.serino@gmail.com (M. Serino).

Available online 17 March 2021

https://doi.org/10.1016/j.pulmoe.2021.02.003
2531-0437/

Literacy on tuberculosis in paediatric population and their caregivers. The importance of an outpatient tuberculosis centre

According to the most recent Tuberculosis Surveillance Report from the European Centre for Disease Prevention and Control, the prevalence of Tuberculosis (TB) has been steadily decreasing, from 21,3 per 100 000 inhabitants in 2014 to 20,5/100000 in 2018.[1] As a result, and also related to the centralization of health care, the general population and healthcare professionals have progressively less contact with TB, increasing misinformation about disease presentation, prevention and treatment, eventually compromising the timely detection and management of cases.[2] Raising awareness about the topic is therefore crucial as a strategy for disease control and public healthcare.[2]

The aim of this study was to assess the general population's knowledge about TB, by identifying, measuring and evaluating the differences between Outpatient Tuberculosis Centre users and Pediatric Hospital Department users, and highlighting the factors that lead to a better understanding of TB.

A comparative cross-sectional observational study was conducted from April to June 2019. Participants were divided into two groups: patients/caregivers admitted to a Pediatric Hospital Department (PHD) and patients/caregivers followed at an Outpatient Pediatric Tuberculosis Reference Centre (OTBC).

Participants filled in a questionnaire designed by the authors featuring fifteen multiple choice questions structured as: demographic information and general knowledge about TB, disease presentation/organ involvement and treatment/prevention. Questionnaires from children older than 10years-old or their caregivers were only included if completed in full.

A TB Knowledge Score (TB KScore) was obtained for intergroup comparison of results; each correct answer scored one point, with the final score ranging from 0 to 15 points. For multiple correct answers 0,1 was added or subtracted if right or wrong answer, respectively.

Data analyses was performed using IBM SPSS Statistics v.25®. General knowledge of TB was reported as absolute and relative frequencies; TB KScore was represented by mean and standard deviation; independent sample t tests were used for intergroup comparison. Multiple linear regression model was used to identify variables associated with TB KScore.

A total of 175 participants were included (Table 1), 50.9% ($n = 89$) from the PHD and 49.1% ($n = 86$) from the OTBC. 143 participants (81.7%) were female and the average age was 34.73 ± 13.07 years. Questionnaires were mostly answered by the mothers ($n = 122$; 69.1%), and the majority of participants ($n = 53$ (30.2%)) had a high school qualification. Fifty-nine percent ($n = 104$) of the caregivers were employed and the monthly family income was mainly between 500€–1000€ ($n = 67$; 38.3%).

In the general knowledge section, 21.1% ($n = 37$) correctly recognized the incidence of TB, with 53.0% ($n = 93$) considering TB as a frequent disease and 23.0% ($n = 40$) as rare. One hundred and seven participants (61,1%) knew that TB is caused by a bacterium. About disease transmission, 23.4% ($n = 41$) answered correctly, with cough and breathing

Table 1 Characteristics of study participants.

	Groups PHD (N = 89)	OTBC (N = 86)	PHD + OTBC (N = 175)	p value
Variable				
Sex: Female, N (%)	79 (88,76)	64 (74,42)	143 (81,70)	0,014
Age in years, mean (± SD)	35,37 (12,23)	34,07 (13,94)	34,73 (13,07)	0,526
Identification of the person responding: N (%)				0,068
Patients' mothers	69 (77,53)	53 (61,63)	122 (69,71)	
Patients' fathers	8 (8,99)	12 (13,95)	20 (11,43)	
Patient himself	7 (7,87)	17 (19,77)	24 (13,71)	
Other	5 (5,52)	4 (4,65)	9 (5,14)	
Level of education, N (%)				0,27
Primary school (1st-4th grade)	9 (10,11)	1 (1,16)	10 (5,71)	
Middle school (5th-6th grade)	8 (8,99)	8 (9,30)	16 (9,14)	
Middle school (7th-9th grade)	27 (30,34)	22 (25,58)	49 (28,00)	
High school degree (10th-12th grade)	25 (28,09)	28 (32,56)	53 (30,29)	
Graduation	14 (15,73)	13 (15,12)	27 (15,43)	
Master	2 (2,25)	2 (2,33)	4 (2,29)	
Household monthly income N (%)				0,008
<500 €	17 (19,10)	5 (5,81)	22 (12,57)	
500–1000 €	37 (41,57)	30 (34,88)	67 (38,29)	
1000–1500 €	17 (19,10)	21 (24,42)	38 (21,71)	
>1500 €	9 (10,11)	20 (23,26)	29 (16,57)	
Professional situation, N (%)				0,001
Employed	48 (53,93)	56 (65,12)	104 (59,43)	
Unemployed	30 (33.71)	9 (16,07)	39 (22,29)	
Student	3 (3,37)	16 (18,60)	24 (13,71)	

Legend: PHD - Pediatric Hospital Department; OTBC - Outpatient Tuberculosis Centre.

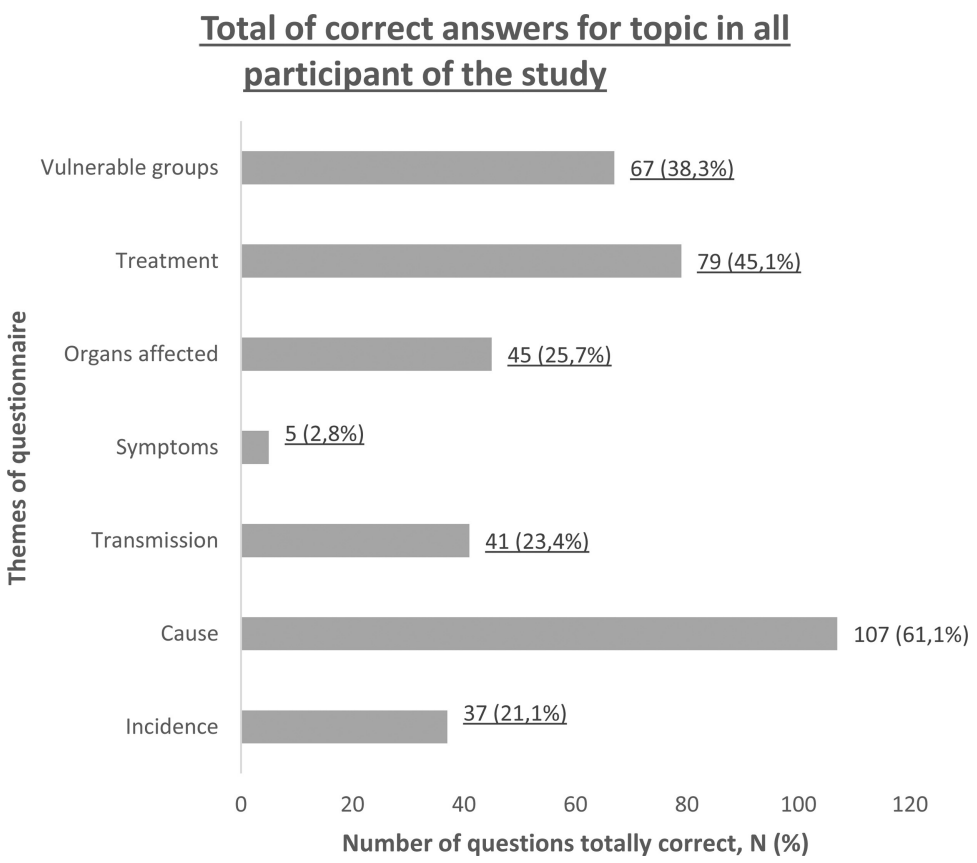


Figure 1 Total of correct answers for topic in all participant of the study.

identified by 76.0% ($n = 133$) and 53.1% ($n = 93$), respectively; 14,3% ($n = 25$) answered that TB could be transmitted by touch or contaminated water or food; the possibility of sexual transmission was considered by 8.0% ($n = 14$) of participants. Regarding presentation, 2.9% ($n = 5$) correctly identified all the symptoms, with cough ($n = 149$; 85.1%) and fever ($n = 122$; 69.7%) being the most commonly provided answers. Twenty participants (11.43%) thought that the disease is asymptomatic. About TB location, 25.7% ($n = 45$) answered it could affect several organs, mostly the lungs ($n = 109$; 62,3%). Regarding treatment of TB, 45,1% ($n = 79$) correctly identified the appropriate treatment, with antibiotics selected in 65.1% of the cases ($n = 114$), rest in 20.0% ($n = 35$) and AINE's in 10.3% ($n = 18$). Six participants (3.43%) chose all possible answers about preventive treatment in childhood and 38,3% ($n = 67$) selected all vulnerable groups (Fig. 1).

The global TB KScore was $8,14 \pm 3,30$ (min = 0,0; max = 12,5), being higher in OTBC group ($40 \pm 3,52$ versus $6,9 \pm 3,52$ for PHD).

In multiple linear regression models, TB KScore was significantly and mainly associated with provenience group (PHD versus OTBC), but also with their age and level of education.

Compared to other studies, a higher knowledge was detected for the topics about the disease cause and presentation.[2–5] However, results also indicate that literacy related to transmission, vulnerable groups and treatment were poorer than similar studies.[2,5] The higher TB Kscore detected on the OTBC group may be related to a closer contact with the disease or its suspicion in a reference centre, with more frequent health education on the theme. As other studies have shown, age and level of education have a positive effect on a person's knowledge of TB.[2,4–7] The authors recognize that most of participants were female and acknowledge that this could be a bias when generalizing results to the general population.

The results reveal that literacy on TB is far from optimal. The correct diagnosis and early treatment depend on popular knowledge about the disease, so the authors highlight the importance of developing a control strategy based on education programs and health campaigns inside the community. Hereupon, it is crucial to create a patient-centred approach to improve knowledge of and alertness for the disease, aiming to achieve a more successful control of TB.

Ethical disclosures

The study was approved by the Ethical Committee and Administrative Council of the hospital and outpatient TB centre. Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data

The authors declare that no patient data appear in this article.

Right to privacy and informed consent

The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Tuberculosis surveillance and monitoring in Europe. European Centre Of Disease Control. World Health Organization; 2020.
2. Marinac SKW JS, McBride D, Hamburger SC. Knowledge of tuberculosis in high-risk populations: survey of inner city minorities. Int J Tuberc Lung Dis. 1998;2(10):804–10.
3. Wang J, Fei Y, Shen H, Xu B. Gender difference in knowledge of tuberculosis and associated health-care seeking behaviors: a cross-sectional study in a rural area of China. BMC Public Health. 2008;8:354.
4. Hoa NP, Thorson AE, Long NH, Diwan VK. Knowledge of tuberculosis and associated health-seeking behaviour among rural Vietnamese adults with a cough for at least three weeks. Scand J Public Health Suppl. 2003;62:59–65.
5. Luba TR, Tang S, Liu Q, Gebremedhin SA, Kisasi MD, Feng Z. Knowledge, attitude and associated factors towards tuberculosis in Lesotho: a population based study. BMC Infect Dis. 2019;19(1):96.
6. Hassan AO, Olukolade R, Ogbuji QC, Afolabi S, Okwuonye LC, Kusimo OC, et al. Knowledge about tuberculosis: a precursor to effective TB control-findings from a follow-up national KAP study on tuberculosis among Nigerians. Hindawi. 2017;2017:6309092.
7. Babatunde OI, Bismark EC, Amaechi NE, Gabriel EI, Olanik AR. Determinants of treatment delays among pulmonary tuberculosis patients in Enugu Metropolis, South-East, Nigeria. Health. 2015;07(11):1506–16.

Joana Pinho*, Vilma Lopes, Isabel Ayres Pereira, Joana Brandão Silva, Maria Adriana Rangel, Isabel Carvalho

Department of Pediatrics, Centro Hospitalar de Vila Nova de Gaia Espinho EPE Vila Nova de Gaia, Vila Nova de Gaia, Portugal

* Corresponding autor.
E-mail address: joana.pinho@chvng.min-saude.pt (J. Pinho).

20 November 2020
Available online 5 March 2021

https://doi.org/10.1016/j.pulmoe.2021.01.003

T790M-EGFR mutation frequency in advanced NSCLC patients on progression from a previous TKI therapy: results from a Portuguese study

The current treatment for advanced non-small cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (EGFR) mutations is centered around EGFR-tyrosine kinase inhibitors (EGFR-TKIs).[1,2] However, resistance to EGFR-TKIs frequently develops. Multiple reports have shown that the T790 M mutation is present in approximately half the patients who develop resistance to a first- or second-generation EGFR-TKIs. Osimertinib is approved for the treatment of NSCLC harboring T790 M, highlighting the clinical relevance of the detection of this mutation.[3] Genotyping for EGFR T790 M initially required a tissue biopsy, with its inherent risks and possible treatment delay. More recently, noninvasive genotyping of cell-free plasma DNA emerged as a safer and faster alternative for detection of EGFR T790M.[4] There was no previous data on the prevalence of T790 M mutation in the Portuguese patients with advanced NSCLC. Therefore, the objective of this study was to determine the frequency of this mutation in patients with advanced NSCLC.

This prospective, analytical, multicenter study included 40 adult patients with locally advanced or metastatic NSCLC treated at 13 Portuguese oncology centers, from November 2017 to March 2019, and who had progressed or discontinued due to adverse effects following therapy or after two or more lines of treatment with EGFR-TKI and chemotherapy. The presence of T790M-EGFR mutation was assessed both in tissue and blood biopsy. Blood samples were analyzed by Ampliseq™ EGFR Hot Spots NGS panel from Thermo Fisher, cobas® EGFR Mutation Test v2 US-IVD from Roche Molecular Diagnostics and digital PCR EGFR T790 M by Thermo Fisher. All patients signed an informed consent form, and the study was previously evaluated and approved by the Ethics Committee of the participating sites.

Patients median age was 69 years (interquartile range 62–74.25 years) and 65% were females. Prior to sample collection, 32 (80%) subjects had received treatment with EGFR-TKIs, 7 (17.5%) had had chemotherapy and EGFR-TKIs, and one received EGFR-TKIs, chemotherapy and immunotherapy. Thirty-nine patients had conclusive results for liquid biopsy (one subject did not perform tissue biopsy and had an inconclusive result in liquid biopsy) and 12 patients for tissue biopsy.

The frequency of T790 M mutation was 44% (95% CI: 28—59%), Table 1.

Table 1 Frequency of T790 M mutation by method.

Frequency of T790 M mutation by method	Relative frequency (%) [CI 95%] (n/total)
At least one positive biopsy	44% [28—59%] (17/39)
Positive in tissue biopsy	42% [14—70%] (5/12)
Positive in liquid biopsy	36% [21—51%] (14/39)

This study was limited by the low recruitment rate that implied the end of the study with 40 patients instead of the target sample of 155 subjects. Moreover, only 12 samples were obtained for tissue biopsy. For these reasons, it was not possible to draw statistically significant conclusions regarding our secondary objectives, namely the concordance between liquid vs. tissue biopsy, and the comparison between techniques for determining the T790 M mutation of the EGFR gene in liquid biopsy.

Nonetheless, the frequency of T790 M mutation in the target population was comparable to that reported in the literature[5] which underlines the relevance of the testing.

In Portugal, the criteria for EGFR genetic screening varies between medical institutions and it is still not a routine assessment in clinical practice. These results, as well our unforeseen low recruitment, highlight the importance of issuing guidelines and implementing them in current practice.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

This work was supported by AstraZeneca-Produtos Farmacêuticos, Lda.

Acknowledgments

We thank all the participating investigators for their contribution in data collection, and patient selection/evaluation during the study: Dr. Gabriela Fernandes, Prof. Dr. António Araújo, Dr. Bárbara Parente, Dr. Ana Barroso, Dr. Ulisses Brito, Dr. José Albino Lopes, Dr. Lourdes Barradas, Dr. Marcos Pantarotto, Dr. Margarida Felizardo, Dr. Ricardo Luz, Dr. António Meleiro, and Dr. Fernando Barata.

References

1. Kimura H, Amino Y, Koba H, Tambo Y, Ohkura N, Hara J, et al. A case of EGFR mutation-positive lung adenocarcinoma in which the T790M allele fraction was increased by repeated EGFR-TKI treatment. Cancer Commun [Internet]. 2019;39(1):67. Available from: https://doi.org/10.1186/s40880-019-0413-5
2. Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. Clin cancer Res. 2011;17(6):1616–22.
3. Zheng D, Ye X, Zhang MZ, Sun Y, Wang JY, Ni J, et al. Plasma EGFR T790M ctDNA status is associated with clinical outcome in advanced NSCLC patients with acquired EGFR-TKI resistance. Sci Rep. 2016;6:20913.
4. Oxnard GR, Thress KS, Alden RS, Lawrance R, Paweletz CP, Cantarini M, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. J Clin Oncol. 2016;34(28):3375–82.
5. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011;3(75):75ra26.

Encarnação Teixeira[a,*]

[a] *Hospital Pulido Valente, Centro Hospitalar Universitário Lisboa Norte, Lisboa, Portugal*

António Araújo[b]

[b] *Hospital de Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal*

Venceslau Hespanhol[c]

[c] *Centro Hospitalar Universitário de São João, Porto, Portugal*

Bárbara Parente[d]

[d] *Hospital CUF Porto, Porto, Portugal*

Fernando Barata[e]

[e] *Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal*

[*] Corresponding author.
E-mail address: encarnacaoteixeira@gmail.com (E. Teixeira).

11 November 2020
Available online 23 June 2021

https://doi.org/10.1016/j.pulmoe.2021.01.007

PULMONOLOGY

www.journalpulmonology.org

CORRESPONDENCE

ROX monitoring in critical COVID-19 patients treated with high flow oxygen: A real added value compared to the respiratory rate?

Dear Editor,

We read with interest the communication by Vega *et al*. recently published in *Pulmonology*, dealing with the particular features of the ROX index in the population of COVID-19 critical patients treated with high flow nasal cannula (HFNC).[1]

We congratulate the authors for having added new evidence in this field, by investigating 120 additional patients with COVID-19-related acute respiratory failure.

However, we would like to correct a misreading by the authors regarding our study published in *Intensive Care Medicine*.[2] Indeed, the oxygen flow used in our study was not "a surprisingly low flow of 10 L/min" as written by Vega *et al*. but the "usual" high flow of 60 L/min for all patients at HFNC initiation ("HFNC was systematically initiated at 60 L min−1 /FiO_2 1" − second paragraph). We think that Vega et al. had mistaken the gas flow rate once HFNC was initiated for the median oxygen flow rate delivered to the patients prior to HFNC initiation in our study ("Prior to HFNC, the median [IQR] RR was 30 [26−36]/min and O_2 flow was 10 [8−15] L/min" − Second sentence of the third paragraph).

In addition, we did not report that "respiratory rate had better accuracy than the ROX index" as suggested by Vega et al. in their discussion. In fact, we showed that the RR and ROX 30 min after HFNC initiation had similar predictive values for HFNC failure (AUROC 0.81 (0.61−0.96) and 0.78 (0.58−0.95), respectively).[2] Since it is easier to monitor the RR than the full ROX index, we entitled our work "less is more, better look at respiratory rate". We believe that the results provided by Vega are concordant with our own, as AUROC at the earliest time point (H2) were strictly similar for RR and ROX (0.64 95%CI(0.51−0.78) vs. 0.64 (0.52−0.77), respectively); thus demonstrating no real advantage of a more complex ROX calculation compared to a simple respiratory rate monitoring. We could further discuss a possible difference in performance between RR and ROX at a later point in time (are the AUROC reported by Vega et al. at H12 for the RR [0.72 (0.61−0.83)] and the ROX [0.78 (0.67−0.89)] really significantly different?). However, we believe that such a late time point might not really impact patient's management in case of HFNC failure as, in both our experience and Vega's, "most intubation occurred between 12 and 24 hrs" after HFNC initiation.

Conflicts of interest

The authors declare that they have no conflict of interest regarding this article.

Funding

This work has not been funded by any external source.

References

1. Vega ML, Dongilli R, Olaizola G, et al. COVID-19 Pneumonia and ROX index: time to set a new threshold for patients admitted outside the ICU. Pulmonology. 2021. https://doi.org/10.1016/j.pulmoe.2021.04.003. S2531-0437(21)00092-1Online ahead of print.
2. Blez D, Soulier A, Bonnet F, Garnier M. Monitoring of high-flow nasal cannula for SARS-CoV-2 severe pneumonia: less is more, better look at respiratory rate. Intensive Care Med. 2020;46: 2094−5. https://doi.org/10.1007/s00134-020-06199-9.

M. Garnier*, D. Blez

Sorbonne University, GRC29, APHP.6, DMU DREAM, Anesthesiology and Critical Care Medicine Department, Paris, France

* Corresponding author.
E-mail address: marc.garnier@aphp.fr (M. Garnier).
Received 14 June 2021; Accepted 18 June 2021
Available online 9 July 2021

https://doi.org/10.1016/j.pulmoe.2021.06.011

Pulmonology 27 (2021) 475—476

PULMONOLOGY

www.journalpulmonology.org

CORRESPONDENCE

COVID-19 pneumonia and ROX index: Time to set a new threshold for patients admitted outside the ICU. Authors' reply

We thank Dr. Garnier and Dr Blez for their careful reading of our study[1] and their useful comments[2]

We agree with them that we may have misinterpreted their setting of High Flow Nasal Cannula (HFNC), and we apologize for the misunderstanding. It makes obviously sense that the flow was delivered at 60 L/min.[3]

Concerning the point of respiratory rate, we think that it is a matter of wording. We believe our statement "ROX H12 had a greater predictive value than respiratory rate alone, in contrast with Blez et al." is true, because in their article, the authors reported an AUROC of RR of 0.81, that is superior to 0.78 (AUROC of ROX). It is a matter of mathematics, despite not being statistically significant. On the other hand, we are a bit concerned about the title of their manuscript "*....better look at the respiratory rate*". We strongly believe that "two is better than one" in particular in patients with COVID-19 infections. The pathophysiology of Acute Respiratory Failure during this pandemic is complex and not fully understood. Everyone dealing with these patients has noticed that the respiratory frequency and tidal volume may be affected differently in specific subgroups of patients. Increases in tidal volume are presumably due to higher recruitment of respiratory premotor neurons, whereas changes in frequency may be related to the network activity of the neurons located in the pre-Botzinger complex. In addition, COVID-19 patients with similar oxygenation efficiency may have markedly different compliance. This makes the combination of respiratory pattern and respiratory mechanics complex and multifactorial. Not surprisingly, a consistent group of patients may show the so-called "non-dyspnogenic acute hypoxia" while others, for the same level of PaO_2, show an important distress. Obviously respiratory pattern may influence the PaO2/FiO2 ratio,[4] but SaO_2 is also determined by the efficiency of the a-c membrane. So to make a long story short, it is not only a matter of "*less is more*".

Indeed, Drs Garnier and Blez argued that the ROX H12 "*is a time point too late to really impact management in case of failure*". The median time of HFNC failure, however, has been reported to vary but it is on average >24 h.[5-7] Thus, this may suggest that a ROXH12 may give the clinician a better overview of the patient's outcomes, than a more praecox measurement.

Conflict of Interest

The authors have no conflicts of interest to declare

References

1. Vega ML, Dongilli R, Olaizola G, et al. COVID-19 pneumonia and ROX index: time to set a new threshold for patients admitted outside the ICU. Pulmonology. 2021. https://doi.org/10.1016/j.pulmoe.2021.04.003. S2531-0437(21)00092-1. Online ahead of print.
2. Garnier M, Blez D. ROX monitoring in critical COVID-19 patients treated with high flow oxygen: a real added value compared to the respiratory rate?Pulmonology. 2021. https://doi.org/10.1016/j.pulmoe.2021.06.011. [Epub ahead of print].
3. Blez D, Soulier A, Bonnet F, et al. Monitoring of high-flow nasal cannula for SARS-CoV-2 severe pneumonia: less is more, better look at respiratory rate. Intensive Care Med. 2020;46:2094—5. https://doi.org/10.1007/s00134-020-06199-9.
4. Prediletto I, D Antoni L, Carbonara P, et al. Standardizing PaO2 for PaCO2 in P/F ratio predicts in-hospital mortality in acute respiratory failure due to Covid-19: a pilot prospective study. Eur J Int Med. 2021. https://doi.org/10.1016/j.ejim.2021.06.002.
5. Calligaro GL, Lalla U, Audley G, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study. EClinicalMedicine. 2020;28:100570. https://doi.org/10.1016/j.eclinm.2020.100570. NovEpub 2020 Oct 6. PMID: 33043285; PMCID: PMC7536126.
6. Guy T, Créac'hcadec A, Ricordel C, et al. High-flow nasal oxygen: a safe, efficient treatment for COVID-19 patients not in an ICU. Eur Respir J. 2020 Nov 12;56(5):2001154. https://doi.org/10.1183/13993003.01154-2020. PMID: 32859678; PMCID: PMC7453734.
7. Patel M, Gangemi A, Marron R, et al. Retrospective analysis of high flow nasal therapy in COVID-19-related moderate-to-severe hypoxaemic respiratory failure. BMJ Open Respir Res. 2020;7(1):e000650. https://doi.org/10.1136/bmjresp-2020-000650. AugPMID: 32847947; PMCID: PMC7451488.

https://doi.org/10.1016/j.pulmoe.2021.07.001

M. L. Vega[a,b,#], R. Dongilli[c,#], G. Olaizola[d], N. Colaianni[a,e], M. C. Sayat[a,e], L. Pisani[f], M. Romagnoli[g], G. Spoladore[h], I. Prediletto[f], G. Montiel[a], S. Nava[f,*]

[a] *Non-Invasive Respiratory Support Unit, Hospital Juan A. Fernández, Ciudad Autónoma de Buenos Aires. Argentina*
[b] *IRCCS Azienda Ospedaliera-Universitaria, Division of Respiratory and Critical Care SantOrsola Hospital, Bologna Italia*
[c] *Division of Respiratory Diseases with intermediate respiratory intensive care units, Central Hospital of Bolzano, Bolzano, Italy*
[d] *Unidad Asistencial Cesar Milstein. Ciudad Autónoma de Buenos Aires. Argentina*
[e] *Intensive Care Unit, Clínica Zabala, Ciudad Autónoma de Buenos Aires. Argentina*
[f] *IRCCS Azienda Ospedaliera-Universitaria, Division of Respiratory and Critical Care SantOrsol Hospital, Bologna Italia. Alma Mater Studiorum University of Bologna Department of Clinical, Integrated and Experimental Medicine (DIMES), Bologna, Italy*
[g] *Pulmonology Unit, Santa Maria di Ca' Foncello Hospital, Treviso, Italy*
[h] *Division of Infectious Diseases, Central Hospital of Bolzano, Bolzano, Italy*

[*] Corresponding author at: University of Bologna Alma Mater, Chair of Respiratory Medicine, Director Post-doctoral School in Respiratory Medicine, University Hospital of Bologna, S. Orsola-Malpighi, Director, Respiratory Diseases and Respiratory Intensive Care Unit, Via Massarenti 9, 401138 Bologna, Italy.
E-mail address: stefano.nava@unibo.it (S. Nava).
Received 1 July 2021; Accepted 2 July 2021
Available online 30 July 2021

[#] Contributed equally to the work and should both be considered as first author

Pulmonology 27 (2021) 477—478

PULMONOLOGY

www.journalpulmonology.org

PHOTO

Foreing body bronchoaspiration in adult: Pharmaceutical blister

Diego Ferrer-Pargada[a,*], Francisco Arnaiz de las Revillas[b], Gerardo Blanco[c]

[a] *Pulmonology Service, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, España*
[b] *Infectous Diseases Service, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, España*
[c] *Radiology Service, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, España*

Received 30 April 2021; accepted 6 June 2021
Available online 7 July 2021

Bronchial foreign bodies are a rare condition in adults. In previous studies, only 6% of all airway foreign bodies occur in patients over 14 years of age.[1]

According to different series, 60—65% of the foreign bodies are located in the right main bronchus, 25—30% in the left main bronchus and 9—12% in the subglottis trachea. There is a similar distribution in pediatric patients. Within the adult population, the presence of foreign bodies in the airway has been reported more frequently in elderly patients, patients with mental health problems, and patients with swallowing problems.[2]

We present a 67-year-old patient who underwent a liver transplant in 2016. A computerized tomography (CT) scan (Lightspeed Pro 32 General Electric Healthcare, Chicago, USA) of the chest was made to study bilateral pulmonary infiltrates. In addition to areas with a crazy-paving pattern, a suspicious image of a foreign body was observed in the right main bronchus. For a better assessment, a 3D reconstruction was carried out. (Fig. 1a and b).

Subsequently, bronchofibroscopy (Olympus BF H-190, Tokyo, Japan) was performed. A foreign body in the right main bronchus was observed, without alteration of the adjacent bronchial mucosa (Fig. 1c and Fig. 1d) and removed with biopsy forceps. Once outside, it was confirmed that the foreign body was a blister pack of a tablet (Fig. 1e).

The images are rare and surprising, first of all because this was an adult patient without swallowing or mental disorders. Secondly, despite the irritant and noxious nature of the material and the long time in the airway, no alteration in the bronchial mucosa was observed and the patient was asymptomatic. Finally, reviewing previous literature, this is the first case in which the presence of a pharmaceutical blister is described as a bronchial foreign body.

We want to particularly acknowledge Joy Selene Osorio for help in the translation of this article.

All authors have seen and approved the manuscript, contributed significantly to the work and declare that they have no conflicting interests that are relevant to this article. There are not organizations that have funded this research.

* Corresponding author.
E-mail address: diegojose.ferrer@scsalud.es (D. Ferrer-Pargada).

https://doi.org/10.1016/j.pulmoe.2021.06.003

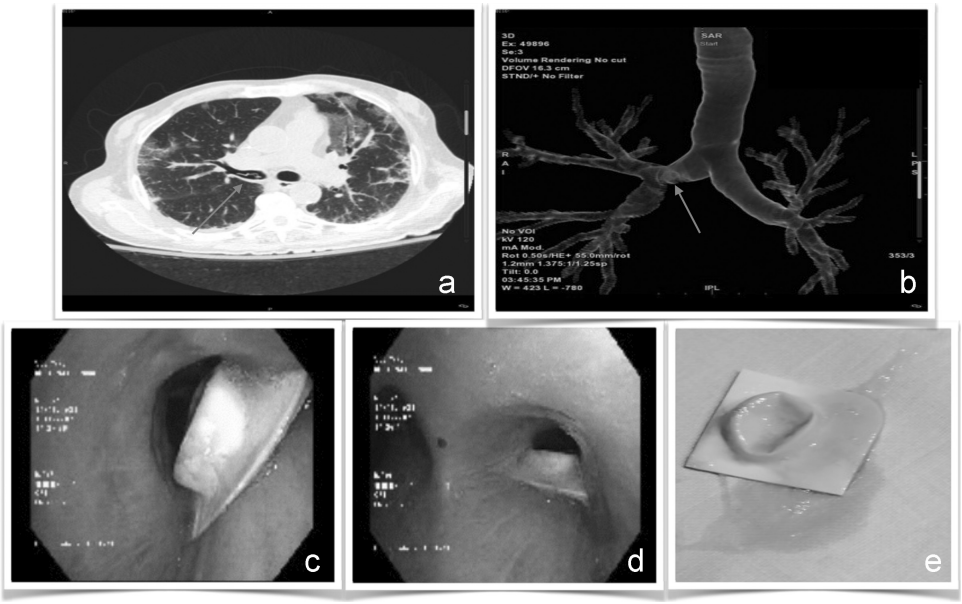


Figure 1 Image a. Visualization of the foreign body in thoracic CT (indicated by the arrow). Image b. Reconstruction of the bronchial tree with foreign body at the level of the right main bronchus (indicated by the arrow). Image c. Impacted foreign body in the right main bronchus with image from the main carina. Image d. Visualization of foreign body impacted at the entrance of the right main bronchus. Image e. Foreign body once removed by biopsy forceps.

References

1. Holinger PH, Holinger LD. Use of the open tube bronchoscope in the extraction of foreign bodies. Chest. 1978;73(5 Suppl):721—4. https://doi.org/10.1378/chest.73.5_supplement.721. MayPMID: 639585.

2. Baharloo F, Veyckemans F, Francis C, Biettlot MP, Rodenstein DO. Tracheobronchial foreign bodies: presentation and management in children and adults. Chest. 1999;115 (5):1357—62. https://doi.org/10.1378/chest.115.5.1357. MayPMID: 10334153.