Year 2021 | Vol. 89 | No. 1 | January–February | ISSN 2451–4934 e-ISSN 2543–6031

Advances in Respiratory Medicine

Formerly Pneumonologia i Alergologia Polska
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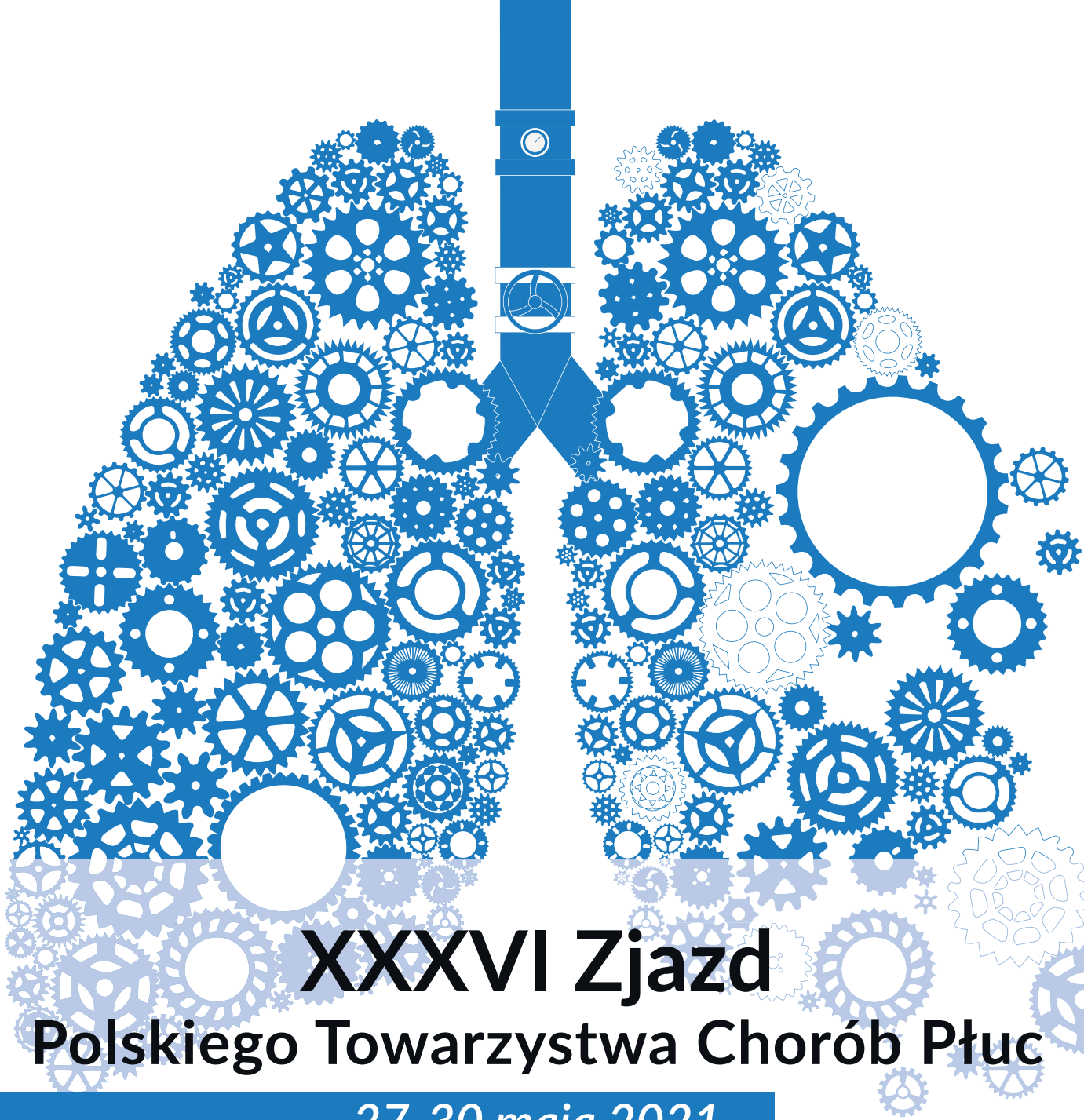

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Advances in Respiratory Medicine (ISSN 2451–4934) is published by VM Media sp. z o.o. VM Group sp.k., ul. Świętokrzyska 73, 80–180 Gdańsk phone: +48 58 320 94 94, fax +48 58 320 94 60, e-mail: redakcja@viamedica.pl
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Polish Ministry of Science and Higher Education score: 40 pts.

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LETTERS TO THE EDITOR

Lucy Abdelmabood Suliman, Taha Taha Abdelgawad, Nesrine Saad Farrag, Heba Wagih Abdelwahab

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Validity of ROX index in prediction of risk of intubation in patients with COVID-19 pneumonia

Abstract

Introduction: One important concern during the management of COVID-19 pneumonia patients with acute hypoxemic respiratory failure is early anticipation of the need for intubation. ROX is an index that can help in identification of patients with low and those with high risk of intubation. So, this study was planned to validate the diagnostic accuracy of the ROX index for prediction of COVID-19 pneumonia outcome (the need for intubation) and, in addition, to underline the significant association of the ROX index with clinical, radiological, demographic data.

Material and methods: Sixty-nine RT-PCR positive COVID-19 patients were enrolled. The following data were collected: medical history, clinical classification of COVID-19 infection, the ROX index measured daily and the outcome assessment.

Results: All patients with severe COVID-19 infection (100%) were intubated (50% of them on the 3rd day of admission), but only 38% of patients with moderate COVID-19 infection required intubation (all of them on the 3rd day of admission). The ROX index on the 1st day of admission was significantly associated with the presence of comorbidities, COVID-19 clinical classification, CT findings and intubation ($p \leq 0.001$ for each of them). Regression analysis showed that sex and ROX.1 are the only significant independent predictors of intubation [AOR (95% CI): 16.9 (2.4– 117), 0.77 (0.69–0.86)], respectively. Cut-off point of the ROX index on the 1st day of admission was ≤ 25.26 (90.2% of sensitivity and 75% of specificity).

Conclusions: ROX is a simple noninvasive promising tool for predicting discontinuation of high-flow oxygen therapy and could be used in the assessment of progress and the risk of intubation in COVID-19 patients with pneumonia.

Key words: ROX index, COVID-19, intubation risk

Adv Respir Med. 2021; 89: 1–7

Introduction

Severe hypoxemia resulting from COVID-19 pneumonia is often associated with near normal respiratory system compliance, which is almost never seen in severe ARDS. However, COVID-19 pneumonia in most cases falls under the Berlin definition of ARDS [1, 2].

Severely hypoxemic patients with COVID-19 pneumonia, despite sharing a single etiology, may have different presentations: markedly dyspneic or normally breathing ("happy" hypoxemia); and either responsive to prone position or not. So, the same disease presents itself with impressive heterogenity. Two primary "phenotypes": type L, characterized by low elastance (i.e., high compliance), low recruitment and low lung weight and type H, characterized by high elastance, high recruitment and high lung weight were reported [3]. For patients with COVID-19 infection, oxygen supplementation via low-flow nasal cannula may be sufficient, however; in patients with acute hypoxemic respiratory failure, higher flow of oxygen may be needed, and noninvasive modalities (HFNC and NIV) may be used rather than proceeding directly to intubation [4]. A systematic review from July 2020 identified one trial evaluating HFNC in patients with COVID-19, which suggested that it reduced the need for mechanical ventilation and improvements in oxygenation compared with standard oxygen therapy [5]. The ROX in-

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DOI: 10.5603/ARM.a2020.0176
Received: 22.07.2020

ISSN 2451–4934

dex defined as the ratio of oxygen saturation as measured by pulse oximetry/FiO_2 to respiratory rate can help identify those patients with low and those with high risk of intubation [6, 7]. One important concern during the management of COVID-19 pneumonia patients with acute hypoxemic respiratory failure is not to delay intubation. So, this study was planned to validate the diagnostic accuracy of the ROX index for COVID-19 pneumonia outcome (the need for intubation) and, in addition, to underline the significant association of the ROX index with clinical, radiological, and demographic data.

Material and methods

This diagnostic study was conducted on 69 RT-PCR positive COVID-19 patients with radiological evidence of pneumonia attending different quarantine places in Egypt from April 2020 to June 2020. Mild COVID-19 patients (presenting with respiratory symptoms without radiological evidence of pneumonia), individuals with chronic respiratory failure and those with conditions that affect pulse oximeter reading (e.g. nail polish) were excluded. This study was conducted within the required ethics guidelines of Mansoura institutional research board ethics committee (code number: R.20.05.832) and approved by the Ministry of Health and Population. Training and research sector (REC) (code: Com. NO/Dec.No:14-2020/2).

The following data were collected:

— medical history, e.g. age, sex, occupation, comorbidities, previous treatment;
— COVID-19 infection clinical classification according to the Ministry of Health and Population in Egypt:
  • moderate case: the presence of symptoms suggestive of COVID-19 infection with radiological evidence of pneumonia;
  • severe case: moderate case who meet any of the following: oxygen saturation < 93%, respiratory rate ≥ 30 breath\min at rest and patients with > 50% pulmonary lesion progression within 24 to 48 h;
— radiological data:
  • pulmonary computerized tomography (CT) pattern of COVID-19 [3]: a) type L COVID-19 pneumonia — subpleural and along the lung fissures ground-glass densities with moderately increased lung weight; b) type H COVID-19 pneumonia — the increased amount of non-aerated tissue;
— the ROX index refers to combination of the ratio of oxygen saturation (as measured by pulse oximetry) to fraction of inspired oxygen and respiratory rate (SpO_2/FiO_2/RR). It was calculated daily for all patients who underwent oxygen therapy from the measured value of SpO_2 and respiratory rates (breaths/ /min) and supplemental oxygen (FiO_2 values) [6, 7];
— other data indicate severity: PO_2/FiO_2, SpO_2/ /FiO_2, other organ failure, d-dimer, serum ferritin, the presence of shock;
— all patients were primarily evaluated for the need for oxygen therapy and follow-up for one week for either clinical improvement (fever drops, better respiratory symptoms, hemodynamics stability, less need for oxygen (< 0.4) or deterioration with the necessity for invasive mechanical ventilation. Mechanical ventilation was considered in the presence of worsening or persistent respiratory distress, respiratory rate more than 40 breaths/min, SpO_2 less than 90% despite maximum oxygen flow and FiO_2, acidemia with pH less than 7.25, significant hemodynamic instability and multiorgan failur;
— failure of oxygen therapy was considered when the patient needed invasive mechanical ventilation within one week from the beginning of treatment with oxygen.

Statistical analysis of data

The collected data was prepared, tabulated, and statistically analyzed using statistical package for social science (SPSS) version 16. Frequencies and percentages were used to present nominal variables, while means (SD), or median (min-max) were used to present continuous data according to the results of Shapiro-Wilk testing of normality of variables. Some variables were calculated: the ROX index using the formula (SpO_2/FiO_2)/respiratory rate as ROX.1:ROX value on the first day of admission, ROX.2:ROX value on the 2nd day of admission, ROX.3:ROX value on the 3rd day of admission. Modified ROX was calculated using the formula: (PO_2/FiO_2)/respiratory rate. Significance testing was done with the help of chi-square test, and the independent-samples Mann-Whitney U test for categorical, non-parametric data, respectively. Also, Spearman correlation was used to test an association between non-parametric data. Multivariate logistic regression was done to determine the independent significant predictors of intubation. Variables found to have a significant association with the intubation outcome (intubat-

ed/not) in univariate analysis were entered in the regression model. Receiver operator curve (ROC) analysis was used to determine the most accurate cut-off point for prediction of intubation. The level of significance was set at $p < 0.05$.

Results

The study included 69 patients (mean age was 53 years old). About 78.3% of them were males. Most of the studied patients had no comorbidity (56.5%). Hypertension was the most common comorbidity (24.6%) reported. Seventy percent of them had CT of Type L, and 65% of them were classified clinically as having moderate COVID-19 infection (Table 1, Figure 1). About 59% of the studied patients were intubated. At intubation, median (min-max) of ROX, modified ROX and PO_2/FiO_2 ratio was 3.88 (3.33–6.09), 5 (3.14–5.52), 90.9 (60–109.09), respectively.

ROX 1, 2, 3 indices were significantly associated with intubation ($p \leq 0.001$ for each of them). COVID-19 clinical classification was significantly associated with intubation ($p \leq 0.001$). All patients with severe COVID-19 infection (100%) were intubated (Table 2), however, only 38% of moderate COVID-19 infection patients who needed oxygen therapy were intubated. All subjects with moderate COVID-19 infection were intubated on the 5th day of admission, but 50% of patients with severe COVID-19 infection were intubated on the 3rd day of admission (Table 2, Figure 1).

Table 1. Clinical characteristics of the patients (n = 69)

Parameter		N	%
Age mean (SD)	53.3 (8.7)		
Sex	Male	54	78.3
	Female	15	21.7
Comorbidity	No	39	56.5
	IDDM	6	8.7
	HTN	11	15.9
	IHD/HTN	6	8.7
	IHD	7	10.1
COVID clinical classification	Moderate	45	65.2
	Sever	24	34.8
CT type	L	48	69.6
	H	21	30.4
Intubation	Non intubated	28	40.6
	Intubated	41	59.4
Day of intubation (n = 41)	3rd from admission	12	29.3
	4th from admission	6	14.6
	5th from admission	23	56.1

HTN — hypertension; IDDM — insulin-dependent diabetes mellitus; IHD — ischaemic heart disease

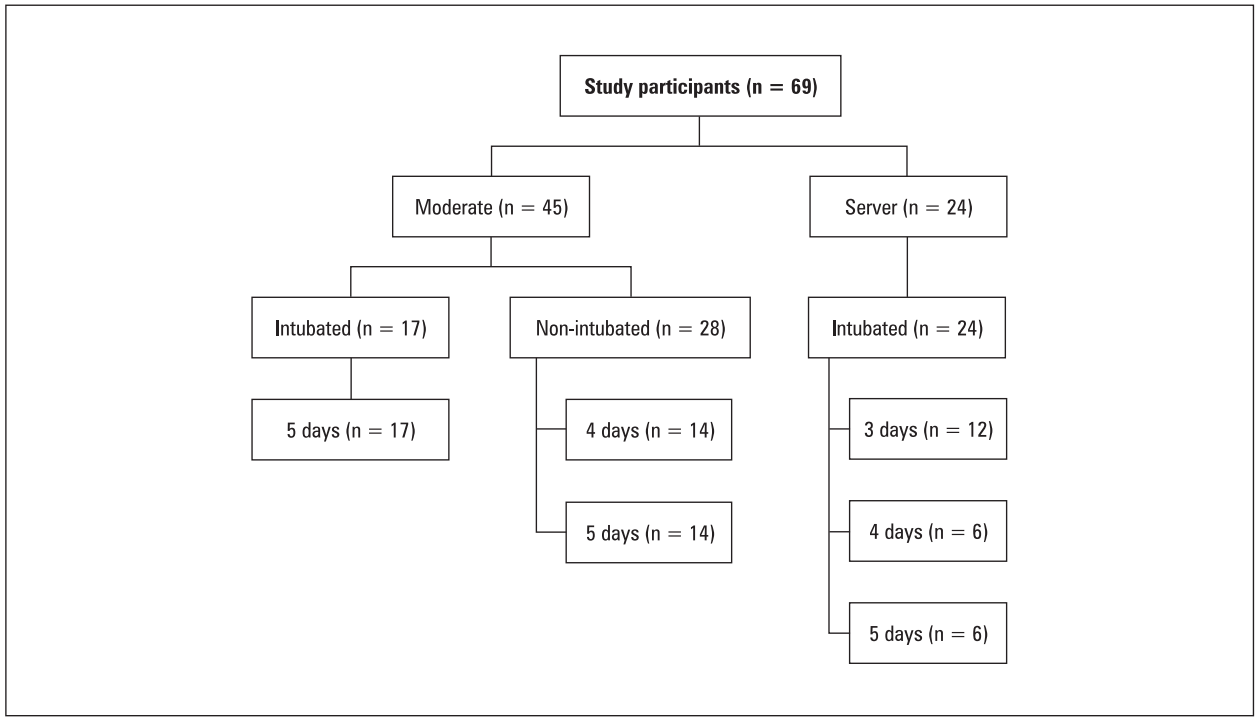

Figure 1. The days spent until day of endotracheal intubation or improvement in non-intubated patients

Table 2. Risk factors of intubation among the patients with COVID-19 (n = 41)

Parameter		Total n	Non intubated n (%)	Intubated n = 41 n (%)	Significance
Age median (min–max)			54 (38-67)	52 (39-67)	Z = -0582, 0:0.561*
Sex	Male	54	26 (48.1)	28 (51.9)	X2: 5.7, p = 0.017
	Female	15	2(13.3)	13 (86.7)	
Comorbidity	Absence	39	21 (53.8)	18 (46.2)	X2:6.5, p = 0.011
	Presence	30	7 (23.3)	23 (76.7)	
COVID-19 classification	Moderate	45	28 (62.2)	17 (37.8)	X2:25.1, p ≤ 0.001
	Sever	24	0	24 (100)	
CT pattern	Type L	48	28 (58.3)	20 (41.7)	X2:20.6, p ≤ 0.001
	Type H	21	0	21 (100)	
ROX.1 median (min–max)			26.3 (16.4–28.6)	10.6 (8.8–26.6)	Z: -5.59, p ≤ 0.001*
ROX.2 median (min–max)			26.6 (12.8–28.6)	7.8 (7.3–25.8)	Z: -5.58, p ≤ 0.001*
ROX.3 median (min–max)			26.6 (12.8–28.9)	7.5 (4.8–18.9)	Z: -6.69, p ≤ 0.001*
ROX.4 median (min–max)			28.6 (26.3–28.9)	6.9 (3.3–7.9)	Z: -6.52, p ≤ 0.001*
ROX.5 median (min–max)			28.3 (28.27–28.57)	3.8 (3.7–4.4)	Z: -5.04, p ≤ 0.001*
Lymphocyte median (min–max)			1400 (1100–2100)	1250 (1000–2100)	Z: -2.38, p = 0.017*
WBCs median (min–max)			7000 (3400–11000)	7600 (3400–12000)	Z: 1.34, p = 0.180*
Platelet median (min–max)			130000 (86000–960000)	130000 (87000–160000)	Z: -0.47, p = 0.637*
Creatinine median (min–max)			0.9 (0.7–1.4)	0.9 (0.5–1.5)	Z: -1.02, p = 0.307*
Albumin median (min–max)			3.3 (2.8–4.1)	3.4 (2.7–4)	Z: 0.259, p = 0.796*
Ferritin median (min–max)			770 (120–1300)	800 (220–1700)	Z: 1.15, p = 0.25*
D dimer median (min–max)			980 (400–1500)	1000 (430–2100)	Z: 1.49, p = 0.134*

*Independent-Samples Mann-Whitney U test. ROX.1 — ROX value in the first day post admission; ROX.2 — ROX value in the 2nd day post admission

Also, sex, comorbidities, CT pattern, lymphocyte absolute count were significantly associated with intubation (p = 0.017, 0.011, ≤ 0.001, ≤ 0.001, 0.017) (Table 2). However, the results of multivariate logistic regression of predictors of intubation among COVID-19 patients showed that female sex and ROX.1 were the only significant independent predictors of intubation [AOR (95% CI): 16.9 (2.4–117), 0.77 (0.69–0.86)], p = 0.004, ≤ 0.001, respectively (Table 3).

ROX.1 was significantly associated with the presence of comorbidities, COVID-19 clinical classification, CT findings, intubation (p ≤ 0.001 for each of them). Also, there was a negative significant association with albumin (r = -0.276, p = 0.022) (Table 4).

The results of ROC analysis for ROX 1, 2, 3 as predictors of intubation have shown (AUC, p value): (0.897, ≤ 0.001), (0.896, ≤ 0.001), (0.967, ≤ 0.001), respectively. Cut-off points of ROX.1, ROX.2, and ROX.3 were ≤ 25.26 (90.2% of sensitivity and 75% of specificity), ≤ 21.34 (90% of sensitivity and 75% of specificity). and ≤ 11.71 (90% of sensitivity and 100% of specificity) (Table 5).

Discussion

Delayed intubation has been shown to be associated with poor clinical outcome, so predicting the failure of noninvasive ventilation or oxygen therapy has remained an important area of research [7]. One important concern during the management of COVID-19 pneumonia is not to delay intubation in patients with acute hypoxemic respiratory failure. An objective method to identify subjects who are likely to fail to respond to oxygen therapy is needed. The ROX index is remarkably simple and has the potential to become a routine parameter in clinical practice.

Roca and colleagues [6, 7] first published an index ROX which can predict whether the patient will fail to use high frequency nasal canula (HFNC) in pneumonia in ICU, and they reported that a ROX value of > 4.88 predicted the success

Table 3. Multivariate logistic regression of predictors of intubation among COVID-19 patients (n = 69)

Predictors		β	p	AOR (95% CI)
Sex	Male			1 (r)
	Female	2.827	0.004	16.9 (2.4–117)
ROX.1	No			1 (r)
	Yes	-0.262	≤ 0.001	0.77 (0.69–0.86)
Constant			147.8	
Model Chi-square			47.2, p ≤ 0.001	
Percent correctly predicted			81.2%	

The variable entered in the analysis included: sex, CT type, COVID clinical classification, comorbidity, lymphocyte count; AOR — adjusted odds ratio; CI — confidence interval; r — reference group; ROX.1 — ROX value in the first day post admission

Table 4. Association of ROX.1 with other parameters of patients

		Median (min–max)	Significance
Sex	Male	16.4 (8.7–28.6)	Z: -0.86, p:0.389*
	Female	24.8 (8.8–28.6)	
Comorbidities	No	25.4 (8.8–28.6)	Z: -3.17, p: 0.002*
	Yes	15.6(8.8–26.6)	
COVID classification	Moderate	25.4 (15.6–28.6)	Z: -6.82, p ≤ 0.001*
	Sever	9.7 (8.8–10.6)	
CT	Low	25.4 (10.5–28.6)	Z: -5.26, p ≤ 0.001*
	High	8.9 (8.8–25.2)	
Intubation	No	26.3 (16.4–28.6)	Z: -5.59, p ≤ 0.001*
	Yes	10.6 (8.8–26.6)	
Lymphocyte absolute count		r = 0.06, p: 0.592**	
WBCs		r = -0.09, p: 0.462**	
Platelet		r = -0.021, p: 0.865**	
Creatinine		r = 0.202, p: 0.096**	
Albumin		r = -0.276, p: 0.022**	
Ferritin		r = -0.071, p: 0.563**	
D dimer		r = -0.187, p: 0.124**	

*Independent-Samples Mann-Whitney U test; **Spearman's Rho

of HFNC. Also, in Nicholas and Robin's study [8], the ROX index was validated in 191 critically ill patients enrolled at 5 centers in France and Spain, and the ROX index score of 4.88 was used as predictive of outcomes. The area under the curve at 12 hours of HFNC use was 0.752. Both studies calculated the ROX index at 0, 2, 6, 12 hours from the onset of oxygen therapy.

Rodriguez *et al*. [9] found that the ROX index in critically ill patients in ICU was higher in the subjects who were successfully separated from HFNC at the first trial than in those who failed (12.7 *vs* 10.2, $p = 0.002$). The ROX index ≥ 9.2 predicted successful separation from HFNC at the first trial (specificity of 50%, sensitivity of 84%, positive predictive value of 93%, negative predictive value of 30%, and accuracy of 80%). They calculated the ROX index up to 48 hours.

All previous studies were conducted on critically illpatients other than COVID-19. To the best of our knowledge, there is only one recent study done by Belz and coworkers [10] using the ROX index for monitoring of oxygen therapy by HFNC in a SARS-CoV-2 severe pneumonia admitted to ICU with proven COVID-19, and the authors found that performance characteristics of ROX

Table 5. Validity of ROX indices in prediction of intubation

Parameter (cut off point)	P value	Sensitivity	Specificity	PPV	NPV	AUC	95% CI
ROX.1 ≤ 25.26	≤ 0.001	90.2%	75%	84.1%	84%	0.897	(0.824–0.970)
ROX.2 ≤ 21.34	≤ 0.001	90%	75%	84.1%	84%	0.896	(0.819–0.974)
ROX.3 ≤ 11.71	≤ 0.001	90%	100%	100%	87.5%	0.976	(0.947–1.004)

AUC — area under the curve; CI — confidence interval; NPV — negative predictive value; PPV — positive predictive value; ROX.1 — ROX value in the first day post admission; ROX.2 — ROX value in the 2nd day post admission

at 0.5 hour using the previous published cut-off value of 4.88 by Roca and colleagues [6, 7] had a 81% sensitivity and a 38% specificity.

In this study, we used the ROX index as a simple noninvasive tool in COVID-19 pneumonia patients for prediction of the need for intubation. In contrast to previous studies, the ROX index was measured daily as we collected data from different medical facilities that dealt with COVID-19 cases, and we found that all patients with severe COVID-19 infection (100%) were intubated (Table 2), however, only 38% of moderate COVID-19 infection patients who needed oxygen therapy were intubated. All persons with moderate COVID-19 infection were intubated on the 5th day of admission but 50% of patients with severe COVID-19 infection were intubated on the 3rd day of admission.

The results of multivariate logistic regression of predictors of intubation among COVID-19 patients have shown that female sex and ROX.1 (the ROX value on the first day of admission) are the only significant independent predictors of intubation in this study. Cut-off point of ROX.1 (the ROX value on the 1st day of admission) was ≤ 25.26 (90.2% of sensitivity and 75% of specificity) (AUC, p): (0.897, ≤ 0.001), ROX.2 (the ROX value on the 2nd day of admission) was ≤ 21.34 (90% of sensitivity and 75% of specificity) and of ROX.3 (the ROX value on the 3rd day of admission) ≤ 11.71 (90% of sensitivity and 100% of specificity). The cut-off value is higher than in other studies because we conducted this study on a heterogeneous cases of different severities as we involved some less severe cases of moderately severe COVID-19 pneumonia. ROX.1 was significantly associated with the presence of comorbidities, COVID-19 clinical classification, CT findings, intubation (p ≤ 0.001 for each of them). Also, there was a negative significant association with albumin.

Clinicians could use the ROX index to assess progress in COVID-19 patients, making serial measurements and incorporating it when considering decisions to increase care. During the 1st day of admission, scores below the cut-offs given in this study would prompt anticipation of the need for earlier intubation. Once the 1st day point is reached, a score > 25.26 increases clinician confidence that the patient will succeed.

Conclusions

ROX is a simple noninvasive promising tool for predicting discontinuation of high-flow oxygen therapy and could be used by clinicians in the assessment of progress and the risk of intubation in COVID-19 patients with pneumonia. Further studies on a large number of COVID-19 patients would be necessary to support our results.

Conflict of interest

None declared.

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Competence in metered-dose inhaler technique among healthcare workers of three general hospitals in Mexico: it is not good after all these years

Abstract

Introduction: Inhaled medication is the cornerstone of pharmacological treatment for chronic respiratory diseases. Therefore, it is important to use a metered-dose inhaler (MDI) correctly to get the appropriate dosage and benefit from the drug. Health-care workers (HCW) are responsible for teaching the correct MDI technique. Unfortunately, numerous studies consistently show that HCW have poor MDI technique. This study aimed to evaluate the current knowledge of MDI technique in HCW working in three general hospitals.

Material and methods: A hospital-based, cross-sectional descriptive study was conducted in three general hospitals in Aguascalientes, México. Three surveyors simultaneously scored through a 14 dichotomic questions list as bad, regular, good, and very good MDI technique. Data were analyzed with SPSS version 16. Statistical analyses were performed using chi-square test or unpaired t-tests. An analysis of one-way ANOVA was used for comparison of three independent general hospitals. Values of $p < 0.05$ were considered to indicate statistical significance.

Results: A total of 244 HCWs were surveyed: 78.3% were nurses whereas 21.3% were physicians. The inter-observer concordance analysis among observers was 0.97. We observed that 32.4% (79) performed a bad technique, 51.6% (126) a regular technique, 13.5% (33) a good one, and 2.5% HCW (6) a very good technique. No difference between gender, labor category, schedule, service, age, seniority, and education degree between the three hospitals was observed. The most common mistakes were "insufficient expiration prior to activation of the device", and "the distance the inhaler was placed for inhalation" (83 and 84% respectively).

Conclusion: We observed that a high percentage of HCW do not follow the MDI technique correctly, being this percentage even higher than the reported in other studies. These observations suggest the urgent need to establish frequent training programs for the correct use of MDI.

Key words: metered-dose inhaler, inhalation devices, inhaler technique, health-care workers, physicians

Adv Respir Med. 2021; 89: 8–14

Introduction

Since the inhalation of vapor of black henbane was known thanks to the papyrus of Ebers an ancient Egyptian (1,554 BC), inhalation therapy has been widely used worldwide and it was until 1829 that Schneider and Waltz developed a system called "hidroconion" to pulverize and atomize liquids [1]. This appliance was used as an inhaler since then [2]. The word aerosol was first introduced by Whitlaw, Grey, and Patterson in 1932 to define the suspension of tiny liquid or solid particles in the air [2]. Controlled-dose inhalers were the primary means for treating respiratory diseases, such as asthma and COPD, both of which have a significant prevalence worldwide [3].

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DOI: 10.5603/ARM.a2021.0027
Received: 27.07.2020

ISSN 2451–4934

The pressurized metered-dose inhaler (MDI) was introduced in 1956 becoming one of the commonest delivery systems for the introduction of drugs into airways. The MDI with a good inhaler technique and adequate adherence are important for delivering the correct doses during treatment. Concerning technique, specific steps and good coordination are necessary for the proper use of this device. A less than optimal technique is commonly observed in respiratory patients and can result in decreased drug delivery and potentially reducing efficacy [4].

Health-care workers (HCW) play a pivotal role in imparting the correct steps in MDI technique. However, several studies have found that among HCW a suboptimal knowledge and skills on the MDI technique are not uncommon [5]. Thus, it is important HCW know the basic steps of the MDI technique because inhaled medications are the mainstay of bronchial disease therapy and their successful use requires both practical skills and theoretic knowledge, in order to obtain the maximum benefit of these inhalers. It is evident that if HCW are unable to apply the MDI technique correctly [6–9], educating patients for its use would be ineffective [10, 11].

Blaiss *et al.* [12] have mentioned that many patients cannot use de MDI correctly, which compromises the treatment of patients with obstructive diseases. There is no doubt that patients actively participate in using the MDI, however, physicians and nurses also participate in administrating drugs using this device, mostly when patients are hospitalized, thus, it is very important HCW know the correct technique while using MDI [2]. The objective of this study was to evaluate the current knowledge of MDI technique in HCW working in three general hospitals, of Aguascalientes, México

Material and methods

An interview hospital-based cross-sectional survey was conducted to evaluate HCW competence on the MDI technique. The protocol was approved by scientific and ethics committees with approval number 2HTM-12/09. It was done in three different general hospitals (GH); two of them, "Tercer milenio" and a "Private Hospital" (PH) are located in the city of Aguascalientes, México, and the other in the municipality of "Rincón de Romos", located approximately 40 km (25 mi) north of this city.

The GH "Tercer Milenio" (GHTM) has 52 beds, and it counts with 108 physicians, 160 nurses, whereas the GH "Rincón de Romos" (GHRR) has 30 beds and their personnel includes 70 physicians and 133 nurses, both of them are considered a second-level unit. The third hospital is a private unit, has a 30-bed capacity, and its personnel is compound by 138 nurses; however, no fixed physicians exist there. Written consent has been obtained from each participant. Evaluation (data collection) tool was adapted from the American Thoracic Society: "Using Your Metered Dose Inhaler (MDI), fact sheet", and checked for suitability to score the competency of use of MDIs by health care workers [13].

Three surveyors who obtained special training on the MDI technique, simultaneously and in an independent manner scored for each of the interviewers through a 14 dichotomic (right or wrong) questions list. Each question corresponds to each one of the steps of the correct technique of MDI [14], with special attention to the essential steps (step 5, 6, 10, and 11) [15], Table 1. Adequacy of the MDI technique was scored according to the number of "right" answers as bad (0–3), regular (4–7), good (8–10), and very good (> 10). For the evaluation, we excluded physicians and nurses older than 65 years old, students, and residents, as well as HCW out of duty because of vacations and or illnesses, as well as those who refused to participate in the study.

Statistical significance for comparison of the categorical variable between groups was determined by the chi-square test or Fisher exact test; for ordinal continuous and non-normal numeric variables between two groups, a two-tailed Student's t-test or Mann-Whitney U test were used. Furthermore, an analysis of one-way ANOVA was used for the comparison of three independent groups (GHTM, HGRR & PH). Statistical significance was considered when $p < 0.05$. Finally, for an inter-observer agreement, we used Fleiss' Kappa Test [16] and interpreted it according to Viera, and Garrett, 2005 [17]. Data entry was done using Epi Info v6 and data, transferred to SPSS version 16, and analyzed with InerSTAT-a v1.3 (Instituto Nacional de Enfermedades Respiratorias, México).

Results

A total of 244 HCW from three regional hospitals were approached and consented to participate in the study: 124 (50.8%) were from GHTM, 65 (26.6%) from GHRR, and 55 (22.5%) were from the private hospital. Among all the surveyed, 173 (70.9%) were female and 71 (29.1%) were

Table 1. Percentage of wrong answers of HCW respondents to demonstrate each step of the metered-dose inhaler technique

	Item	GHTM [%]	GHRR [%]	PH [%]	Total [%]	P
1.	Wash hands technique before using MDI	100	100	100	100	NS
2.	Shake the MDI 10–15 times before puff.	90	52	62	68	< 0.001*
3.	Verify if the mouthpiece is clean	95	94	96	95	NS
4.	Puffing MDI before to expelled drug	95	92	96	94	NS
5.**	Breathe out all of the way before activating MDI	77	86	85	83	NS
6.**	Hold the mouthpiece 2.5 to 5 cm (1 to 2 inches) from the mouth	89	77	85	84	NS
7.	Half-open mouth	85	72	80	79	NS
8.	Placement of the mouthpiece down	3	9	2	6	NS
9.	Inhaling immediately after puff	18	22	9	16	NS
10.**	Breathe in slowly and deeply through the mouth and actuate the MDI once	76	65	53	65	< 0.05*
11.**	Hold breath for 10–20 seconds after inhaling MDI	69	60	55	61	NS
12.	Activating MDI one time for each puff	15	32	9	19	< 0.05***
13.	Exhale & wait one minute before the second dose	73	63	33	56	< 0.001*
14.	If a second puff is necessary, wait 30 seconds, shake and actuate the MDI again	57	63	56	59	NS

P-values from ANOVA analysis. *Comparison among GHTM *vs* PH; **Essential step of the metered-dose inhaler technique; ***Comparison among GHRR *vs* PH. NS — not statistically significant; GHTM — General Hospital Tercer Milenio; GHRR — General Hospital Rincón de Romos; PH — private hospital

male. The mean age was 33.4 ± 10.8 years old and, the average seniority was 10.5 ± 9.1 years.

From the total population, a greater proportion of surveyed were nurses 191 (78.3%), whereas only 53 (21.7%) correspond to physicians. The most common nurse degree was nursing technicians (61%), whereas physicians, 49% were primary care physicians and the rest were different types of medical specialists.

One hundred sixty-four surveyed (67.2%) worked in one institution, 75 surveyed (30.7%) in two and, 5 surveyed (2%) in three. Most surveyed worked in the morning whereas a lower amount of them worked in the afternoon (Table 2).

The main services where surveyed labored were: 27% in the Internal medicine service, 22% in an adult emergency room and, 12% in the pediatric emergency room (Table 3). The inter-observer concordance analysis among observers showed a kappa index of 0.97.

The survey analysis showed that bad and regular performances were the frequent action carried out. Thus, among all HCW surveyed, it was observed that 79 (32.4%) performed a bad technique, 126 (51.6%) a regular technique, while only 33 (13.5%) and 6 (2.5%) of all surveyed performed a good or very good technique, respectively. A comparison of correct performance with the site of work did not show a statistically significant difference in all steps.

Table 2. Health-care workers distribution according to schedule and hospital

Schedule	GHTM n = 124 [%]	GHRR n =65 [%]	PH n = 55 [%]	All n = 244 [%]
Morning	44 (35%)	25 (38%)	14 (25%)	83 (34%)
Afternoon	35 (28%)	10 (15%)	15 (27%)	60 (25%)
Night A	21 (17%)	16 (25%)	16 (29%)	53 (22%)
Night B	24 (19%)	14 (22%)	10 (18%)	48 (20%)

GHTM — General Hospital Tercer Milenio; GHRR — General Hospital Rincón de Romos; PH — private hospital

Among the different steps for the correct use of MDI some steps are considered critical for a good deposition of inhaled drugs, thus the most common critical mistakes in the technique exhibited by all the surveyed were: step 5: "insufficient expiration prior to activation of the device" and step 6: "the distance the inhaler was placed for inhalation" (83 and 84% respectively), step 10: "the lack of slow and deep inhalation" (65%) and, step 11: "the maintenance of inspiration shorter than 10 seconds after the activation of the MDI" (61%) (Table 1). It is important to emphasize that

Table 3. Health-care worker's distribution according to hospital and service they labor

Clinical service	GHTM n = 124	GHRR n = 65	PH n = 55	All n = 244
Internal medicine	22 (18%)	20 (31%)	24 (43%)	66 (27%)
Pediatric	16 (13%)	6 (9%)	7 (12%)	29 (12%)
Out patient	12 (10%)	6 (9%)	0	18 (7%)
Surgery	11 (9%)	1 (2%)	0	12 (5%)
Adult outpatient service	12 (10%)	4 (6%)	0	16 (6%)
Adult ER	28 (22%)	15 (23%)	10 (20%)	53 (22%)
Pediatric ER	8 (6%)	0	0	8 (3%)
UCIP	4 (3%)	5 (8%)	3 (5%)	12 (5%)
UTIA	7 (6%)	5 (8%)	7 (13%)	19 (8%)
Supervision	4 (3%)	3 (5%)	4 (7%)	11 (5%)

GHTM — General Hospital Tercer Milenio; GHRR — General Hospital Rincón de Romos; PH — private hospital; ER — emergency room; UCIP — Pediatric Intensive Care Unit; UTIA — Adult Intensive Care Unit

these steps are critical to the correct use of MDI, particularly step 6; therefore if 84% of surveyed subjects did not perform this step correctly, we may consider that a very high percentage of HCW have a bad practice.

Next, we analyzed the performance between all surveyed concerning the type of profession. It was found that among all 53 physicians, 20 (37.7%) developed a bad technique, 25 (47.2%) a regular, 7 (13.2%) a good one, and just 1 (1.9%) a very good technique. In the case of all 191 nurses, the technique was bad in 58 (30.4%), in 101 (52.9%) was regular, in 27 (14.1%) was good and only 5 (2.6%) performed a very good procedure (Figure 1).

When comparing mistakes in technique by the hospital, we found that GHTM in comparison with PH had a greater percentage of mistakes, denoted by step 2: "agitation of the MDI" (90 *vs* 62, $p < 0.001$), step 10: "slow and deep inhalation" (76 *vs* 53%, $p < 0.05$), and step 13: "waiting a minute between each puff" (73 vs 33%, $p<0.001$). In contrast, the GHRR had a greater frequency of mistakes in step 12: "Activating MDI one time for each puff" (32 *vs* 9%, $p < 0.05$) than PH. There were no further differences in other steps between the three hospitals, neither among the frequency of each step with the different variables like physicians *vs* nurse, gender, labor category, schedule, service, age, seniority, and education degree ($p > 0.05$).

Discussion

The results of this survey showed that a very poor MDI technique is frequent in health care workers from three general hospitals from Aguascalientes, Mexico.

Several studies have been shown that HCW [18], and even patients [19] do not know the correct technique of applying MDI, this problem is greater in elderly patients [20]. This situation seems to be originated by the lack of teaching this technique by experts (pulmonary specialists, pulmonary therapists) to HCW, besides the common belief that "this technique is easy and well-performed by everybody".

In this survey, the high percentage of HCW that do not apply the MDI technique correctly is even higher than the reported in other studies. Therefore, while in our study we found that only 14% of HCW performed a good and a very good technique, Plaza V *et al*. [21], found that only 14.2% of physicians had adequate knowledge of MDI technique, regarding medical specialty. Furthermore, Riduan and Ismail [22] evaluated 41 physicians who worked at a hospital in Malaysia and reported that 48.9% of them used the MDI technique correctly. However, in this same study, they observed that outpatient physicians performed a worse technique in comparison with inpatient care physicians. O`Donnell *et al*. [23] developed a study including nurses and physicians laboring in an Accident and Emergency (A&E) Department, but even though 22 (88%) physicians knew the "Thoracic British Society guidelines for applying MDI", only 10 (40%) performed the technique properly. In another study, Resnick *et al*. [24] observed that only 26% (38 pediatricians) developed a correct MDI technique. Besides, when 83 third grade pharmacy students

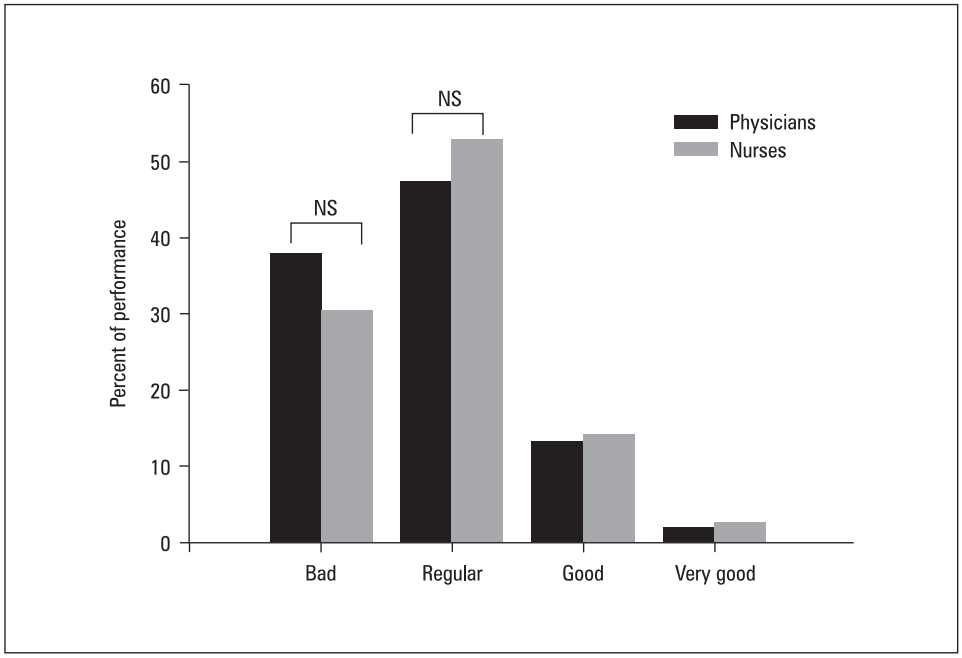

Figure 1. Distribution of studied HCW and percent of performance score of meter-dose inhaler technique. NS — not significant value for this X^2 test

were asked to perform the MDI technique after 20 minutes of listening to the correct technique, there was no difference among males and females in using the MDI [25].

In our study, we observed that more than half of surveyed failed in step 11 " to maintain a deep breath after MDI was activated", being this results similar to those found by Riduan [22]. Besides, other recurrent mistakes were also found like: "not washing hands before using MDI (100%)", "not verifying if mouthpiece was clean (95%), breathing out before activating MDI" (83%), "incorrect distance between mouth and MDI" (84%) and not performing "deep and slow inspiration after activating MDI" (65%). In contrast, Larsen *et al*. [26] found in 501 patients that the most common errors were "expiration before activating MDI", and the "lack of coordination of inspiration and activation of MDI, whereas, Sotomayor *et al*. [27] in Chile, found that the most common errors in physicians and nurses were: not "waiting for 60 seconds between each puff" (33.3% and 56.7%, respectively), not "doing it slowly and deeply" (13.4% and 30% respectively), and not "agitating MDI before using it" (60% physicians and 26.7% nurses). It can be observed that these different studies report similarities of the errors of the steps of the MDI technique.

Lastly, in our study, we also observed that the frequency of errors in the MDI technique was not influenced by different factors such as labor category, seniority, clinical service, age, nor labor schedule. Similar observations were reported by Chafin *et al*. [25] with pharmacy students and by Van Beerendonk *et al*. [28] in a study done with patients, where they did not find differences among genders.

In this survey, despite the involvement of all the responders, none of them were able to perform all steps of the MDI technique correctly, which will be reflected in the patients that will not have adequate instruction. It is also well known that only 8–20% of the drug reaches bronchial airways when MDI is used correctly, thus when the MDI technique is not properly applied, the amount of drug delivered into the lungs is lower than it should be producing worse disease outcomes [4, 29–31]. Therefore, for the proper administration of drugs using MDI, each one of the different steps of the MDI technique must be performed correctly. An incorrect MDI use due to poor education of patients leads to poor control of respiratory diseases and an increased in emergency department visits [32].

Conclusion

Several studies have been published regarding MDI technique worldwide, and in all of them have encouraged different levels of HCW to spread MDI technique to others, however, after all these studies and all these years, the problem continues, being this problem greater in HCW laboring in Mexican institutions than

those reported in other countries. Our study demonstrated that HCW of three general hospitals from Aguascalientes, Mexico, do not follow the MDI technique correctly and consequently the optimal biological dose in patients might not be achieved. These observations suggest the urgent need to establish frequent training programs for the correct use of MDI, which also must include general practitioners, pharmacists, and health educators. Special attention should be given to correct the errors in the essential steps of the inhaler technique. Associations, higher education, governmental and non-governmental organizations should take part in resolving the problem. The proper use of the technique by health care workers will bring enormous benefits to patients affected with pulmonary diseases being easier to control. Limitations of the study are that most nurses and physicians are not exclusively involved with respiratory patients such as respiratory therapists and patient's relatives.

Acknowledgments

We thank Georgina Diaz Herrera for her helpful advice during the preparation of this work.

Conflict of interest

None declared.

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Efficacy of pulmonary rehabilitation for bronchiectasis and related factors: which patients should receive the most treatment?

Abstract

Introduction: Pulmonary rehabilitation (PR) is an effective approach for patients with chronic pulmonary disease, and it is also recommended for patients with bronchiectasis. The aims of the current study were to evaluate the efficacy of a multidisciplinary PR program and identify factors associated with improvement in patients with bronchiectasis.

Material and ethods: We obtained data from patients with bronchiectasis who completed our PR program which consisted of education and training regarding bronchial hygiene. Pulmonary function test results, body composition, exercise capacity, quality of life, and psychological status were assessed before and after the PR program.

Results: We enrolled 130 patients in this retrospective study. Most patients had a history of pneumonia. The Medical Research Council (MRC) dyspnea scale, incremental shuttle walking test (ISWT), endurance shuttle walking test (ESWT), St. George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Questionnaire (CRQ), and Hospital Anxiety and Depression (HAD) scores statistically improved after the PR program (all $p < 0.001$). Improvements were similar regardless of sex, etiology, smoking status, or number of hospitalizations. Age was negatively correlated with ΔSGRQ ($p = 0.024$, $r = -0.203$). Baseline forced expiratory volume in 1s (FEV_1) was positively correlated with ΔCRQ ($p = 0.015$, $r = 0.213$) and negatively correlated with Δanxiety ($p = 0.014$, $r = -0.215$). Baseline MRC was negatively correlated with ΔMRC ($p < 0.001$, $r = -0.563$) and ΔSGRQ ($p < 0.001$, $r = -0.308$). Baseline ISWT was negatively correlated with ΔISWT ($p = 0.043$, $r = -0.176$) and Δanxiety ($p = 0.007$, $r = -0.237$). Baseline SGRQ was negatively correlated with ΔMRC ($p = 0.003$, $r = -0.267$) and ΔSGRQ ($p < 0.001$, $r = -0.648$).

Conclusions: Our PR program is efficacious for patients with bronchiectasis regardless of sex, etiologic cause of bronchiectasis, concomitant chronic obstructive pulmonary disease, smoking status, and/or number of hospitalizations. Improvement varied among patients which highlights the need for more studies to determine which patients will benefit most from the program.

Key words: bronchiectasis, dyspnea, exercise capacity, pulmonary rehabilitation

Adv Respir Med. 2021; 89: 15–22

Introduction

Bronchiectasis is a chronic disease characterized by permanently dilated airways. Possible underlying mechanisms include inflammation, structural airway damage, impaired mucociliary clearance, and infection [1].

The main signs of bronchiectasis are dyspnea, cough, and exercise intolerance [2]. Recurrent infection, chronic respiratory symptoms, and limited exercise capacity result in a poorer quality of life [3]. Treatment requires reduction of clinical symptoms such as dyspnea and exercise intolerance in order to improve quality of life and reduce the number of recurrent infections.

Pulmonary rehabilitation (PR) is a comprehensive multidisciplinary approach for patients with chronic lung disease, functional limitation, and dyspnea. PR includes exercise training, education, behavioral modification, and components of nutritional and psychosocial support [4, 5]. Guidelines for the management of bronchiectasis highlight the importance of PR [6–9] regardless of disease severity, pulmonary function, or the findings of high-resolution computed tomography (HRCT). Although PR is an efficacious

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DOI: 10.5603/ARM.a2021.0029
Received: 29.08.2020

ISSN 2451–4934

intervention, the factors that modulate its effects have not been determined. The aims of the current study were to evaluate the efficacy of our multidisciplinary PR program and the factors associated with improvement in patients with bronchiectasis.

Methods

Study design

This was a retrospective observational cohort study. We obtained data from patients included in the database of our PR center, which is a referral center in a tertiary chest disease hospital in the capital city of our country. We evaluated the data of patients who completed our PR program between March 2013 and March 2019. Informed consent was obtained from all patients and information about the PR program was provided before it began. The consent form stated that data regarding the parameters of interest and patient information would be recorded. Approval for this study was obtained from our hospital review board.

Patient characteristics

All diagnoses were confirmed by our chest physician who reviewed each patient's medical history, health records, physical examination results, chest radiographs, thorax HRCT scans, and pulmonary function tests. We also reviewed the genetic test results of patients with genetic disorders or immune deficiencies. Chronic obstructive pulmonary disease (COPD) was diagnosed according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [10].

We included patients who completed the PR program and had no missing data, had COPD, varicose and/or cystic bronchiectasis, emphysema on HRCT, and no acute infection (as confirmed by review of the medical history, serum C-reactive protein level, and chest radiography and HRCT findings). We excluded patients who had an exacerbation of disease during the PR program.

PR program

The PR program was a comprehensive, multidisciplinary, hospital-based, and supervised outpatient program. PR was performed twice per week, and the patient also completed one unsupervised home exercise session per week. The program consisted of exercise training, psychological support, nutritional support, and educational courses (on disease pathology, disease exacerbation control, medications, nutrition, bronchial hygiene, breath control techniques, energy conservation, and relaxation). The educational courses were provided by a pulmonologist, three physiotherapists, a dietician, a respiratory nurse, and a psychologist. The PR program was tailored to suit the needs of each individual patient.

Bronchial hygiene involved a series of exercises performed in a sitting position and designed to promote breathing control, thorax expansion after holding an inspired breath, and forceful expiration of the breath [11, 12]. Each patient performed these exercises before every training session for 15–20 min. Patients and caregivers were also educated about postural drainage, manually assisted thoracic-abdominal compression, and controlled coughing [11, 12]. A physiotherapist applied the techniques before a session if necessary.

The training sessions included cycle ergometry and treadmill training (15 min each), strength training of both the upper and lower extremities (5–10 min), and breathing and relaxation therapies (15–20 min each). Patients performed these exercises for a total of 70–90 min/day. Workloads during cycling and walking were calculated based on the results of the incremental shuttle walking test (ISWT). Patients were trained at 50% of their peak workload on the cycle ergometer, and 60–85% of peak oxygen consumption (VO_2) on the treadmill. Exercise intensity was increased according to the progress of the individual patient. Strength training of the upper and lower extremities was performed according to each patient's one-repetition maximum (1RM). Each patient performed two sets at 45–50% of the 1RM, and then performed 10 repetitions per set for the first 3–5 sessions. For the following sessions, the weight was increased to 70% of the 1RM. Physiotherapists closely supervised the patients, and heart rate, blood pressure, and oxygen saturation (SpO_2) were monitored during the training sessions. Supplemental oxygen was administered to maintain oxygen saturation above 90% [13].

Outcome measures

Exercise capacity, quality of life, sensation of dyspnea, pulmonary function, body composition, and psychological status were recorded at baseline and immediately after the PR program. We also recorded smoking status and the number of hospitalizations in the previous year.

Exercise capacity was evaluated with the ISWT and endurance shuttle walking test (ESWT) [14]. The tests were performed according to guidelines for field walking tests [15]. The minimal

clinically important difference (MCID) of ISWT is 47.5 m [16].

Health-related quality of life was assessed with the St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Questionnaire (CRQ). A 4-point change in the SGRQ total score corresponds to the MCID (17), while the MCID of the CRQ is 0.5 points [18]. Dyspnea was assessed with the Medical Research Council (MRC) dyspnea scale.

We used a spirometer (AS-507; Minato Medical Science, Tokyo, Japan) to determine forced vital capacity (FVC), forced expiratory volume in 1s (FEV_1), and the FEV_1/FVC ratio. Spirometry was performed in accordance with the guidelines of the American Thoracic Society/European Respiratory Society [19]. We used a TANITA analyzer (TBF-300A Total Body Composition Analyzer; TANITA, Tokyo, Japan) to measure bioelectrical impedance and body composition. Body mass index (BMI) and the fat-free mass index (FFMI) were calculated as weight in kilograms divided by the square of height in meters (body mass was used to calculate BMI; fat-free mass was used to calculate FFMI). Hospital Anxiety and Depression (HAD) scores were used to assess psychological status [20].

Statistical analysis

We used SPSS for Windows software (version 18.0; SPSS, Inc., Chicago, IL, USA) to perform the statistical analysis. Assuming a two-sided alpha level of 0.05, we performed Cohen's d analysis [21] with G*Power 3.1.9.2 software (Heinrich-Heine-Universität, Düsseldorf, Germany) to determine that the beta level was 0.20 and the effect size was medium. We used the Shapiro-Wilk test to evaluate the distributions of the variables. Descriptive statistics are expressed as mean ± standard deviation or median (range). Categorical variables are expressed as number and percentage (%). Improvements in parameters were calculated by subtracting the absolute pre-PR value from the post-PR value, denoted by 'Δ'.

We compared continuous variables among groups with one-way analysis of variance or the Kruskal-Wallis test. Spearman correlation analysis was also performed. Pre-post values were analyzed with the Wilcoxon signed-rank test (for non-normally distributed data) or the paired T-test (for normally distributed data). Binary logistic regression was used to assess the association between sex and score improvement. All other associations were analyzed by regression analysis. Baseline ISWT and FEV1 were adjusted for age, sex, and BMI. $P < 0.05$ indicates statistical significance.

Results

We enrolled 130 patients who completed the PR program. Sixty-eight (52%) patients were men. The mean age was 47 ± 15 years. Five (4%) patients were current smokers, forty-one (31%) were former smokers, and eighty-four (65%) had never smoked. In total, 78 (60%) patients had a history of pneumonia, 33 (24%) had concomitant COPD, 8 (6%) had a history of tuberculosis, 2 (2%) had immune deficiency, 3 (2%) had Kartagener syndrome, 4 (3%) had primary ciliary dyskinesia, and 2 (2%) had cystic fibrosis. Seventy-eight (58%) patients had an obstruction according to the pulmonary functional test. The mean FEV_1 was 42% ± 19% and the mean FVC was 53% ± 21% of the predicted value.

MRC, ISWT, ESWT, SGRQ, CRQ, and HAD scores were significantly higher after the PR program ($p < 0.001$). The improvements exceeded the MCID values.

We also investigated the relationships of the improvements in MRC, ISWT, ESWT, SGRQ, CRQ, and HAD scores with age, sex, presence of concomitant or underlying disease, number of hospitalizations, and baseline FEV_1, MRC, ISWT, and SGRQ scores/values (Figures 1–3). The improvements were not associated with sex, underlying disease, smoking status, or the number of hospitalizations in the previous year. Age was negatively correlated with ΔSGRQ ($p = 0.024$, $r = -0.203$). Baseline FEV_1 was positively correlated with ΔCRQ ($p = 0.015$, $r = 0.213$) but negatively correlated with Δanxiety ($p = 0.014$, $r = -0.215$). Baseline MRC was negatively correlated with ΔMRC ($p < 0.001$, $r = -0.563$) and ΔSGRQ ($p < 0.001$, $r = -0.308$). Baseline ISWT was negatively correlated with ΔISWT ($p = 0.043$, $r = -0.176$) and Δanxiety ($p = 0.007$, $r = -0.237$). Baseline SGRQ was negatively correlated with ΔMRC ($p = 0.003$, $r = -0.267$) and ΔSGRQ ($p < 0.001$, $r = -0.648$).

Discussion

Multidisciplinary PR proved to be an efficacious approach for improving dyspnea, exercise capacity, quality of life, and psychological status in patients with bronchiectasis regardless of sex, etiology of bronchiectasis, presence of concomitant COPD, smoking status, and/or the number of hospitalizations in the previous year

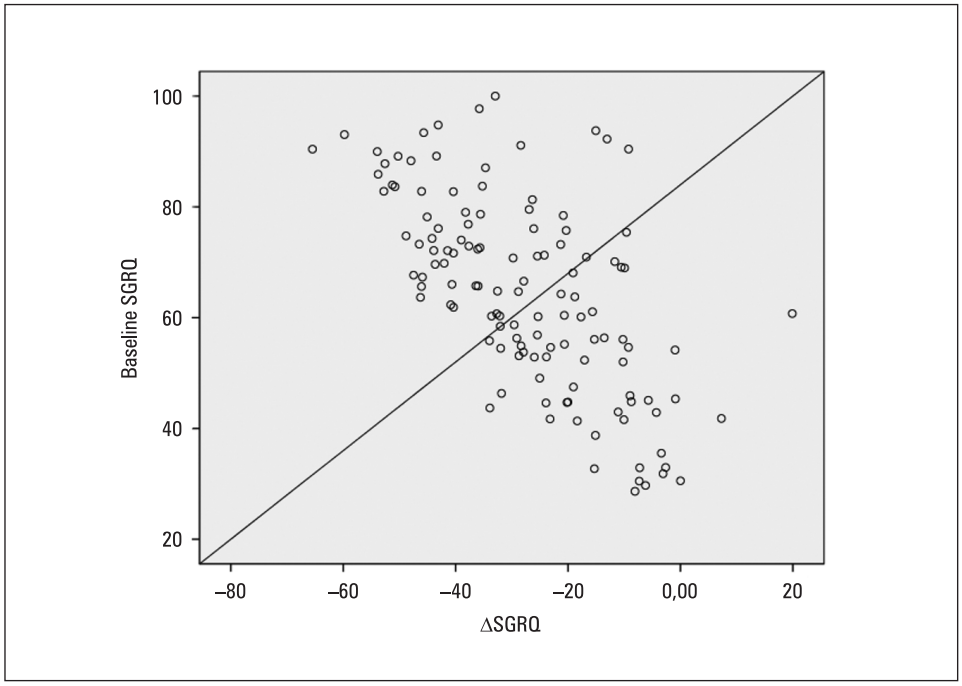

Figure 1. The relation between baseline St. George's Respiratory Questionnaire (SGRQ) and ΔSGRQ

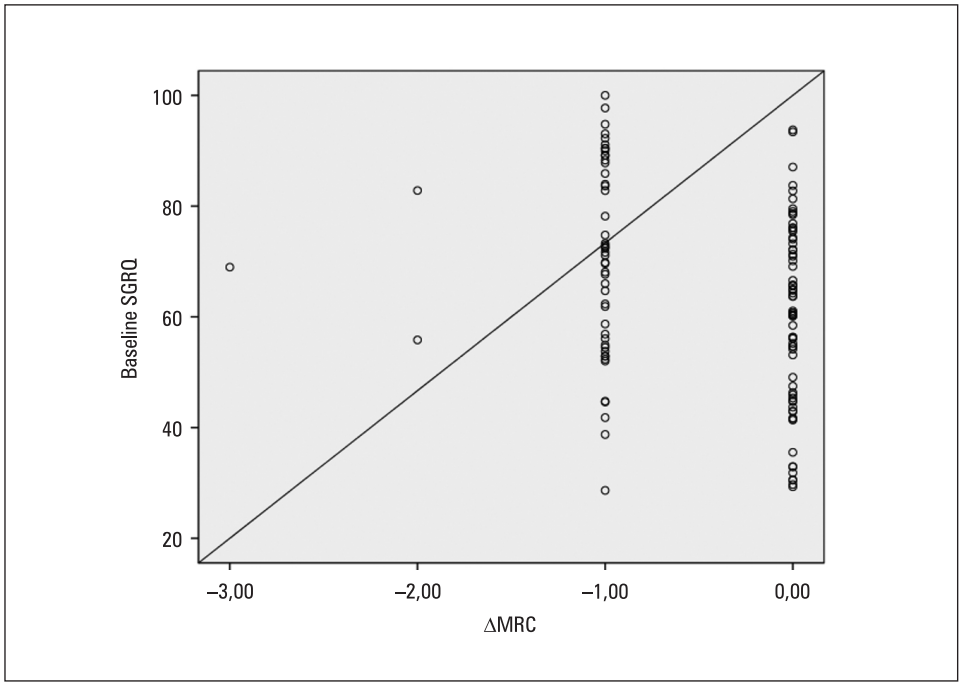

Figure 2. The relation between baseline St. George's Respiratory Questionnaire (SGRQ) and Δ Medical Research Council (MRC)

(Tables 1, 2). Improvements in quality of life were greater among patients who were younger and had less severe dyspnea, better quality of life, and better FEV_1 at baseline. Improvements in dyspnea were greater among patients who had less severe dyspnea and a better quality of life at baseline. Patients who had lower exercise capacity or FEV_1 showed greater improvements in anxiety scores, and patients who had poorer exercise capacity showed greater improvements in exercise capacity.

Bronchiectasis is associated with a variety of common and rare diseases, some of which impact mucociliary clearance and immunity. Immune

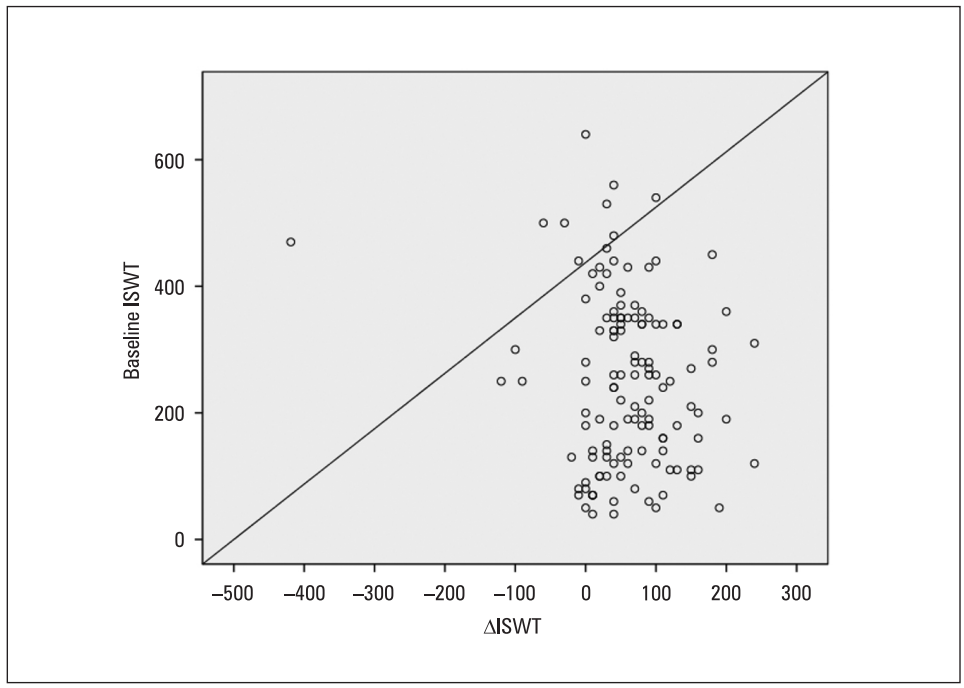

Figure 3. The relation between baseline incremental shuttle walking test (ISTW) and ΔISWT

Table 1. Features of patients and parameters before and after PR

	Before PR mean ± SD	After PR mean ± SD	P
Age [years]		47±15	
Current/former/never smoker		5 (4%) / 41 (31%) / 84 (65%)	
Cigaratte		10 ± 20 (0:90)	
FEV_1% predicted	42 ± 19	43 ± 19	0.475
FVC% predicted	53 ± 21	53 ± 20	0.723
FEV_1/FVC	66 ± 13	65 ± 14	0.213
BMI [kg/m^2]	25 ± 7	25 ± 6	0.207
FFMI [kg/m^2]	18 ± 3	18 ± 3	0.313
MRC scale	3 ± 1	2 ± 1	**< 0.001**
ISWT [m]	250 ± 137	310 ± 144	**< 0.001**
ESWT [min]	8 ± 7	13 ± 8	**< 0.001**
CRQ total score	67 ± 16	91 ± 20	**< 0.001**
SGRQ-total score	64 ± 17	37 ± 14	**< 0.001**
HAD score	10 ± 2 10 ± 2	8 ± 2 8 ± 2	**< 0.001**

PR — pulmonary rehabilitation; FEV_1 — forced expiratory volume in 1 sec; FVC — forced vital capacity; BMI — body mass Index; FFMI — fat-free mass index; MRC — Medical Research Council; ISWT — incremental shuttle walking test; ESWT — endurance shuttle walking test; CRQ — chronic respiratory questionnaire; SGRQ — St. George's Respiratory Questionnaire; HAD — hospital axiety and depression

deficiency syndromes and metabolic pathologic conditions are the most common etiologies of bronchiectasis in developed countries, while bacterial and viral infections are major causes of bronchiectasis in developing countries [22]. In our study, the most common etiology was a history of pneumonia. As expected, genetic and immunologic disorders were uncommon because we only included adult patients (mean age of 47 ± 15 years).

Table 2. Relation between some baseline values and improvements

	p/r*						
Baseline values	ΔMRC	ΔISWT	ΔESWT	ΔSGRQ	ΔCRQ	ΔAnxiety	ΔDepression
Age [years]**	0.077	0.521	0.085	**0.024 -0.203**	0.875	0.221	0.093
Sex[#]	0.689	0.882	0.957	0.585	0.648	0.079	0.192
Hospitalization[£]	0.095	0.486	0.756	0.518	0.555	0.332	0.110
Disease[$]	0.220	0.890	0.651	0.335	0.135	0.438	0.997
Smoking status[$]	0.110	0.491	0.188	0.312	0.325	0.250	0.174
Baseline FEV_1[+]	0.148	0.699	0.682	0.798	**0.015 0.213**	**0.014 -0.215**	0.318
Baseline MRC**	**< 0.001 -0.563**	0.822	0.488	**< 0.001 -0.308**	0.106	0.289	0.358
Baseline ISWT[+]	0.129	**0.043 -0.176**	0.284	0.932	0.062	**0.007 -0.237**	0.374
Baseline SGRQ**	**0.003 -0.267**	0.958	0.207	**< 0.001 -0.648**	0.478	0.349	0.158

*Correlation coefficients were given when p values were statistically significant; **spearmans' correlation; [#]Binary logistic regression; [£]Linear regression; [$]Kruskal-Wallis test; [+]Adjusted for age, sex, and BMI using linear regression analysis
FEV_1 — forced expiratory volume in 1 sec; MRC — Medical Research Council; ISWT — incremental shuttle walking test; SGRQ — St. George's Respiratory Questionnaire

Bronchiectasis can coexist with other lung diseases such as COPD. In our study, 33 (24%) patients had COPD. In another study from our country, the mean age of 304 patients with bronchiectasis was 56 ± 25 years; 65.8% of patients were non-smokers and 47.4% showed obstruction on pulmonary function tests [23]. In our study, 65% of the patients had never smoked and 58% had an obstruction. Obstruction may be associated with concomitant COPD, and bronchiectasis itself may also cause obstruction.

The main clinical manifestations of bronchiectasis are chronic cough, sputum production, dyspnea, fatigue, anxiety, depression, and functional limitations that negatively impact quality of life [1]. In our study, patients had dyspnea, limited exercise capacity, poor quality of life, borderline anxiety, and depression. Several studies have shown the positive impacts of PR, especially on exercise capacity and quality of life [24–28]. Recent guidelines also emphasize PR in the management of bronchiectasis [6–8]. In our study, after completion of the multidisciplinary PR program, patients showed significant improvements in dyspnea, exercise capacity, quality of life, and psychological status. It is important to note that these improvements exceeded the MCID values. In a recent review, ISWT increased from 52 to 82 m in patients with bronchiectasis after PR [25]. In our study, ISWT increased by 60m. In another study, the total CRQ score increased by 12.8 after completion of a multidisciplinary PR program [29]. In our study, the total CRQ score increased by 24 points. Other studies may have enrolled patients with significantly different baseline CRQ scores and exercise capacities although, similar to our study, another recent study reported that HAD scores changed in response to PR in patients with bronchiectasis with an estimated MCID of -2 points [30].

The short and long-term outcomes of PR for patients with bronchiectasis have been evaluated in several studies of various PR programs and these studies concluded that the degree of improvement in exercise capacity was not affected by program intensity or duration [1]. Our program, which was conducted in accordance with recent guidelines, was a comprehensive, multidisciplinary, hospital-based, and supervised outpatient program where all the components were tailored to the needs of the individual patient. Education, an important component of PR programs, is an issue in patients with bronchiectasis. In a previous study, quality of life improved in patients with bronchiectasis even after they received only education [31]. A recent review asserted that education should include bronchial hygiene and breath control techniques which improve sputum expectoration, certain measures of lung function, symptoms, and quality of life [32, 33]. All airway clearance techniques showed similar clinical outcomes [31]. We believe that education about airway clearance techniques may have improved the outcomes of our patients.

Few studies have investigated the factors predicting the efficacy of PR in patients with bronchiectasis [24, 26]. In a recent review, most studies of patients with COPD indicated that PR can be effective for patients of any age in terms of improving exercise capacity, health status, and anxiety and depression [34, 35]. Similarly, in our study, age was not associated with improvements in exercise capacity or anxiety and depression, but it was associated with an improved quality of life. In a propensity-matched control study that compared patients with bronchiectasis to those with COPD, similar improvements in exercise, quality of life, and CRQ scores were seen [29]. In our study, dyspnea, exercise capacity, quality of life, and psychological status improved regardless of concomitant COPD. In another study, 108 patients with bronchiectasis who completed a 3-week PR program showed improvements in exercise capacity and quality of life. In this same study, male sex, baseline FEV_1, vital capacity less than 70%, and more than two disease exacerbations in the previous year were independent predictors of PR efficacy [27]. In another study, 41 patients with bronchiectasis underwent PR. After PR, pulmonary function, arterial blood gas levels, and 6-minute walking distance (6MWD) improved. However, they did not improve significantly, and PR outcomes were not associated with sex, bacterial colonization, or disease exacerbation [24]. In our study, sex and the number of hospitalizations were not associated with improved outcomes, and only low exercise capacity at baseline was associated with an improvement in exercise capacity. This may have been due to the enrollment of a heterogeneous group of younger patients with lower baseline exercise capacity compared to the patients enrolled in the other two studies. Similar to our findings, patients with COPD and limited exercise capacity had higher exercise capacity after PR [36, 37].

The efficacy of PR has been proven but the factors associated with beneficial outcomes and the patients that respond best have not been determined. In another study, patients with COPD and MRC grade 5 dyspnea showed smaller improvements in exercise capacity and quality of life after PR in comparison with patients with less severe dyspnea [38]. Similar to the patients in our study, patients with less severe dyspnea showed greater improvements in quality of life. In a multicenter study of patients after completion of a PR program, 2,068 patients with COPD and 49% of predicted FEV_1 were grouped according to MRC, 6MWD, endurance time, scores on measures of performance and satisfaction, and HAD and total SGRQ scores. Patients in the "very good responder" group had more severe signs of dyspnea, more hospitalizations, and worse exercise performance, satisfaction scores, anxiety, depression, and health status [39]. In our study, improvements in quality of life were greater among patients who were younger, had less severe dyspnea, and had a better quality of life and FEV_1 at baseline. Patients who had lower exercise capacity or FEV_1 showed greater improvements in anxiety scores. These findings may have been due to the study design, number of patients enrolled, and exercise capacity and diagnoses thereof. Although the mechanisms underlying dyspnea and quality of life may be similar between patients with COPD and those with bronchiectasis, these mechanisms are multifactorial and other as-yet unidentified factors may exist.

A major limitation of this study was its single-center design which limits the generalizability of the results.

Conclusion

Multidisciplinary PR is an efficacious approach to improve dyspnea, exercise capacity, quality of life, and psychological status in patients with bronchiectasis regardless of sex, etiology of bronchiectasis, presence of concomitant COPD, smoking status, and the number of hospitalizations in the previous year. Improvements in quality of life and dyspnea were greater for patients who were younger, had less severe dyspnea, and had better FEV_1. Improvements in quality of life, exercise capacity, and anxiety were greater for patients who had poorer exercise capacity and FEV_1 at baseline. All patients with bronchiectasis should be referred for PR regardless of age, pulmonary function, exercise capacity, and quality of life because their outcomes may be improved. More studies are needed to determine which patients will likely benefit most from PR.

Conflict of interest

None declared.

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The utility of HACOR score in predicting failure of high-flow nasal oxygen in acute hypoxemic respiratory failure

Abstract

Objectives: To assess the diagnostic performance of HACOR scoring system using bedside variables and to predict failure of HFNO in patients with acute hypoxemic respiratory failure (AHRF).

Material and methods: 150 patients with AHRF who were receiving HFNO were enrolled in this study; to predict HFNO treatment failure. A scoring scale (HACOR score) consisted of Heart rate (beats/minute), acidosis (assessed by pH), consciousness (assessed by Glasgow coma score), oxygenation, and respiratory rate. Failure was defined as the need for intubation or death.

Results: Patients were analyzed according to the success or failure of HFNO. Total 150 patients, of which 100 (66.7%) had a successful treatment while 50 (33.3%) failed with such intervention. There was an improvement in HR and RR, and PaO_2/FiO_2 within the first hour (T1) in the success group and these parameters continued to improve even after 24 hours (T2) of HFNO treatment. Patients with HFNO failure had a higher HACOR score at initiation and after 1, 12, 24 and 48 hours. Before intubation, the highest value of the HACOR score was reached in the failure group. At 1 h of HFNO assessment, the area under the receiver operating characteristic curve was 0.86, showing good predictive power for failure. We found that HACOR score at a cutoff point > 6 had 81.2% sensitivity and 91% specificity, 92.5% positive predictive value, and 71.4% negative predictive value with a diagnostic accuracy was 85%. Furthermore, the overall diagnostic accuracy exceeded 87% when the HACOR score was assessed at 1, 12, 24 or 48 h of HFNO.

Conclusions: The HACOR scale is a clinically useful bedside tool for the prediction of HFNO failure in hypoxemic patients. A HACOR score < 6 after 1 hour of HFNO highlights patients with $< 85\%$ risk of failure.

Key words: hypoxemic respiratory failure, critical care

Adv Respir Med. 2021; 89: 23–29

Introduction

High-flow nasal oxygen (HFNO) is an innovative system that allows for delivering a high flow of heated and humidified gas up to 60 L/min^{-1} and 0.21–1.0 of FiO_2 through a special nasal cannula [1].

HFNO has been increasingly conducted to treat acute hypoxemic respiratory failure (AHRF) patients [2]. Recent studies have compared the efficacy and outcome of HFNO with conventional oxygen therapy in (ICU) settings; indicate that HFNO demonstrates beneficial effects in terms of better oxygenation, as well as reduction of respiratory rate and dyspnoea, resulting in improving patient comfort [2, 3].

Using of HFNO can avoid intubation in patients with respiratory failure by temporarily supporting ventilation during initial treatment, but many subjects failed and ultimately need intubation. Patients at risk for HFNO failure may benefit from early intubation or close observation. There is a limited prediction tool to help clinicians to determine clinical outcomes and success rate in patients treated with HFNO.

Duan *et al*. have derived and validated a scoring system which accurately predicts patients that would be at risk of noninvasive (NIV) failure such that the clinician can plan for the decision to implement invasive mechanical ventilation. In a derivation cohort of 449 patients, the authors used stepwise multivariable regression analysis

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DOI: 10.5603/ARM.a2021.0031
Received: 07.09.2020

ISSN 2451–4934

to identify variables predicting NIV failure. Each of the five parameters identified — heart rate, acidosis, consciousness (defined by the Glasgow Coma Scale [GCS] score), Oxygenation, and Respiratory rate (HACOR) — was assigned points, that added together to give an overall HACOR score. Hypothesizing that, the combination of these bedside variables has the potential to increase the predictive power for the prediction of NIV failure [4].

Hence, this study aims to assess a bedside scoring system based on five variables easily assessed in the emergency room (the HACOR score: heart rate, acidosis, consciousness, oxygenation, respiratory rate), to predict failure risk in patients with hypoxemic ARF treated with HFNO, the need for intubation. Hence the clinician can plan for the decision to implement invasive mechanical ventilation.

Material and methods

We conducted an observational prospective study in a 30-bed respiratory ICU at Assuit University Hospital between January 2018 and February 2020. This study was approved by the Faculty of Medicine Ethics Committee, Assiut University.

All the consecutive patients fulfilling the diagnostic criteria of acute hypoxic respiratory failure (AHRF) admitted to the ICU [5], and treated with HFNO were included after taking proper consent.

The inclusion criteria were age > 18 years, presence of clinical signs and symptoms of AHRF; defined by 1) recent dyspnea with a breathing frequency > 25 breaths/min and/or use of accessory muscles of respiration with pulmonary infiltrates on chest X-ray; 2) a PaO_2/FIO_2 of > 300 mm Hg recorded during spontaneous oxygen ventilation at 15 L/min^{-1} [5].

Patients who had an underlying chronic respiratory disease, who require emergent endotracheal intubation, Inability to protect airway (excess secretions, drowsy, or comatose patient), severe hemodynamic instability (patient on inotropic or vasopressor support), uncooperative patient, facial trauma or burns, facial surgery, or facial anatomical abnormality) were excluded [6].The demographic data of patients such as age, sex, the aetiology of acute respiratory failure, and presence of associated comorbid illnesses were recorded. The disease severity was calculated using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission to ICU [7].

Variables for HACOR score including; [heart rate (HR), respiratory rate (RR), consciousness (Glasgow Coma Scale (GCS), and arterial blood gases parameters collected at baseline during spontaneous ventilation with a conventional face mask and after 1, 12, 24, and 48 hours of initiation of HFNO.

These five variables were used to develop a risk-scoring system to predict HFNO failure. Each data point is assigned such that the sum represented the HACOR score. The HACOR score ranged between 0 to 25 points; higher score suggest an increased risk of HFNO failure [4]. We recorded the duration of HFNO therapy, length ICU and hospital stay and survival. Also, associated complications of HFNO were identified. Patients were followed up until death or hospital discharge.

High flow nasal oxygen settings

Patients who met inclusion criteria were treated by HFNO. The HFNO device (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand) was applied through a heated humidifier and delivered continuously through large-bore bi-nasal prongs. HFNO was initially administered with a gas flow rate of 50 $Lmin^{-1}$ and an FiO_2 of 1.0 and subsequently adjusted to maintain SpO_2 of 92% or more.

The following criteria were used for endotracheal intubation [ETI]:

loss of consciousness; hypotension (e.g, systolic arterial blood pressure < 90 mmHg or mean arterial blood pressure < 65 mm Hg) despite adequate fluid resuscitation, or need for vasopressors;

or two of the following criteria: frank worsening of respiratory distress, RR > 40 breaths/min, $SpO_2 \leq 92\%$ despite an FiO_2 of 1.0, and/or pH < 7.35. Failure was defined by the need for endotracheal intubation [5].

Statistical analysis

Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous variables were expressed as mean ± SD while nominal data was expressed in the form of frequency (percentage).

Chi-squared or Fisher's exact tests were used to determine the significance of differences in the observed data. A stepwise multivariate regression analysis performed to assess HFNO failure, and results presented as odds ratio (OR) with 95% confidence interval (CI). Diagnostic accuracy of

Table 1. Clinical characteristics of the patients at the enrolment

Variables	Success (n = 100)	Failure (n = 50)	P
Age [year]	65.89 ± 5.67	66.78 ± 10.54	0.09
Male sex	80 (80%)	30 (60%)	0.009
Smoking status			
Smoker	55 (55%)	28 (56%)	
Ex-smoker	25 (25%)	16 (32%)	0.06
Non-smoker	20 (20%)	6 (12%)	
Causes of acute respiratory failure			
Community acquired pneumonia	80 (80%)	40 (80%)	
Pulmonary embolism	15 (15%)	5 (10%)	
Cardiogenic pulmonary edema	2 (2%)	3 (6%)	0.51
Acute respiratory distress syndrome	3 (3%)	2(4%)	
Hypertension [n%]	40 (40%)	15 (30%)	0.32
Diabetes mellitus [n%]	32 (32%)	18 (36%)	0.42
C-reactive protein	26.4 ± 8.7	28.8 ± 12.3	0.321
LDH	442 ± 321	657 ± 432	0.001
APACHE-II score	13.77 ± 3.68	19.78 ± 4.09	0.001
HACOR score	5.56 ± 2.09	7.50 ± 1.11	0.001

Data expressed as frequency (percentage), mean (SD). HFNO — high flow nasal oxygen; LDH — lactate dehydrogenase; APACHE-II — acute physiology and chronic health evaluation; HACOR — heart rate, acidosis, consciousness, oxygenation, and respiratory rate

HACOR scale in the prediction of failed HFNO was determined with a ROC curve. Level of confidence was kept at 95% and hence, the P-value was significant if < 0.05.

Results

150 patients with acute hypoxemic respiratory failure, who were receiving HFNO, were enrolled in the study, out of them 100 (66.7%) subjects had successful HFNO while 50 (33.3%) patients had failed HFNO. Patient's clinical data were presented in Table 1. There were no significant differences found in age, sex, and aetiology of respiratory failure at the time of admission. Patients who failed HFNO had significantly higher LDH, APACHE-II and HACOR score.

Changes of physiological parameters between baseline T0 (on the initiation of HFNO), the first hour after enrolment (T1) and after 24 hours (T2) in nasal oxygen success and failure groups are shown in Table 2.

One hour after the enrolment (T1), HR, and RR improved in success group as compared to failure group (111 ± 16 *vs* 120 ± 20 beats/minute, 29 ± 12 *vs* 34 ± 14 breath/minute), respectively. Improvement was maintained after 24 hours of therapy (T2). There was also improvement in PaO_2/FiO_2 after one hour in success group (185.58 ± 58.5 *vs* 155.07 ± 52.7), which was maintained after 24 (201.53 ± 66.9 *vs* 175.6 ± 63.1) hours of therapy. No difference was found in blood pressure and $PaCO_2$.

A summary of HACOR scores at different time point from the initiation of HFNO treatment to 48 h of HFNO is shown in Table 3. Patients with HFNO failure had a higher HACOR score at initiation and after 1, 12, 24 and 48 hr than those with success group. Before intubation, the highest value of the HACOR score was reached in patients with HFNO failure.

As presented in Table 4, the predictors for failure of HFNO were HACOR score (odds ratio = 4.44, 95% confidence interval = 3.09–8.07; P < 0.001) and APACHE-II score (odds ratio = 1.43, 95% confidence interval = 2.01–5.78; P < 0.001) with adjusted R^2 was 0.65.

The predictive power of HFNO failure diagnosed by HACOR score is summarized in Table 5. After 1 hr of HFNO assessment, the area under the receiver operating characteristic curve was 0.86, showing good predictive power for failure. It was noticed that using HACOR score at cut off point > 6 had 81.2% sensitivity, 91% specificity, 92.5% positive predictive value, and 71.4% negative predictive value for prediction of HFNO failure with a diagnostic accuracy was 85%. Moreover, the overall diagnostic accuracy exceeded 87% when the HACOR score was assessed at 1, 12, 24 or 48 hr of HFNO.

Table 2. Comparisons of physiological parameters between high flow nasal oxygen success and failure groups

	Success (n = 100)	Failure (n = 50)	P
SBP [mm Hg]			
Baseline (T0)	120.7 ± 13.8	120.7 ± 12.1	0.32
After one hour (T1)	123.5 ± 16.5	121.5 ± 14.5	0.43
After 24 hours (T2)	124.5 ± 18.9	123.5 ± 16.9	0.61
DBP [mm Hg]			
Baseline (T0)	72.3 ± 12.7	70.9 ±12.4	0.36
After one hour (T1)	76.2 ± 14.5	73.2 ± 12.8	0.31
After 24 hours (T2)	76.2 ±13.7	76.6 ± 14.0	0.34
Heart rate [beat/minute]			
Baseline (T0)	124 ± 22	123 ± 23	0.32
After one hour (T1)	111 ± 16	120 ± 20	0.01
After 24 hour (T2)	98 ± 13	110 ± 18	0.01
RR [breath/minute]			
Baseline (T0)	34 ± 14	33 ± 16	0.321
After one hour (T1)	29 ± 12	34 ± 14	0.001
After 24 hours (T2)	22 ±10	30 ±13	0.001
pH^+			
Baseline (T0)	7.39 ± 0.11	7.38 ± 0.10	0.04
After one hour (T1)	7.40 ± 0.09	7.38 ± 0.09	< 0.001
After 24 hour (T2)	7.43 ± 0.08	7.39 ± 0.10	0.01
PaO_2/FiO_2			
Baseline (T0)	144.7 ± 56.8	139.8 ± 44.5	< 0.001
After one hour (T1)	185.58 ± 58.5	155.07 ± 52.7	< 0.001
After 24 hours (T2)	201.53 ± 66.9	175.6 ± 63.1	< 0.001
$PaCO_2$			
Baseline (T0)	38.3 ± 13.7	38.9 ±14.4	0.51
After one hour (T1)	39.2 ± 12.6	38.2 ± 12.8	0.42
After 24 hours (T2)	40.0 ±9.7	37.6 ± 13.0	0.21
GCS			
Baseline (T0)	14.2 ± 1.4	14.3 ± 1.2	0.32
After one hour (T1)	14.4 ± 1.2	14.5 ± 1.4	0.23
After 24 hours (T2)	14.5 ±1.2	14.1 ±1.1	0.41

Data expressed as mean (SD). P value was significant if < 0.05. (T0) — at initiation of HFNO; SBP — systolic blood pressure; DBP — diastolic blood pressure; $PaCO_2$ — arterial carbon dioxide tension; FiO_2 — fraction of inspired oxygen; GCS — Glasgow Coma Scale

Table 3. HACOR score at different time point

Time points	Success (n = 100)	Failure (n = 50)	P value
Initiation of HFNO	4.8 ± 2.3	7.4 ± 3.4	0.001
After 1 hour	2.5 ± 2.2	7.5 ± 3.7	0.001
After 12 hours	2.0 ± 2.1	8.3 ± 4.1	0.001
After 24 hours	1.6 ± 1.7	8.1 ± 4.3	0.001
After 48 hours	1.3 ± 1.4	8.4 ± 4.1	0.001
Intubation	—	9.5 ± 4.3	—

HFNO — high flow nasal oxygen; HACOR — heart rate, acidosis, consciousness, oxygenation, and respiratory rate

Table 4. Predictors of failure of HFNO

Predictors	OR	95% CI	P value
APACHE-II	1.43	1.01–3.78	< 0.001
HACOR	4.44	3.09–8.07	< 0.001
LDH	1.21	1.11–2.03	0.324
C- reactive protein	1.01	0.9–1.9	0.541
Variables after 1 hour of HFNO			
$pH^+ \geq 7.35$	2.32	1.3–3.2	0.432
$PaO_2/FiO_2 \geq 200$	2.03	1.2–3.6	0.02

OR — odds ratio; CI — confidence interval; LDH — lactate dehydrogenase; APACHE-II — acute physiology and chronic health evaluation; HFNO — high flow nasal oxygen; HACOR — heart rate, acidosis, consciousness, oxygenation, and respiratory rate

Table 5. Predictive power of HACOR score assessed at 1, 12, 24, and 48 hours in prediction of failed HFNO

Indices	1 h	12 h	24 h	48 h
		Cut off point > 6		
Sensitivity [%]	81.2	78.2	75.4	75.2
Specificity [%]	91	90	88	88
Positive predictive value [%]	92.5	90.2	91.3	91.1
Negative predictive value [%]	71.4	72.2	70.4	70.2
Diagnostic accuracy [%]	85	84	85	87
AUC [95% CI]	0.86 (0.84–0.90)	0.84 (0.82–0.90)	0.82 (0.80–0.88)	0.83 (0.82–0.86)

HACOR — heart rate, acidosis, consciousness, oxygenation, and respiratory rate; AUC — area under the curve of receiver operating characteristics; CI — confidence interval

Table 6. Mortality rate, length of stay and incidence of complications associated with HFNO

	Success (n = 100)	Failure (n = 50)	P
Duration of high-flow nasal oxygen treatment [days]	4.1±1.3	3.5 ± 2.5	0.229
Length of ICU stay [days]	4.7 ± 2.22	12.2 ± 3.30	0.001
Length of hospital stay [days]	8.2 ± 3.2	15.1 ± 5.1	0.001
Mortality at day 28 [n %]	3 (3%)	7 (14%)	0.01
In-hospital mortality, n° [%]	3 (3%)	12 (24%)	0.001
Complications associated with HFNO			
Gastric distension	10 (10%)	24 (48%)	0.001

Data expressed as mean (SD), frequency (percentage)

The mean lengths of ICU and hospital stay were significantly higher in HFNO failure in comparison to the success group Table 6. In-hospital mortality rate was higher in HFNO failure patients compared to success group [12 (24 %) *vs* 3 (3%); p = 0.008] respectively. The only reported complication associated with HFNO was gastric distension in 24 (48%) failure patients *vs* 10 (10 %) in success groups (p = 0.001; Table 5).

Discussion

HFNO has been gaining traction as an initial treatment in patients with acute hypoxemic respiratory failure. High-flow nasal oxygen was associated with an increased degree of comfort, a reduction in the severity of dyspnea, and a decreased respiratory rate [8]. However, many patients fail HFNO and ultimately need intubation. Early intubation or close observation can benefit patients at risk for HFNO failure [9]. Hence, we evaluate the diagnostic performance of the HACOR score to predict HFNO failure in patients with hypoxemic respiratory failure admitted to a respiratory ICU to avoid delaying intubation and decreased hospital mortality.

This score takes into account heart rate, acidosis, consciousness, oxygenation, and respiratory rate. Because the parameters in the HACOR score are simple bedside measurements, it can serve as a rapid and useful tool for predicting HFNO failure. The current study revealed that 33% of patients ultimately failed HFNO and predicting the need for intubation. Moreover, we noted that HACOR score at the first hour of initiation and a cutoff point of 6 has a sensitivity of 81% and a specificity of 91%, with a good diagnostic accuracy 85%.

In agreement with our results, a study conducted by Duan et al. who assessed the usefulness of HACOR scale for prediction of NIV failure in patients with acute hypoxemic respiratory failure. The authors found that HACOR score of > 5 had a higher risk of NIV failure. Thus, recognition of high risk patients and early intubation may presumably reduce hospital mortality [4].

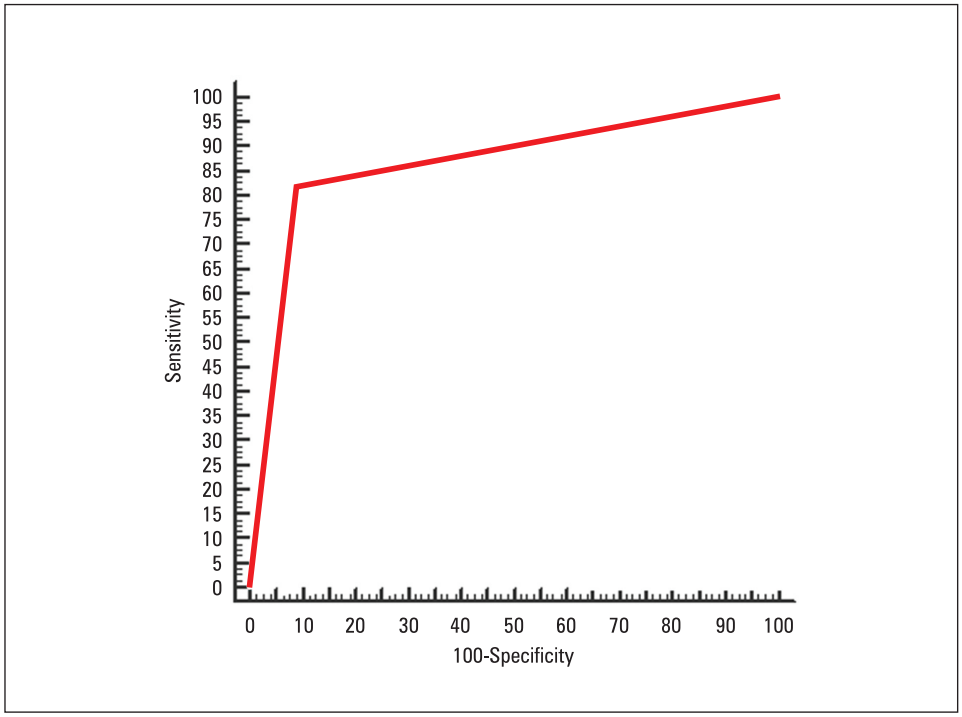

Figure 1. Accuracy of HACOR score in prediction of failed high flow nasal oxygen

Also, Duan *et al.* studied a novel and practical risk-scoring system to predict noninvasive ventilation (NIV) failure, using bedside clinical variables; 500 chronic obstructive pulmonary disease (COPD) patients were enrolled in a derivation cohort. The authors demonstrated that NIV failure rate was 18.8%, 18.9% and 8.9% in derivation, internal-validation and external-validation cohorts, respectively. In addition, the HACOR score had good diagnostic power for NIV failure when it was assessed at 1 hr of NIV initiation [10].

The present study, the overall mortality was 24% in patients with HFNO failure. Therefore, early identification of HFNO failure and intubation is a promising strategy to improve outcome. Recently, in a FLORALI study, a randomized trial consisting of 310 patients with acute hypoxemic respiratory failure allocated to HFNO and standard oxygen therapy. The authors noted that intubation and mortality rate was significantly lower in the HFNO group than in standard oxygen [11].

The points of strength in this study; we assessed the performance of a very useful and a newly developed score in hypoxemic subjects using HFNO. This score has not been previously addressed in High flow nasal oxygen aiming to improve the clinical management and patient's outcome. Limitation in this study, we didn't assess mean flow and FIO_2 used by HFNO in the studied population.

Conclusions: HACOR is a newly developed scoring system which takes into account heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict failure of HFNO in patients with hypoxemic respiratory failure. The score appears to be an effective way of predicting HFNO failure. This could be a promising tool for the clinician to recognize and detect early failure; to ensure that there is no delay in intubation. Patients with a higher HACOR score are more likely to experience failed HFNO. With a cutoff value < 6, the diagnostic accuracy of the HACOR scale was high. Thus, the HACOR score has been identified as a useful tool to pinpoint patients that will benefit from such intervention.

Ethical approval and consent to participate

The research received ethical approval from the Ethics Committee of the Faculty of Medicine. The data were confidential. All procedures in the current study were performed according to the ethical standards of the institutional research committee.

Acknowledgements

We thank all the staffs and patients in ICU who participate in data collection.

Institutional review board statement

This study was approved by the Faculty of Medicine Ethics and Scientific Research Committees.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

None declared.

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Vascular patterns on narrow band imaging (NBI) video bronchoscopy of lung cancer patients and its relationship with histology: an analytical cross-sectional study

Abstract

Introduction: Narrow band imaging (NBI) video bronchoscopy provides better visualisation of submucosal vascular patterns in malignant airway lesions compared to white light bronchoscopy. This analytical cross-sectional study was aimed to look for any relationship between these NBI vascular patterns and the histologic type of lung cancer.

Material and methods: After screening 78 patients with suspected lung cancer, 53 subjects underwent video bronchoscopy. Thirty-two patients showing abnormal bronchial mucosa or endobronchial growth with any of the NBI vascular patterns on bronchoscopy were enrolled in the study. These abnormal areas were then biopsied and sent for histologic examination.

Results: NBI bronchoscopy revealed a dilated tortuous vascular pattern in 54.8% of the patients, a non-specific pattern in 32%, a dotted pattern in 9.7% and an abrupt ending vessels pattern in 3.2% of the patients. We did not find any statistically significant relationship between a dilated tortuous pattern and squamous-cell carcinoma ($p = 0.48$), adenocarcinoma ($p = 0.667$) or small-cell carcinoma ($p = 1$); between a dotted pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 0.54$) or small-cell carcinoma ($p = 1$), and between an abrupt ending capillary pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 1$) or small-cell carcinoma ($p = 1$).

Conclusion: No relationship exists between NBI vascular patterns and the histology of lung cancer. Endobronchial lesions showing any vascular pattern on NBI needs to be adequately sampled for proper histologic and molecular studies in lung cancer patients.

Key words: bronchoscopy, histology, lung cancer, narrow band imaging

Adv Respir Med. 2021; 89: 30–36

Introduction

Among all cancers, lung cancer is the most common cancer across the world, both in terms of incidence and mortality, accounting for 2.1 million new cases and 1.76 million deaths in 2018 [1]. The World Health Organisation estimates that lung cancer deaths will continue to rise worldwide, largely as a result of an increase in global tobacco use, principally in Asia. Diagnostic bronchoscopic techniques have now become widely available for detection and staging of lung cancer. New tools such as autofluorescence imaging (AFI), narrow band imaging (NBI) and endobronchial ultrasound (EBUS) have found their place in many bronchoscopy suites. Angiogenesis and structural changes of the mucosa are the basic and hallmark lesions of neoplasia [2]. NBI uses two bandwidths of light; 390 to 445 nm (blue) light that is absorbed by superficial capillaries and 530 to 550 nm (green) light that is absorbed by blood vessels below the mucosal capillaries [3]. These wavelengths coincide with the peak absorption spectrum of oxyhaemoglobin and make blood vessels more pronounced. Studies have shown the utility of NBI by identifying capillary loop patterns in early diagnosis of oesophageal and gastric carcinoma [4, 5]. As far

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DOI: 10.5603/ARM.a2021.0014
Received: 1.10.2020

ISSN 2451–4934

as bronchoscopy is concerned, NBI is still a tool in search of proper indications. Shibuya *et al.* [6] first described the pathological patterns on bronchial mucosa that are known as Shibuya's descriptors (dotted, tortuous and abrupt ending vessels). We conducted this study to find whether any relationship exists between different NBI vascular patterns and the histology of lung cancer.

Material and methods

This was an analytical cross-sectional study conducted in the department of pulmonary medicine at the All India Institute of Medical Sciences, Jodhpur, India over a period of twelve months. The study protocol was approved by the institutional ethics committee (project no. AIIMS/RES/(02)/2015-16/068). Informed written consent was obtained from each participant before enrolment in the study.

Inclusion criteria

Lung cancer patients in whom bronchoscopy showed endobronchial lesions with different NBI vascular patterns.

Exclusion criteria

Patients with endobronchial growth or abnormal mucosa not showing any enhanced vascularity on NBI mode, uncooperative patient, refractory hypoxaemia, hypercarbia, hypotension, recent/unstable angina, myocardial infarction within last six weeks, arrhythmias, bleeding disorders, uraemia and platelet count < 50,000/mm^3.

Methodology

Video bronchoscopy was performed using a flexible video bronchoscopy system (Olympus EVIS EXERA III model BF-1TH190 video bronchoscope, CLV-190 light source, CV-190 video processor and SONY LMD-2451MD high definition TV monitor). All patients were monitored using standard monitoring and alert systems during each procedure. The bronchial tree of each patient was examined by two experienced bronchoscopists, first, under white light (WL), and then, under narrow band imaging (NBI) mode. An abnormal appearance under NBI mode was defined as any area looking abnormal either by blood vessel concentration or appearance as per Shibuya's descriptors. Based on consensus among the two bronchoscopists, a particular NBI pattern was labelled for each patient. In situations where consensus could not be attained, opinion of a third bronchoscopist was taken — who reviewed and labelled the NBI pattern after watching the stored high-definition video of the procedure. The target biopsy sites were areas showing an endobronchial growth and/or abnormal appearing mucosa as seen by both WL and NBI. A minimum of three biopsies were taken from one site using biopsy forceps (Olympus rotatable biopsy forceps; model no. FB-55CR-1). Different forceps were kept to sample a different abnormal area in the same patient to avoid cross-contamination. Biopsy specimens were sent for histologic examination in a 10% formal saline solution. Immunohistochemistry was performed whenever required. Dysplastic and cancerous lesions were classified according to the WHO classification system [7].

Statistical analysis

Continuous variables were presented as mean ± SD; categorical variables were expressed in actual numbers and percentages. Fischer's exact test was used to compare two categorical variables. All statistical analyses were performed with SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

We screened 78 patients, out of whom 46 persons were excluded. Among those who were excluded, 21 patients did not show enhanced vascularity on NBI video bronchoscopy, 7 individuals had platelet count of less than 50,000/mm^3 and 18 patients had unstable cardiovascular status. There were 32 patients who were finally enrolled in the study. One person was excluded from analysis as histology revealed tuberculosis. The results of 31 patients were analysed. A flow chart of the study patients is shown in Figure 1.

The mean age of the patients was 60.3 ± 12.5 years. The majority of the subjects were males (90.3%) and smokers (87.1%). The most commonly encountered lung malignancy was squamous-cell carcinoma (58.1%), followed by adenocarcinoma (22.3%) and small-cell carcinoma (19.4%). Cough was the most common symptom (64.5%), followed by dyspnoea (58.1%), weight loss (51.6%), chest pain (48.4%) and haemoptysis (22.6%). Computed tomography (CT) of the chest showed mass-lesion (90.3 %), pulmonary nodules (12.9%), pleural effusion (12.9%), superior vena cava (SVC) syndrome (6.5%) and mediastinal adenopathy (35.5 %). Baseline characteristics of the patients are mentioned in Table 1.

A dilated tortuous vascular pattern seen in 54.8% of the study subjects was the commonest

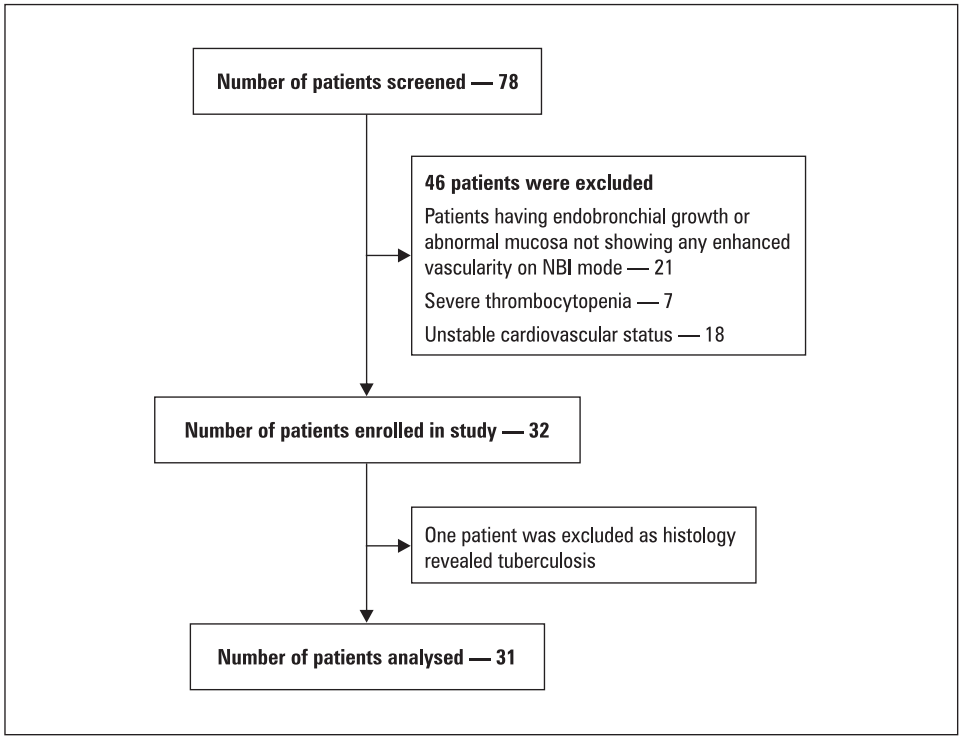

Figure 1. Flow chart of patients included in the study

Table 1. Baseline characteristics

Age, years [mean ± SD]	**60.32 ± 12.5**
Gender	N [%]
Male	28 (90.3)
Female	3 (9.7)
Symptoms	
Cough	20 (64.5)
Dyspnea	18 (58.1)
Weight loss	16 (51.6)
Chest pain	15 (48.4)
Hemoptysis	7 (22.6)
Smoking status	
Smoker	27 (87.1)
Never smoker	4 (12.9)
Comorbidities	
COPD	15 (48.4)
Diabetes mellitus	3 (9.7)
Systemic hypertension	3 (9.7)
Ischaemic heart disease	5 (16.1)
CT chest findings	
Mass	28 (90.3)
Pulmonary nodules	4 (12.9)
Pleural effusion	4 (12.9)
SVC syndrome	2 (6.5)
Mediastinal adenopathy	11 (35.5)

observed pattern on NBI. A non-specific pattern was observed in 32% of the cases, a dotted pattern in 9.7% and abrupt ending vessels in 3.2% of the cases. A dilated tortuous vascular pattern was seen in 61% of the cases of squamous-cell carcinoma, 42.9% of the cases of adenocarcinoma and 50% of the cases of small-cell carcinoma. A non-specific pattern was seen in 50% of the cases of small-cell carcinoma, 42.8% of the cases of adenocarcinoma and 22% of the cases of squamous-cell carcinoma. An abrupt-ending pattern was seen only in one patient of squamous-cell carcinoma. A dotted pattern was seen in 14% of the cases of adenocarcinoma and 11% of the cases of squamous-cell carcinoma. Figure 2 shows the frequency of NBI patterns in the study patients with different histological types of lung cancer. Few of these NBI patterns and the corresponding histopathology images observed in our patients are depicted in Figure 3.

In suspecting squamous-cell carcinoma, the sensitivity and specificity of a dilated tortuous pattern was 61% and 53.8%, respectively, and for a dotted pattern, it was 11% and 92%, respectively. For adenocarcinoma, the sensitivity and specificity of a dilated tortuous pattern was 42.8% and 41.6%, respectively, and for a dotted pattern, it was 14.2% and 91.6%, respectively. Sensitivity and specificity of a dilated tortuous pattern for small-cell carcinoma was 50% and

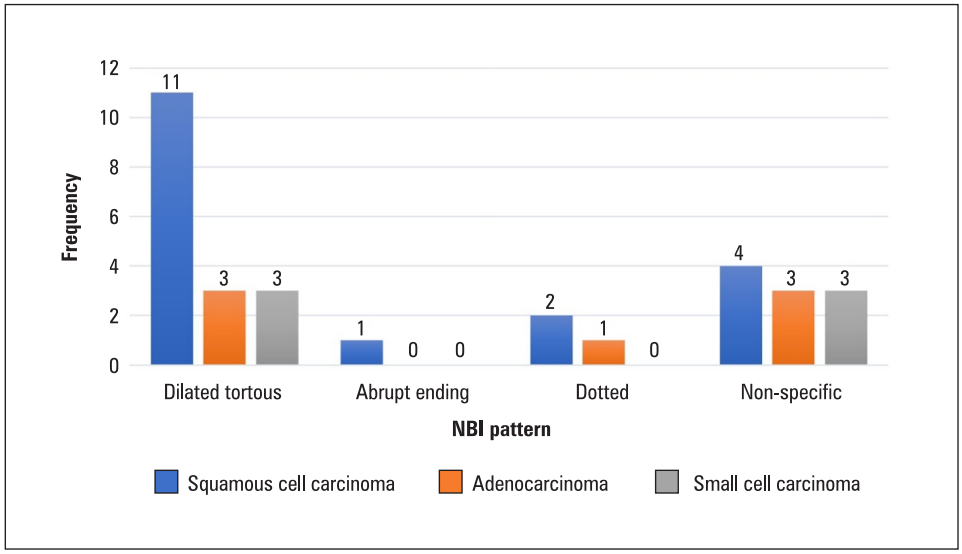

Figure 2. Frequency of various vascular patterns observed on NBI in various histological types of lung cancer

45.8%, respectively. Sensitivity, specificity, positive predictive value and negative predictive values of various vascular patterns observed on NBI in identifying various histological types of lung cancer are shown in Table 2.

There was no statistically significant relationship between a dilated tortuous pattern and squamous-cell carcinoma ($p = 0.48$), adenocarcinoma ($p = 0.667$) or small-cell carcinoma ($p = 1$). There was no statistically significant relationship between a dotted pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 0.54$) or small-cell carcinoma ($p = 1$). There was no statistically significant relationship between an abrupt-ending capillary pattern and squamous-cell carcinoma ($p = 1$), adenocarcinoma ($p = 1$) or small-cell carcinoma ($p = 1$).

Discussion

Despite improved imaging capability of video bronchoscopy, early central lung cancers are difficult to detect solely with white light bronchoscopy as these lesions are usually small, relatively flat with subtle endobronchial changes [8]. Enhanced magnification, improved image quality and better visual contrast have been an area of ongoing research and implementation in the field of endoscopy to differentiate normal from abnormal areas. NBI bronchoscopy has been found to be useful in detecting increased vascularisation and complex vessel networks in the bronchial mucosa ranging from tortuous vessels, dotted vessels to spiral or screw type vessels during the process of carcinogenesis [9]. A combination of high magnification video bronchoscopy with advanced imaging techniques like AFI and NBI has shown promising results [10–12]. A significant association was seen between dotted vessels by NBI-B1 imaging and tissues confirmed pathologically as angiogenic squamous dysplasia [10]. The first study to specifically look for any relation between different NBI patterns and histology of lung cancer was done by Zaric *et al.* [13]. They found that a dotted visual pattern of blood vessels was highly suggestive of adenocarcinoma ($p < 0.0001$), while a tortuous and abrupt-ending blood vessels was significantly suggestive of squamous-cell lung cancer ($p < 0.0001$). This is in contrast to the findings of our study which found no statistically significant relationship between any NBI pattern and the histology of lung cancer. The authors also mention about situations when they faced difficulty in attaining consensus on the NBI pattern but ultimately labelled these pathological patterns based solely on Shibuya's descriptors. This is the second difference from our study where we observed a non-specific NBI pattern in about one-third of the patients not fulfilling the pattern based on Shibuya's descriptors. This pattern consisted of one or two superficial vessels seen over some part of the entire endobronchial growth or abnormal mucosa. Among those whom we screened, 26.9% of the patients actually did not show any increased vascularity or pattern over the endobronchial lesion on NBI mode and were thus excluded from the study as depicted in Figure 1.

After searching PubMed and Google with keywords like histology, narrow band imaging, relation and bronchoscopy, we could find only one

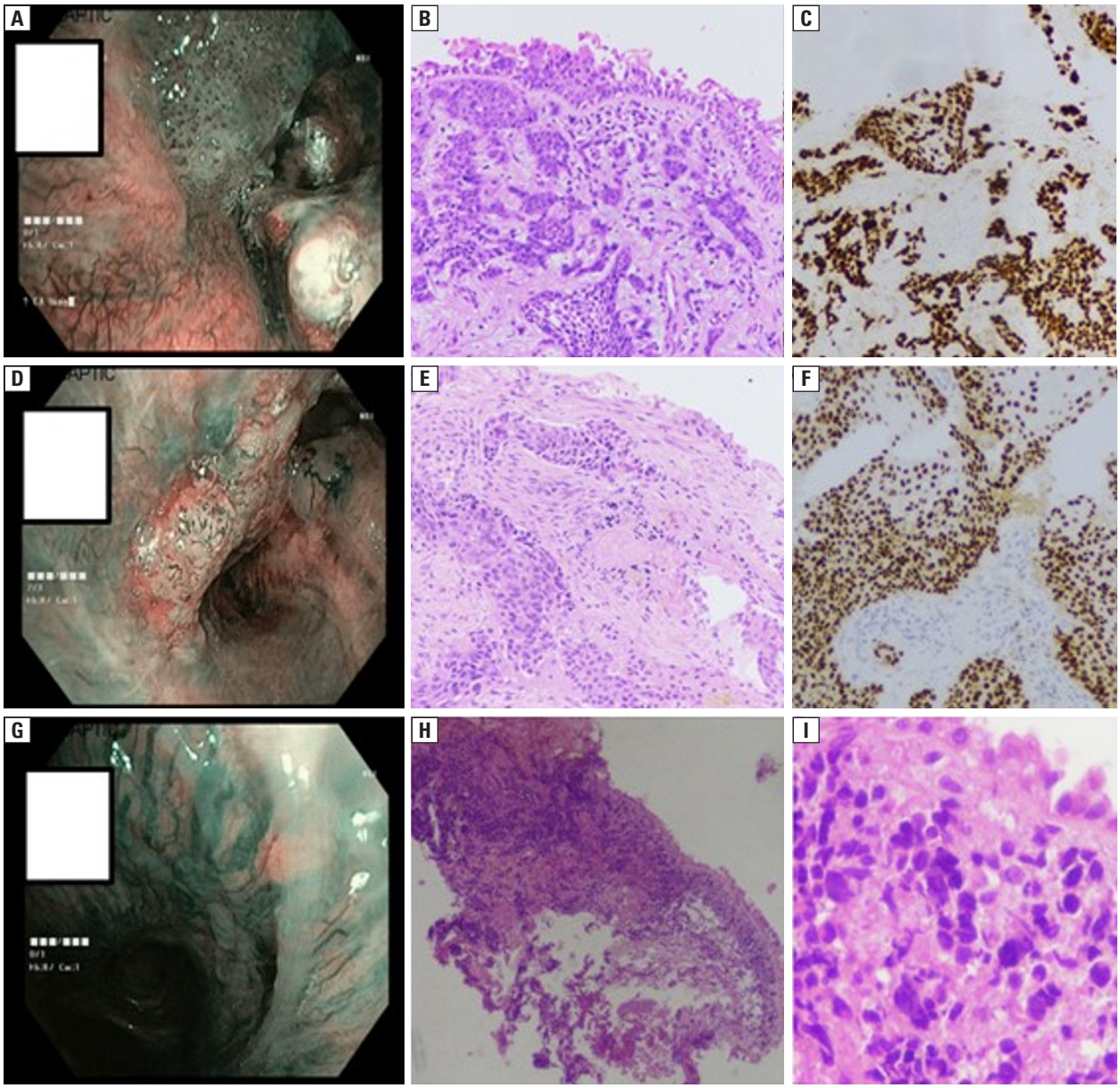

Figure 3. Images of few NBI vascular patterns observed in our patients and the corresponding histopathology slides. **A.** NBI image showing dotted pattern; **B.** Hematoxylin and eosin stained slide of the patient (A), 10×, showing strands and sheets of invasive tumour with squamoid differentiation; **C.** Immunohistochemistry (IHC) for p63 showing intense immunoreactivity; **D.** NBI image showing abrupt ending blood vessels; **E.** Hematoxylin and eosin stained slide of the patient (D), 10×, showing strands and sheets of invasive squamous cell carcinoma; **F.** IHC for p63 showing intense immunoreactivity; **G.** NBI image showing dilated tortuous blood vessels; **H.** Hematoxylin and eosin stained slide of the patient (G), 4×, showing small cell carcinoma; **I.** Hematoxylin and eosin stained slide of the patient (G),10×, showing small cell carcinoma beneath ciliated columnar epithelium

article by Zaric *et al*. [13] that mentions about the relation between different NBI vascular patterns and histology of lung cancer. The majority of clinical research on NBI technology has been in gastroendoscopy. This is due to difference in the luminal vascular anatomy of the airway and digestive tract. The vascular supply of the gastrointestinal tract has an extensive intramural distribution which is well developed with plexuses in the different layers of the bowel wall [14]. The architecture of this prominent vascular network gets distorted in various pathological conditions, which gets detected relatively easier and in a much better way with the use of additional digital imaging technologies like NBI. Various studies in different gastrointestinal pathologies reveal the diagnostic accuracy and relationship of NBI patterns with the histologic diagnosis [15–17]. Unlike these studies, we did not find any relation between the NBI image of airway lesions and histology.

Table 2. Sensitivity, specificity, positive predictive value, negative predictive value of various vascular patterns observed on NBI in diagnosis of histological subtypes of lung cancer

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Fischer's exact test P value
Dilated tortuous in squamous cell carcinoma	61%	53.8%	64.7%	50%	0.48
Dotted pattern in squamous cell carcinoma	11%	92%	66.67%	42.8%	1
Dilated tortuous for adenocarcinoma	42.8%	41.6%	17.64%	71.4%	0.67
Dotted pattern for adenocarcinoma	14.2%	91.6%	33.33%	78.57%	0.54
Dilated tortuous pattern in small cell carcinoma	50%	45.8%	17.64%	78.57%	1

In a recent interesting study on mixed-type early gastric cancers, a fine network pattern was seen in differentiated-type-predominant and a corkscrew pattern was seen in undifferentiated--type-predominant mixed-type lesions [18]. The authors of this study concluded that a combination of these NBI findings with magnifying endoscopy and biopsy could actually change the clinical practice by reducing the number of additional surgeries because of incorrect diagnosis based solely on histology. Although the utility of NBI in detecting precancerous and cancerous lesions in the airways has been proven, our study has shown that it performs poorly in predicting the histology of a cancerous lesion.

We wish to highlight some of the strengths of this study. Firstly, the labelling of NBI vascular pattern was based on consensus. Secondly, we observed a non-specific NBI pattern which affected the results and conclusions of our study. The limitations of our paper are also worth mentioning. Being a single-centre study, despite observing many endobronchial lesions during bronchoscopies, we did not find any NBI abnormality in significant number of patients. This affected our actual sample size for the final analysis. Labelling of NBI patterns is subjective, so the authors feel that a large, multicentric study would help in looking at the reproducibility and variability of NBI assessment between bronchoscopists and finding the relevance of these patterns in malignant as well as benign airway lesions.

Conclusions

No relationship exists between vascular patterns observed on NBI video bronchoscopy and the histologic type of lung cancer. Any abnormality found during bronchoscopy on either WL or NBI, needs to be adequately sampled for proper histologic and molecular studies when suspecting lung cancer. An inconclusive histologic finding of a biopsy sample showing a specific NBI pattern does not obviate the need for repeat tissue sampling.

Conflict of interest

None declared.

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Miniforceps EBUS-guided lymph node biopsy: impact on diagnostic yield

Abstract

Introduction: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is the standard diagnostic method for sampling mediastinal and hilar lymph nodes. Non-diagnostic samples have led some pulmonologists to add a miniforceps biopsy (EBUS-TBFB) in order to increase diagnostic yield. Our study aims to analyze the impact of adding EBUS-TBFB to the EBUS-TBNA in cases where Rapid On-site Evaluation (ROSE) was negative for malignancy or was non-diagnostic.

Material and methods: This retrospective chart review included 91 patients who were aged 18–90 years old and underwent EBUS with both TBNA and TBFB between January 1, 2013 and July 1, 2018.

Results: There was no significant statistical difference in the diagnostic yield of TBNA *vs* TBFB with a McNemar value of 0.167, and this conclusion was the same when stratified by race, age and lymph node size. Using TBNA as a gold standard, the sensitivity and specificity of TBFB was 87% and 69%, respectively. Out of the non-diagnostic TBNA samples on ROSE and cell-block, subsequent TBFB resulted in additional pathologic diagnoses in 16% of cases, of which 67% were non-caseating granulomas. Furthermore, two additional malignant cases were identified by TBFB consisting of small cell carcinoma and non-Hodgkin's lymphoma.

Conclusion: In conclusion, TBFB is a useful adjunctive tool in the diagnosis of non-malignant conditions (i.e. granulomatous diseases) with the potential to spare the patient from more invasive surgical biopsies. Training of future fellows in performing TBFB in addition to TBNA should be strongly encouraged.

Key words: EBUS-TBNA, EBUS-TBFB, sarcoidosis, Rapid On-site Evaluation, ROSE

Adv Respir Med. 2021; 89: 37–42

Introduction

Since its introduction in 1983 [1, 2], transbronchial needle aspiration (TBNA) has been a minimally invasive procedure for the sampling of mediastinal lymph nodes using bronchoscopy. However, the TBNA technique, in its infancy, was underutilized by clinicians because of its "blind" nature without direct real time visualization. In 2002, with the introduction of the convex probe endobronchial ultrasound (CP-EBUS), clinicians were finally able to perform real-time endobronchial visualization for TBNA. By 2007, EBUS-TBNA had become the routine method utilized by pulmonologists for the sampling of mediastinal and hilar lymph nodes [1–3].

The diagnostic yield of EBUS-TBNA varies greatly based on pathology. High yields have particularly been seen in the staging and diagnosis of non-small cell lung cancer (NSCLC) [1, 4–7].

Diagnostics yield for mediastinal lymphadenopathy in conditions such as lymphoma and granulomatous disease, however, remain under investigation. With regard to sarcoidosis, results are divided, with some reports of obtaining sufficient tissue for analysis, while others frequently resort to more invasive techniques such as mediastinoscopy for diagnosis [6, 8, 9]. The

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DOI: 10.5603/ARM.a2021.0024
Received: 01.10.2020

ISSN 2451–4934

underlying reason for such variance in samples have been associated with the low tissue sample volume that is obtainable while using the standard 20–22–gauge needles for EBUS-TBNA.

The introduction of an additional biopsy using miniforceps (EBUS-TBFB) has been used to attempt to increase yield. Sample acquisition is performed through the initial hole made by the TBNA needle for obtaining diagnostic material from enlarged lymph nodes [6, 10–12]. Recent studies using TBFB for lymphadenopathy have shown improved yields; however, these studies have had their limitations that included lack of EBUS guidance, use of initial TBNA puncture site prior to performing TBFB, and/or Rapid On-site Evaluation (ROSE).

The use of the initial TBNA site as the entrance point for TBFB along with ROSE for both TBNA and TBFB sampling has been previously described to improve diagnostic yields with varying degrees of success. Our study aimed to analyze the impact of adding EBUS-TBFB to the EBUS-TBNA in cases where ROSE was deemed negative for malignancy or was non-diagnostic.

Material and methods

Data collection and patient inclusion

This study is a retrospective chart review of patients who underwent EBUS with both miniforceps biopsy and fine needle aspiration. Patients were eligible for analysis within age ranges of 18 to 90 years who had an EBUS procedure during the period from January 1, 2013 to July 2018. Data were collected only from those patients who underwent both EBUS-TBFB and EBUS-TBNA.

Exclusion criteria included any patient who had a diagnosis of cancer established with other testing modalities and any patient who did not have both EBUS with TBNA and miniforceps biopsy. Patients eligible for the chart review were identified from billing data. Data were collected by chart review from the electronic medical record eCare®.

Statistical analysis

Descriptive statistics were generated to characterize the study group. Categorical variables, such as sex, were described using frequency distributions. Continuous variables were described as the mean with standard deviation for normally distributed variables, and mode with an interquartile range for non-normally distributed variables. Sensitivity, specificity, positive predictive value, and negative predictive value were computed. Univariable analysis was done using the chi-squared test, Student's t-test, and analysis of variance. Multivariable regression was done using logistic regression. The diagnostic yields of EBUS-TBNA and a combined approach with EBUS-TBNA and EBUS-TBFB were compared with the McNemar test for dependent samples. $p < 0.05$ was considered statistically significant. All data were analyzed using SPSS v. 25.0, and a p-value of 0.05 or less indicated statistical significance.

This study was approved by the Ascension St. John Hospital Institutional Review Board.

Endobronchial ultrasound-guided transbronchial needle aspiration

A real-time EBUS scope (Model: Olympus BF-UC180F, Japan) was used in all cases. The EBUS scope uses a 6.9 mm outer diameter, a 2.0 mm working channel, and 30-degree oblique forward-viewing scope. A linear 7.5hz ultrasound transducer with 50 mm penetration capability was used for the visualization of each lymph node.

TBNA was performed using a 21-guage needle (Model: Olympus ViziShot EBUS-TBNA NA-201SX-4022, Japan). If visualization of adjacent vasculature was needed during TBNA, an integrated color Doppler US was utilized on a case-by-case basis under the discretion of the interventional pulmonologist. A minimum of 3 to 5 passes were performed at each station.

Endobronchial ultrasound-guided transbronchial forceps biopsy

For all TBFB biopsies, Boston Scientific "SpyBite biopsy" Forceps (Model: M00546270 USA) were used. After obtaining an EBUS-TBNA sample which was found to be non-diagnostic on initial ROSE, the sampled lymph node was evaluated by EBUS-TBFB. Our method of EBUS-TBFB for each sample was similar to that which had been previously described by Chrissian *et al.* [10]. While at the TBNA site, and after obtaining a sample via the jabbing technique, forceps were advanced to the orifice of the TBNA puncture site by direct visualization and confirmed via ultrasound (Figures 1, 2). When visualization of the puncture site was limited, an approximation of the initial angle of TBNA sampling was performed under ultrasound (Figure 2). Closed forceps were advanced into the lymph node through the initial puncture site at the same angle as our TBNA. The forceps were subsequently opened and advanced to obtain a sample against tissue resistance under continuous EBUS surveillance. Finally, the forceps were closed and withdrawn through the working

channel. In patients in whom TBNA or TBFB was unrevealing, the diagnosis was confirmed through surgical biopsy specimens of the mediastinum via mediastinoscopy, video-assisted thoracic surgery (VATS), or via a follow-up computerized tomography (CT) scan of the thorax.

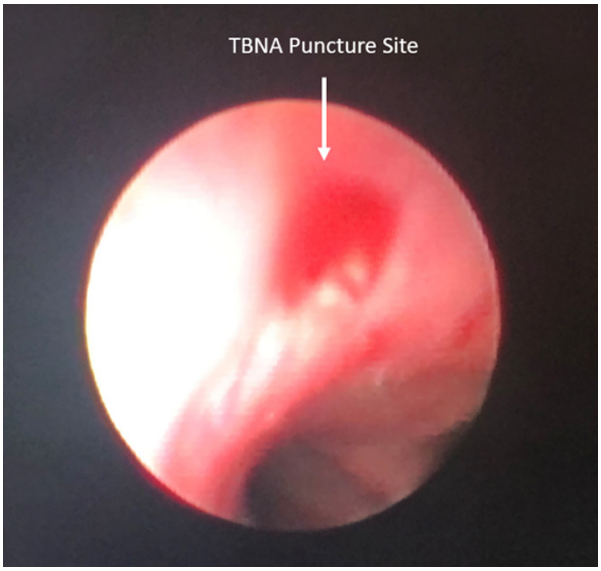

Figure 1. Direct visualization of the initial transbronchial needle aspiration puncture site prior to transbronchial forceps biopsy

Rapid on-site analysis

Fine needle aspiration samples obtained by TBNA were transferred onto glass slides, air dried, and subsequently mounted by the on-site pathologist. Rapid on-site cytology was performed and each of the three TBNA samples were processed individually by the on-site pathologist. TBFB samples were obtained only when TBNA samples were deemed non-diagnostic on initial ROSE. Tissue samples which were obtained from TBFB were placed in formalin immediately after acquisition. For TBNA samples, the Diff-Quick (Diff-Quik) Staining Protocol and light microscopy was performed by board certified on-site cytopathologists. Samples were subsequently sent for cell block analysis after ROSE was completed.

Post-operative monitoring

All patients were observed in the post-operative monitoring unit for 2 hours after the procedure. All patients with concerning post-procedur-

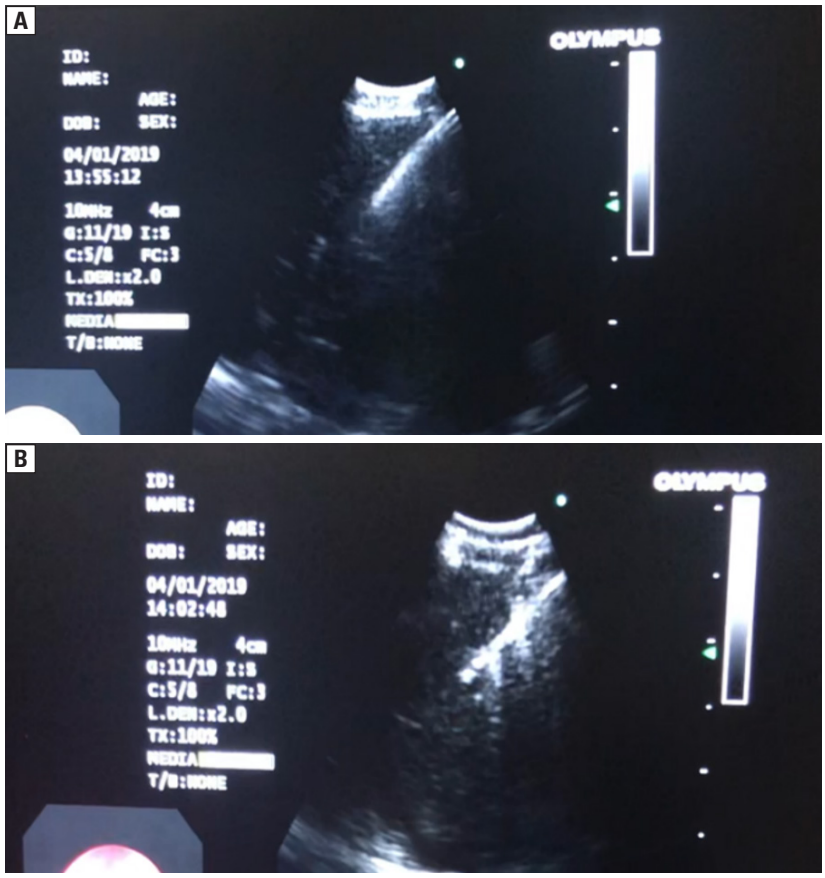

Figure 2. Correct angling of forceps within the lymph node. **A**. The original angle of transbronchial needle aspiration (TBNA); **B**. Angling of the transbronchial forceps biopsy to approximate the same approach as our initial TBNA with the forceps in an open position

al symptoms (i.e. chest pain, dyspnea, hemoptysis, or persistent tachycardia) underwent chest X-ray.

Results

The study group consisted of 91 patients who met the inclusion criteria. The mean age of patients in the study at the time of procedure was 57 ± 12.31 years old. 51.5% (47) were male and 58.2% were white (53). The mean BMI of patients was 28.2 ± 7.27. Subsequent lymph node biopsies were performed at stations shown in (Table 1) by the interventional pulmonologist with the most frequent locations being subcarinal (station 7), lower paratracheal (station 4), and interlobar (station 11). The mean lymph node size per CT imaging was 28.5 mm with a range from 6.0 to 90.0 mm.

ROSE was diagnostic of the final pathology in 39 cases (42.9%). There was no significant statistical difference in the diagnostic yield of TBNA *vs* TBFB with a McNemar value of 0.115. This conclusion was the same when stratified by age and size of lymph nodes with respective t-test values of 0.954, 0.651, and 0.139, as well as by gender and race with respective chi-square values of 0.923 and 0.280. Using TBNA as a gold standard, the sensitivity and specificity of TBFB was 87% (confidence interval of 73.74% to 95.06%) and 69% (confidence interval of 53.35% to 81.83%), respectively. Out of non-diagnostic TBNA samples on ROSE and cell-block, subsequent TBFB sampling resulted in additional pathologic diagnoses in 16% of cases, of which 67% were non-caseating granulomas. Furthermore, two additional malignant cases were identified via TBFB which were not diagnosed on TBNA. These consisted of small cell carcinoma and non-Hodgkin's lymphoma.

Table 1. Frequency of mediastinal and hilar lymph nodes examined by TBNA and TBFB

Station name	Station no	Frequency
Subcarinal	7	67
Lower paratracheal	4	60
Interlobar	11	44
Hilar	10	6
Lobar	12	4
Upper paratracheal	2	2

TBNA — transbronchial needle aspiration; TBFB — transbronchial forceps biopsy

Complications

No clinical complications were observed during EBUS-TBNA, EBUS-TBFB, or induction of anesthesia. All patients with concerning post-procedural symptoms (i.e. chest pain, dyspnea, hemoptysis, or persistent tachycardia) underwent chest X-ray without any complications being reported.

Discussion

In our study, we investigated the clinical utility provided by the addition of EBUS-TBFB

Table 2. Diagnostic yield of EBUS-TBNA, EBUS-TBFB, and ROSE

		EBUS-TBNA	EBUS-TBFB	Combined	ROSE
Overall diagnostic yield		54/91 (59.3%)	46/91 (50.5%)	60/91 (65.9%)	39/91 (42.9%)
Malignant		29			29
Small cell cancer		9/11	9/11		
NSCLC — total		20/20	11/20		
	Squamous cell cancer	5/5	4/5		
	Adenocarcinoma	14/14	6/14		
	Large cell carcinoma	1/1	1/1		
Benign					10
	Sarcoidosis	19/23	22/23		
Other*		6/6	6/6		
EBUS-TBFB *vs* EBUS-TBNA using the McNemar test					
Combined *vs* EBUS-TBNA using the McNemar test					

*Other: final diagnosis showing *Seminoma*, *Mycobacterium tuberculosis*, *Lymphangioma*, and bronchus-associated lymphoid tissue. EBUS-TBNA — endobronchial ultrasound-guided transbronchial needle aspiration; EBUS-TBFB — endobronchial ultrasound-guided transbronchial forceps biopsy; NSCLC — non-small-cell lung carcinoma; ROSE — Rapid On-site Evaluation

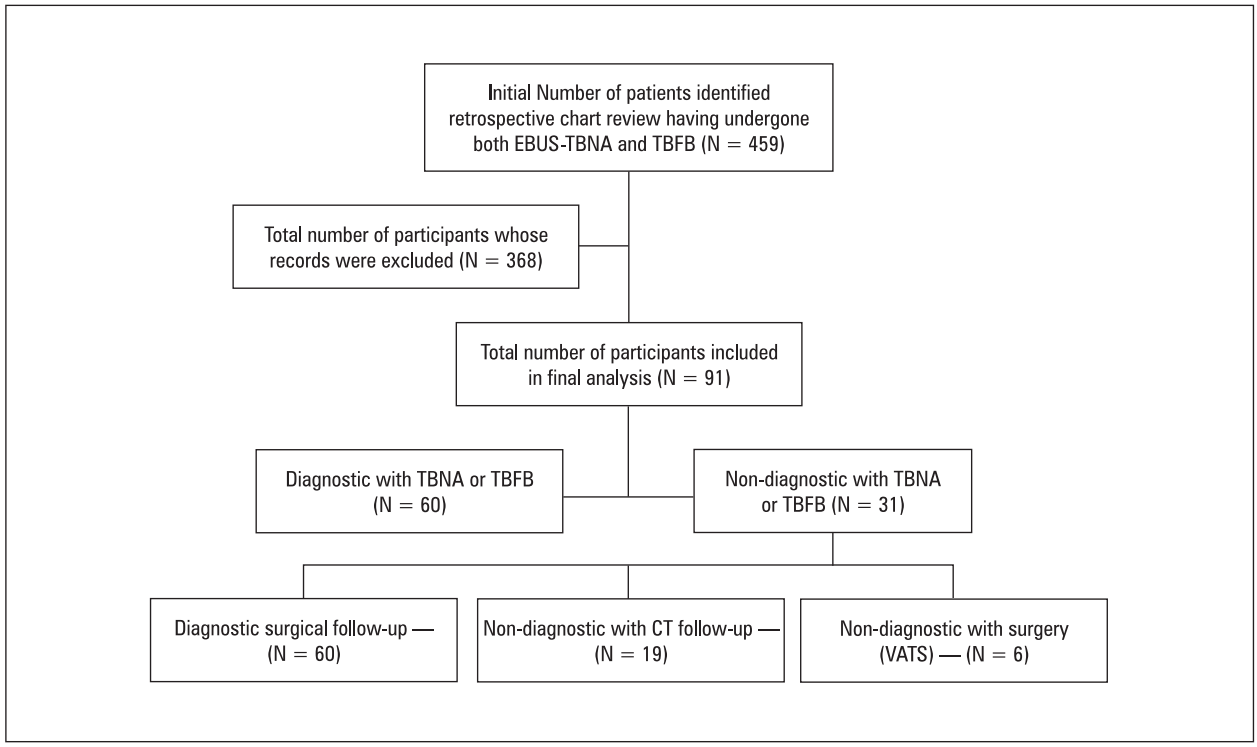

Figure 3. Flow chart illustrating the review, exclusion, and analysis of 459 patients who were initially selected, 91 of whom were eligible for analysis. VATS — video-assisted thoracic surgery; TBNA — transbronchial needle aspiration; TBFB — transbronchial forceps biopsy

to TBNA for obtaining the primary diagnosis and for sampling mediastinal and hilar lymph nodes. In the past, many patients underwent more invasive surgical biopsies via mediastinoscopy as the first line diagnostic modality. However, after the advent of EBUS-TBNA and many subsequent investigations of its utility, it has become the standard as a minimally invasive modality for evaluating concerning hilar and mediastinal lymph nodes. The sensitivity of EBUS-TBNA for diagnosing and staging NSCLC and SCC has been reported to be approximately between 84–94% [5, 6, 13–15]. In our study, the diagnostic yield achieved by EBUS-TBNA for NSCLC and SCLC were 100% (20/20) and 81% (9/11), respectively.

However, in granulomatous disease and lymphoma, EBUS-TBNA yield had been varied and, once again, many patients required the utilization of mediastinoscopy in order to obtain larger tissues samples than obtainable by TBNA [6, 8, 9]. Thus, in our study we have utilized EBUS-TBNA results on ROSE to examine the additive yield provided by the EBUS-TBFB especially in granulomatous diseases such as sarcoidosis. The diagnostic yield for Sarcoidosis within our study was 83% (19/23) which is higher than those reported in previous studies showing approximately 61% [16]. This, in turn, is likely multifactorial and can be affected by population prevalence, operator skill, and sample sizes obtained. Furthermore, the diagnostic yield of TBFB in our study was 96% (22/23), which is again higher than the previous value reported by Darwiche *et al.* [16] of approximately 89%. Finally, using TBNA as a gold standard, the sensitivity and specificity of EBUS-TBFB was 87% and 69%, respectively.

In this study, we have demonstrated that EBUS-TBFB appears to be safe. We had no significant bleeding, mediastinitis, pneumothorax, or intraprocedural death. Post-procedural chest X-rays were performed in patients with concerning symptoms (i.e. chest pain, dyspnea, hemoptysis, or persistent tachycardia) without any complications being reported.

In addition to its larger sample size and utilization of ROSE in each patient's sampling to ensure adequate sample volume acquisition, our study also utilized standard EBUS tools for both TBNA and TBFB. This allowed for easy replication and integration into current practice. This differs from previous studies which had utilized proprietary developed forceps with sharpened edges for easier penetration of the bronchial wall. Our study was also a single operator study as this procedure is very technique-dependent. As a result, the conclusions of this paper would

be stronger if it showcased results from multiple operators and multiple centers.

In conclusion, TBFB is a useful adjunctive tool in the diagnosis of non-malignant conditions such as granulomatous diseases with the potential to spare the patient from undergoing more invasive surgical biopsies. This approach is shown to be safe without increasing complication rates. Furthermore, in the current age of individualized targeted therapy for lung cancer, the additional tissue sample volume provided by TBFB may provide additional value to its incorporation into routine practice. Training of future fellows in performing TBFB in addition to TBNA should be strongly encouraged.

Conflict of interest

None declared.

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Evidence-based review of bronchoscopic lung volume reduction

Abstract

Emphysema sequentially leads to the loss of gas exchanging surface and an abnormal shape of the diaphragm generating dyspnea refractory to standard medical therapy. Lung volume reduction surgery (LVRS) is a surgical treatment option for patients with severe emphysema whose symptoms are uncontrolled on standard therapy. Bronchoscopic LVR (bLVR) is a process by which lung volume reduction is achieved in a minimally invasive manner using bronchoscopy-guided insertion of valves, coils, sealants, or by thermal vapour ablation like techniques. These therapies have developed over the last few years and have variable results in patients. We have summarized the current evidence available on each of these methods in this review.

Key words: bronchoscopy, pulmonary emphysema, treatment outcome

Adv Respir Med. 2021; 89: 43–48

Introduction

Emphysema is a form of chronic obstructive pulmonary disease (COPD) defined by the abnormal and permanent enlargement of the airspaces distal to the terminal bronchioles. Emphysema is associated with destruction of the alveolar walls leading to loss of elastic recoil, early airway closure during exhalation, and air trapping in the distal air spaces. These changes cumulatively lead to a loss of gas exchanging surface and an abnormal shape of the diaphragm.

Lung volume reduction surgery (LVRS) is a surgical treatment in advanced emphysema where dyspnea is uncontrolled on standard therapies. Bronchoscopic Lung Volume Reduction (bLVR) is an advanced bronchoscopic technique to treat hyperinflation due to emphysema [1].

The endoscopic techniques use one-way valves, coils, and sealants, as well as thermal ablation which result in the collapse of overinflated lung segments and achieve benefits similar to that of surgery [1].

Valves

One-way valves allow air and mucus to exit the treated area but do not allow air to re-enter, thus causing atelectasis of the hyperinflated segments distal to the valve. Two types of valves have been designed for this purpose. There is an endobronchial valve, known as the Zephyr valve (duck bill shaped), and an umbrella shaped intrabronchial Spiration valve [2]. The Zephyr valves are self-expanding valves made of nitinol with a silicone coating along with a unidirectional Hemilich valve. The intrabronchial valve has a similar mechanism of action. Its umbrella shape compresses against the airway acting as the valve. They are designed in such a way that they can be inserted bronchoscopically into the desired segment or subsegment and are available in different sizes to fit the airway properly so as to cause complete lobar occlusion. The VENT trial was an international, multicenter (USA and Europe), randomized control trial (RCT) to assess the efficacy and safety of endobronchial valve treatment in pa-

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DOI: 10.5603/ARM.a2020.0172
Received: 16.07.2020

ISSN 2451–4934

tients with heterogeneous emphysema (Table 1). The main inclusion criteria were COPD with a predicted forced expiratory volume in one-second (FEV_1) of 15–45%, predicted residual volume (RV) of > 150%, and heterogeneous emphysema on a chest computed tomography (CT) scan. The trial reported significant improvement in FEV_1, St. George's Respiratory Questionnaire (SGRQ) scores, and six-minute walking distance (6MWD). Notable findings included increased heterogeneity, increased benefit, and a more clinically significant benefit of fissure integrity [3, 4]. The results of the VENT trial gave the insight that the absence of collateral ventilation (CV) between the treated lobe and the adjacent lobe is important. The finding led to the development of the Chartis system to measure functional collateral ventilation.

The STELVIO trial had 68 patients randomized to valve treatment *vs* standard care. This trial had used the Chartis system and also allowed for re-bronchoscopy to adjust the initial valve placement in case of a lack of target volume reduction. Endobronchial valve treatment demonstrated a +20.9% improvement in FEV1 for the treatment group *vs* +3.1% for the controls, an improvement in 6MWD of +60 m for the treatment group *vs* -14 m for the controls, and a SGRQ score difference of -14.7 points in favour of the treated patients (all $p < 0.001$) [5]. Post hoc analysis of these trials using quantitative CT (QCT) analysis also showed significant results for pulmonary func-

Table 1. The summary of clinical trials in valve therapy

Trial	Patient	Intervention	Duration of study	Comparison	Outcome	Adverse effects
VENT [3, 4]	Heterogeneous emphysema	EBV	6 months and 12 months	Usual care	Mean between-group difference of 6.8% in the FEV_1 ($p = 0.005$) at 6 months	Complications composite EBV group *vs* Control group (10.3% *vs* 4.6%; $p = 0.17$) Rate of exacerbation of COPD requiring hospitalization (7.9% *vs* 1.1%, $p = 0.03$) Hemoptysis (6.1% *vs* 0%, $p = 0.01$) Pneumonia in the EBV group — 4.2%
STELVIO [5]	Severe emphysema and a confirmed absence of collateral ventilation	EBV	6 months	Usual care	Mean between-group difference of $FEV_1 = 140$ mL (95% CI 55 to 225) FVC = 47 mL (95% CI, 107 to 588) 6MWD = 74 m (95%CI, 47 to 100) ($p < 0.01$ for all comparisons)	Serious adverse events EBV *vs* control group, (23 *vs* 5; $p < 0.001$) Pneumothorax (18%) Events requiring valve replacement (12%) or removal (15%)
IMPACT [7]	Homogeneous emphysema with absence of collateral ventilation assessed with the Chartis system	EBV	3 months	Usual care	Mean between-group difference FEV_1 17 % ($p = 0.0002$)	Procedure-related pneumothoraces occurred in 11 subjects (25.6%)
TRANSFORM [8]	Homogeneous emphysema with absence of collateral ventilation assessed with the Chartis system	EBV	3 months and 6 months	Usual care	FEV_1 improvement of 12% or more 55.4% EBV *vs* control (55.4% *vs* 6.5%; $p < 0.001$) EBV subjects (89.8%) — target lobe volume reduction ≥ 350 mL, mean 1.09 ± 0.62 L ($p < 0.001$)	Pneumothorax was the most common adverse event, occurring in 19 of 65 (29.2%) of EBV subjects

6MWD — 6 minute walk distance; COPD — chronic obstructive pulmonary disease; EBV — endobronchial valve; FEV_1 — forced expiratory volume in one-second; FVC — forced vital capacity; SGRQ — St. George's Respiratory Questionnaire

tion, exercise, and quality of life in patients with a homogeneous emphysema distribution [5, 6].

Consequently, there was a prospective, multicenter RCT called the IMPACT trial where endobronchial valve treatment was evaluated in patients (n = 93) with homogeneous emphysema in the absence of collateral ventilation (using Chartis). At 3 months after treatment, FEV1 improved by +13.7% from baseline in the valve treatment group *vs* -3.2% in the controls, 6MWD improved to 22.6 m *vs* -17 m, and quality of life measured by the SGRQ score improved by -8.6 *vs* +1.0 points (all $p < 0.001$) [7].

The encouraging results of the above trial lead to a multicenter trial in patients with heterogeneous emphysema and absent collateral ventilation (TRANSFORM trial). The trial showed that FEV_1 improved +20.7% in the treatment group *vs* -8.6% for controls with a between-group difference in residual volume (RV) of 700 mL, 6MWD of 78.7 m, and SGRQ score of 6.5 points (all $p < 0.001$) [8].

The REACH trial, which focused on the adapted intrabronchial valve, demonstrated significant target lobar volume reduction on CT with a mean reduction of 779 mL. Also, at 6 months, the mean FEV1 improved to +12.9% for the treatment group *vs* -1.7% for controls ($p < 0.001$), and the SGRQ score improved to -9.1 *vs* +3.5 points ($p = 0.0023$) [9].

All the above trials using either endobronchial or intrabronchial valves have reported complications of pneumothorax, pneumonia, and exacerbation of COPD.

The Cochrane review of five studies using endobronchial valve treatment has shown significant improvements in FEV1 (standardized mean difference (SMD) 0.48, 95% CI 0.32 to 0.64) and in scores on the SGRQ (-7.29 units, 95% CI -11.12 units to -3.45 units). There were no significant differences in mortality between the two groups (OR 1.07, 95% CI 0.47 to 2.43) but adverse events were more common in the endobronchial valve group (OR 5.85, 95% CI 2.16 to 15.84) [10]. The quality of evidence ranged from low to high [10].

Studies have since been conducted to identify the best method to detect CV. CT-based analysis has been compared with the Chartis system with equivocal results, hence a combination of both these methods is best to achieve the best prediction with regards to CV [11, 12]. The ideal way to assess CV will hopefully come about along with improvement in technology in the near future. It is important to note that the use of valves has its own complications, most common of which are COPD exacerbation (9.3–64%) [3, 13], pneumothorax (4.2–25.6%) [3, 7], and pneumonia (3.2–11.7%) [3, 6]. These complications arise due to the insertion of the valve. This causes a constitutional change in the lobe of the lung leading to its collapse resulting in pneumothorax, with pneumonia causing further exacerbation. Selecting the right patient in terms of CV, ability to handle these complications, and a physician trained in handling these complications is important for the success of valve therapy.

Coils

The coils are nitinol devices delivered bronchoscopically using a unique delivery system into subsegmental airways. The first (1:1) RCT using coils (RESET trial) included patients (n = 45) with both homogeneous and heterogeneous severe emphysema, and these patients were treated bilaterally (Table 2). In this trial, the FEV_1 improved by +10.6%, RV by -0.31 L, and 6MWD by +64 m, with a mean SGRQ score showing an improvement of -8.4 points when compared with the control group [11]. Afterward, two large randomized controlled trials (REVOLENS and RENEW) observed significant benefit in clinically important parameters [12, 13].

The Cochrane systematic review of the three studies comprising 461 patients showed that treatment with endobronchial coils had a significant between-group mean difference in FEV_1 (10.88%, 95% CI 5.20% to 16.55%) and SGRQ score (-9.14 units, 95% CI -11.59 units to -6.70 units). There were no significant differences in mortality (OR 1.49, 95% CI 0.67 to 3.29), but adverse events were significantly more common for participants treated with coils (OR 2.14, 95% CI 1.41 to 3.23). The quality of evidence ranged from low to high [10]. The most common adverse events associated with coil treatment are pneumonia (18–46%) [14, 15] and COPD exacerbation (10–87%) [16, 17], with other less common events including pneumothorax, chest pain, and hemoptysis.

Bronchoscopic thermal vapour ablation

The technique utilizes bronchoscopically applied heat water vapour delivered through a dedicated catheter system leading to a local inflammatory reaction and tissue damage. The result is fibrosis and local atelectasis thus causing the reduction in lung volume [1]. The STEP-UP study was a multicenter, RCT assessed result of

Table 2. The summary of clinical trials in coil therapy

Trial	Patient	Intervention	Duration of study	Comparison	Outcome	Adverse effects
RESET [11]	Homogeneous and heterogeneous emphysema	Coil	3 months	Usual care	Change from baseline SGRQ: -8.4 points ($p = 0.04$) RV: -0.31 L ($p = 0.03$) 6MWD: +63.6 m ($p < 0.001$) FEV_1 +10.6% ($p = 0.03$) at 90 days follow-up after the final treatment	No between group differences in adverse effects
REVOLENS [12]	Bilateral emphysema	Coils	12 months	Usual care	Between-group difference of 6MWD -18% (1-sided 95% CI, 4% to ∞; $p = 0.03$) FEV_1: +0.09 L (95% CI, 0.05 L to ∞) ($p = 0.001$)	Pneumonia within 1 year 1.Coil *vs* control group (18% *vs* 4%) Difference between groups of 14% (95% CI, 2–26%; $p = 0.03$)
RENEW [13]	Bilateral emphysema	Coils	12 months	Usual care	Between-group difference of 6MWD: 10.3 m (IQR, -33.0 to 45.0 m) in coil-treated patients *vs* -7.6 m (IQR, -40.0 to 26.0 m) for usual care Change in FEV_1: s 3.8% (IQR, -6.3% to 16.1%) in coil-treated patients *vs* -2.5% (IQR, -8.9% to 4.4%) for usual care	Total major complications occurred more frequently in the coil group ($n = 54$; 34.8%) *vs* the usual care group ($n = 30$; 19.1%; $p = 0.002$ Increased lower respiratory tract infections (18.7% *vs* 4.5%; $p < 0.001$)

EBV — endobronchial valve; FEV_1 — forced expiratory volume in one-second; RV — residual volume; SGRQ — St. George's Respiratory Questionnaire; 6MWD — 6 minute walk distance

BTVR in patients with predominantly upper lobe emphysema. The trial results documented a mean difference between the active treatment group and controls for FEV1 as +14.7% ($p < 0.001$), for 6MWD as +30.5 m ($p = 0.06$), for RV 0.30 L ($p = 0.015$), and for the SGRQ score as -9.7 points ($p = 0.0021$). There was no significant between-group difference in mortality (OR 2.82, 95% CI 0.13 to 61.06), but vapour ablation led to significantly more adverse events (OR 3.86, 95% CI 1.00 to 14.97) [14]. The adverse events mainly seen were excessive inflammatory response leading to cough, fever and dyspnea, pneumonia (18–23%) [18], and COPD exacerbation (9–24%) [18, 19].

Lung sealant

The lung sealant (AirSeal) is a cross-linking compound made from aminated polyvinyl alcohol (4.5 mL, 2.1% w/v) and glutaraldehyde (0.5 mL, 1.25% w/v). These two compounds are mixed with air to create a foam which is then immediately delivered using a dedicated catheter via a bronchoscope to the desired segments. It mechanically closes off smaller airways and alveoli and locally blocks collateral channels preventing gas from entering the region and leading to absorption atelectasis [1]. The ASPIRE study, a multicenter RCT, evaluated 57 patients with advanced upper lobe predominant emphysema. Unfortunately, the study was stopped early due to financial reasons. That being said, the available data from 3 months of trials showed a median FEV_1 improvement of +11.4% for the AirSeal treatment *vs* -2.1% in the controls ($p = 0.0037$). The improvement in SGRQ score was significant (-11 *vs* -4 points; $p = 0.026$). However, the number of adverse effects was greater in the treatment group [15]. Further studies using this methodology are currently withheld due to financial reasons and major concerns about post procedure inflammation related side effects. There is an ongoing trial NCT02877459 where the original method is redesigned into a sequential procedure to use 20–25% of the original dosage.

Airway bypass

In this technique, extra-anatomical (airway-bypass) passages are created using drug-eluting stents in order to empty the lungs on exhalation [1]. The EASE trial, a multicenter RCT,

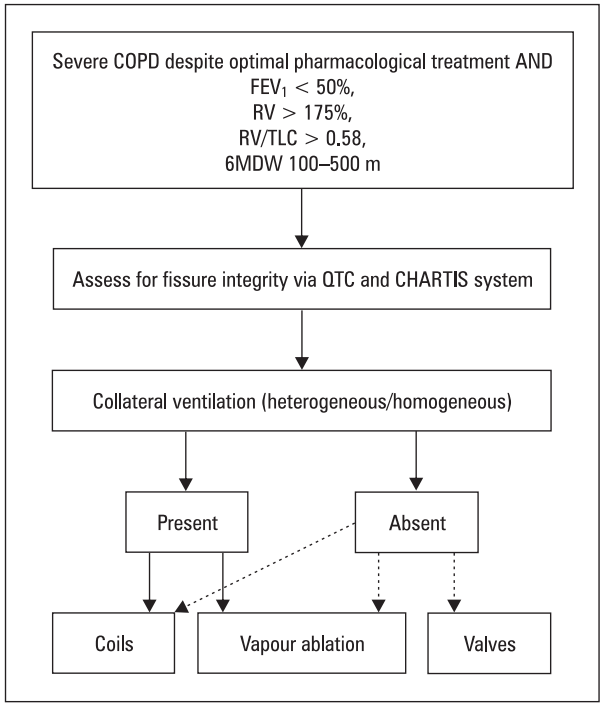

Figure 1. The schematic flowchart summarizing bLVR. 6MWD — 6 minute walk distance; COPD — chronic obstructive pulmonary disease; EBV — endobronchial valve; FEV_1 — forced expiratory volume in one-second; FVC — forced vital capacity; QTC — quantitaive computer assisted tomography; SGRQ — St. George's Respiratory Questionnaire

documented a significant improvement in pulmonary function on Day 1 of the procedure. At 6 months, no difference between treatment arms were noted with respect to the co-primary efficacy endpoint (30 of 208 for airway bypass *vs* 12 of 107 for sham control; posterior probability 0.749, below the Bayesian success threshold of 0.965). The 6-month composite primary safety endpoint was 14.4% (30 of 208) for airway bypass *vs* 11.2% (12 of 107) for sham control [judged non-inferior, with a posterior probability of 1.00 (Bayesian success threshold > 0.95)] [16]. The immediate striking effects seen in these severely diseased emphysema patients nevertheless potentially point to airway bypass as a concept to investigate and develop further in the future. The summarized approach to bLVR is depicted in Figure 1.

Conclusion

The existing evidence for various bLVR techniques shows promising results in terms of improvement in lung function and quality of life. Nevertheless, these methods are yet to document any benefits regarding mortality. Additionally, each of these techniques is associated with immediate adverse effects. Proper patient selection and execution in experienced centers is the key to achieve clinically favourable long term results. A learning curve of each of these techniques is yet to be established. The choice of procedure will mainly depend upon the pulmonologist's expertise, available techniques at the respective treatment center, and capability of dealing with the complications.

Conflict of interest

None declared.

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The prognostic value of fixed time and self-paced walking tests in patients diagnosed with idiopathic pulmonary fibrosis

Abstract

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia that has an unknown etiology. The natural history of the disease is characterized by a progressive decline in pulmonary function and overall health and well-being. The median survival time is between 2–3 years; however, the disease course is variable and unpredictable.

The twelve-minute walking test (12MWT) and six-minute walking test (6MWT) are two fixed time tests that are commonly used in clinical practice. Our short and clinically oriented narrative review attempted to summarize current evidence supporting the use of fixed time, self-paced walking tests in predicting the outcome of patients diagnosed with IPF.

A number of studies have justified that the 6MWT is a simple, cost-effective, well documented, fixed time, and self-paced walking test which is a valid and reliable measure of disease status and can also be used as a prognostic tool in patients with IPF. However, there is a need for dedicated and validated reference equations for this population of patients.

It is also necessary to fill the knowledge gap about the role of the 12MWT. We hypothesize that it would be useful in evaluating patients that are in the early stages of the disease.

Key words: idiopathic pulmonary fibrosis, walking tests, 6MWT, 12MWT, Cooper test

Adv Respir Med. 2021; 89: 49–54

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia with an unknown etiology representing one of the most common entities of the heterogeneous group of interstitial lung diseases (ILDs). The prevalence of this rare disease is estimated to be at 2–29 cases per 100,000 in the general population [1–5]. The natural history of the disease is characterized by a progressive decline in pulmonary function as well as overall health and well-being. The median survival time is between 2–3 years but the disease course is variable and unpredictable [6–9].

The most common symptoms of this progressive disease include exertional dyspnea and dry cough. The symptoms usually appear insidiously and many patients are unable to pinpoint the date of their appearance. It is important to note that deteriorating exercise tolerance often fails to alarm patients about the early stages of IPF because these patients tend to attribute their symptoms to the ageing process or treat them as a consequence of long-term tobacco smoking [10].

Progression dynamics clearly have an effect on the prognosis in IPF. Objective measurement of exercise capacity is one of the ways to monitor the disease course [11].

Cardiopulmonary exercise testing (CPET) is an objective assessment of exercise capacity and, in recent times, has become a more commonly used tool in clinical settings. However, CPET

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DOI: 10.5603/ARM.a2020.0193
Received: 12.08.2020

ISSN 2451–4934

involves the use of specialized facilities that are not universally available. That is why simple fixed time and self-paced walking tests are more frequently used in the clinical assessment of exercise capacity. The twelve-minute walking test (12MWT) and six-minute walking test (6MWT) are two fixed time tests commonly used in clinical practice.

Our short and clinically oriented narrative review attempted to summarize current evidence supporting the use of fixed time and self-paced walking tests in predicting the outcome for patients diagnosed with IPF.

Selected aspects of exercise pathophysiology in fibrotic interstitial lung diseases

The background of exercise intolerance in IPF patients is a complex, multidimensional, and multi-faceted issue. Most of the previous studies on exercise intolerance in patients with ILDs were performed on broad ILD populations which also included patients suffering from other fibrotic interstitial lung diseases, not only IPF. That being said, we may assume that these entities are comparable because the disease mechanisms involve a fibrotic process. From a pathophysiological point of view, fibrotic changes in the lungs lead to decreased lung compliance, which in turn results in an increased work of breathing and decreased lung volumes. These abnormalities present clinically as a classic restrictive pattern of lung disease. Patients develop a decreased total lung capacity, vital capacity, and inspirational capacity. These, in turn, result in a decreased tidal volume and an increased respiratory rate which leads to increased ventilation and, eventually, hypocapnia. Alveolar-capillary membrane thickening causes decreased oxygen diffusion and a ventilation-perfusion mismatch. In order to compensate for the resulting hypoxemia, the body increases ventilation. Clinically, hypoxemia is associated with a sensation of dyspnea. It also results in the constriction of pulmonary vessels and a subsequent decrease in cardiac output which leads to decreased delivery of oxygen to the muscles and resulting fatigue. IPF patients commonly present with weakness of the musculature of the lower limbs which contributes to exercise intolerance. It is important to mention that pulmonary microvasculopathy also contributes to decreased cardiac output. These vascular changes are a result of endothelial proliferation, remodeling, and capillary obliteration. Decreased oxygen delivery to the muscles will also result in increased oxygen extraction and, subsequently, decreased venous oxygen capacity which potentiates hypoxemia [12–29].

In summary, the complex aforementioned mechanisms lead to primary symptoms of dyspnea and fatigue which, together, form the basis of exercise intolerance.

General principles of the 12MWT and the 6MWT

The 12MWT is based on a 12-minute performance test introduced by Cooper *et al*. as a guide to determine the state of physical fitness in healthy young men [30]. The authors observed that field testing can provide a good assessment of maximal oxygen consumption in young and well-motivated subjects. However, the accuracy of the estimate is related directly to the motivation of the subjects [30]. The test requires the patient to cover the maximum possible distance in 12 minutes by running, walking, or using a combination of both [31]. Results of the 12MWT are highly reproducible [32]. The prediction of cardiorespiratory fitness in this test is described by the following equation [31]: VO_2max (mL/kg/min) = (distance [m] – 504.9)/44.73.

The 6MWT is considered a simple, cost-effective, and well-documented field test for the assessment of the functional exercise capacity. It can also be used to assess the response to medical interventions in various diseases. It was introduced as a therapeutic tool in respiratory medicine by Butland *et al.* [33] in their study comparing three fixed time tests (2-, 6-, and 12-minute walking tests) and they concluded that shorter distance tests would be just as beneficial as the 12MWT. The authors also observed high correlation coefficients between the 2-, 6-, and 12-minute tests. This indicates that they were similar measures of exercise tolerance. All of these tests showed equal reproducibility. However, the longer tests presented a greater discrimination than the shorter ones [33]. Therefore, the 6MWT seems to be a satisfactory compromise between test validity and patient acceptability. Nowadays, this is the most common fixed distance test used in clinical and research settings.

Mänttäri *et al.* observed that the 6MWT performed on a 15 m track may predict a VO_2 max in healthy adults with an accuracy of about 1 metabolic equivalent (MET). The following equations were proposed [34]:

— For men:
VO_2max (mL/kg/min) = 110.546 + 0.063 × distance – 0.250 × age – 0.486 × BMI – 0.42 ×

height [cm] – 0.109 × heart rate at the end of the test,

— For women:
VO_2max (mL/kg/min) = 22.506 – 0.271 × weight + 0.051 × distance – 0.065 × age.

The prognostic value of the 12MWT and the 6MWT in IPF

The 12MWT is less commonly used for IPF patients because it requires greater effort by the patient than the 6MWT. We hypothesize that it would be useful in evaluating patients in the early stages of the disease. However, it is important to mention that our research is currently in progress and that this is only a running hypothesis.

On the other hand, there is a growing body of evidence supporting the role of the 6MWT in the evaluation of IPF patients. Caminati *et al.* [35] performed a retrospective analysis of 44 patients with IPF of whom 29 had an additional evaluation at follow-up after 12 months. During a mean follow-up period of 19.8 months, 11 patients died because of IPF. The authors observed that the distance walked in 6 minutes (6MWD) was independently related to mortality and that patients who walked less than 212 meters had a significantly lower survival rate than those who were able to walk a longer distance. Changes in distance walked upon evaluation at 12 months were also predictive of survival. Du Bois *et al.* aimed to assess the reliability, validity, and responsiveness of the 6MWD. At the conclusion of their study, they estimated the minimal clinically important difference in IPF patients as 24–45 m [36]. The 6MWD was measured at baseline and at 24-week intervals. A comparison of two proximal measures of the 6MWD demonstrated good reliability. As was previously cited in the Caminati *et al.* study, these authors also observed that a change in the results of the 6MWD was highly predictive of mortality. Moreover, test results weakly correlated with forced vital capacity, diffusion capacity of the lung for carbon monoxide, resting alveolar–arterial gradient, and health-related quality of life. Measured values were consistently and significantly lower for patients with the poorest functional status. For example, a patient who, at baseline, covered a distance of less than 250 m was associated with a 2.65-fold increased risk of death over the following year when compared with a patient who was able to cover a distance of more than 350m. On the flip side, a decline in distance covered of 50 meters or more was associated with a 4.27-fold increased risk of death over the following year when compared with patients whose deterioration was capped at a maximum of 25 meters [36]. Three years later, the authors published another paper in which they proved that both the 6MWD and resulting changes in 6MWD results were independent predictors of mortality in patients with IPF [37].

Moreover, in a study of 197 patients conducted by Flaherty *et al.*, the authors observed that desaturation during the 6MWT was associated with an increased mortality rate even though a threshold of 88% was not reached. Moreover, for patients with a baseline saturation of 88% or less, the strongest observed predictor of mortality was a serial change in the lung transfer factor for carbon monoxide. However, for patients who had a saturation over 88% during their baseline walking test, serial decreases in forced vital capacity (FVC) and increases in desaturation area significantly predicted subsequent mortality [38].

Another interesting and clinically important study was performed by Lederer *et al.* who analyzed the association between the 6MWD and survival in 454 patients with IPF who were listed for lung transplantation. This study showed that a shorter 6MWD result was associated with an increased mortality rate. Moreover, patients who covered a distance of less than 207m had a fourfold greater mortality rate even after adjusting for demographics, anthropomorphic measurements, FVC expressed as percent of predicted, pulmonary hypertension, and medical comorbidities. They stated that the 6MWD was a significantly better predictor of six-month mortality than FVC expressed as a percent of predicted value [39].

Kozu *et al.* [40], in their prospective, cross-sectional observational study, assessed the relationship between the Medical Research Council (MRC) dyspnea grade and peripheral muscle force, activities of daily living performance, health status, lung function, and exercise capacity in 65 IPF patients in a stable clinical state. The authors noted a strong association between MRC grade and the 6MWD. Similarly, Manali *et al.* [41] prospectively studied the relationship between the MRC chronic Dyspnea Scale with cardiopulmonary exercise testing (CPET) and the 6MWT in 25 IPF patients. They found significant correlations between the MRC score and the following parameters of the 6MWT: distance walked, SpO_2 at initiation and at the end of the test, and the difference in saturation before and after the test. Correlations with the pulse at the initiation and at the end of the test, the blood pressure,

and the Borg dyspnea scale were not significant. A multiple stepwise logistic regression analysis that tested a number of physiologic parameters showed that the only variable independently related to the MRC score was the distance walked at the 6MWT.

Confounding factors

A considerable number of factors, both internal and external, can affect the result of the 6MWT. That is why a low 6MWD may be non-specific and non-diagnostic. In the event of a low 6MWT test result, it is important to further research whether or not such a result is reliable and accurate. Moreover, it would be helpful to analyze the 6MWT results in the context of pulmonary function tests, cardiac function, nutritional status, muscle strength, ankle–brachial index, orthopedic function, and cognitive function. From a constitutional point of view, age, height, weight, and sex independently affect the 6MWD in healthy adults [42]. It is important to note that a shorter walking corridor, decreased patient motivation, comorbidities, medications, oxygen supplementation, and previous experience with the test can affect the result [43]. This information highlights the need for specific reference equations.

Reference equations

There are some reference equations for the 6MWT published in literature [44–52] which are not validated for the IPF population. However, in this context, it is worth to discuss a prospective, non-randomized controlled study conducted by Igarashi *et al*. In this study, the authors investigated the effect of an outpatient pulmonary rehabilitation program and the use of 6MWD (expressed as a percentage of the predicted value) to quantify the response to pulmonary rehabilitation in elderly patients with ILDs. They concluded that 6MWD, expressed as a percentage of the predicted value, might be more useful than the absolute 6MWD as an outcome measure of pulmonary rehabilitation, and as a predictor of response to pulmonary rehabilitation in elderly patients with ILDs [53]. The authors used reference equations proposed by Enright *et al.* [52].

Therefore, the body of evidence regarding the reference equations for the 6MWT in IPF shows that there are considerable gaps of knowledge in this area and highlights the need for comprehensive exploration of this topic.

Conclusions

The 6MWT is a simple, cost-effective, well-documented, fixed time, and self-paced walking test evaluating functional capacity which is broadly used for clinical and research purposes. The 6MWT result is a valid and reliable measure of disease status and prognosis in patients with IPF. Nevertheless, there is a need to establish dedicated and validated reference equations for this population of patients.

There is also a need to fill the knowledge gap regarding the role of the 12MWT in this population. We hypothesize that it would be useful in evaluating patients in the early stages of the disease.

Conflict of interest

None declared.

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Birt-Hogg-Dubé syndrome — an unique case series

Abstract

Birt-Hogg-Dubé syndrome (BHDS) is an uncommon autosomal dominant syndrome. It is also known as Hornstein–Knickenberg syndrome. It is an inherited disorder culminating in mutations in folliculin coding gene (FLCN). The clinical exhibitions of the syndrome are multi-systemic, comprising of a constellation of pulmonary, dermatologic and renal system manifestations. The most common presentations include fibrofolliculomas, renal cell carcinomas, lung cysts and spontaneous pneumothorax. The treatment is conservative with regular monitoring of the renal and lung parameters. Fibrofolliculomas may require surgical excision and recurrent events of pneumothorax may warrant pleurodesis. We reported a case series of 2 patients presenting with symptoms of progressive breathlessness along with dermatological manifestations and subsequently showing radiological manifestations of Birt-Hogg-Dubé syndrome in the form of lung cysts.

Key words: autosomal dominant, lung cysts, fibrofolliculomas, FLCN gene

Adv Respir Med. 2021; 89: 55–59

Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare, inherited syndrome involving skin, lungs and kidneys [1]. It is also known as Hornstein-Knickenberg syndrome. BHDS is an autosomal dominant monogenic disorder caused by constitutional mutation in the folliculin coding gene (FLCN) [2–4]. Folliculin coding gene is a tumor suppressor gene, and it codes for the protein folliculin. Dermatological manifestations include fibrofolliculomas, trichodiscomas, and acrochordons, which primarily occur in the face, neck, and on the upper torso [1, 5]. Lung cysts are the hallmark of the lung involvement, causing an increased risk of spontaneous pneumothorax [6–9]. Birt-Hogg-Dubé syndrome increases the risk of kidney lesions like cysts, benign tumors, and kidney cancer. Many different types of kidney tumor (histologies) have been seen in people with BHDS, with the most common forms being hybrid oncocytic tumors (HOTs), chromophobe, and oncocytoma. The most severe manifestation of the syndrome is the predisposition to renal cell carcinoma (RCC) [8]. Birt-Hogg-Dubé syndrome is a rare disorder that affects males and females equally. A diagnosis of BHDS is based upon a thorough clinical evaluation, a detailed patient history, and identification of characteristic manifestations (symptoms), including 2 or more fibrofolliculomas, history of spontaneous pneumothorax or bilateral, multiple chromophobe or hybrid oncocytic renal tumors. We herein report 2 cases of BHDS who fulfilled the diagnostic criteria after a thorough clinical, radiological, histopathological and genetic evaluation.

Case 1

A 34-year-old lady hailing from Kolkata followed up to our outpatient department with chief complaints of predominantly dry cough and progressive breathlessness of 3 years duration, with a progression of her symptoms over the last 4 months. There was a history of infective exacerbations about 2 episodes per year, managed with symptomatic treatment. The general examination was suggestive of the presence of multiple skin tags in the right axilla. The respiratory system examination was within normal limit. Her chest X-ray was suggestive of right lower zone fibrocystic opacity. Her baseline blood investigations

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DOI: 10.5603/ARM.a2020.0180
Received: 23.07.2020

ISSN 2451–4934

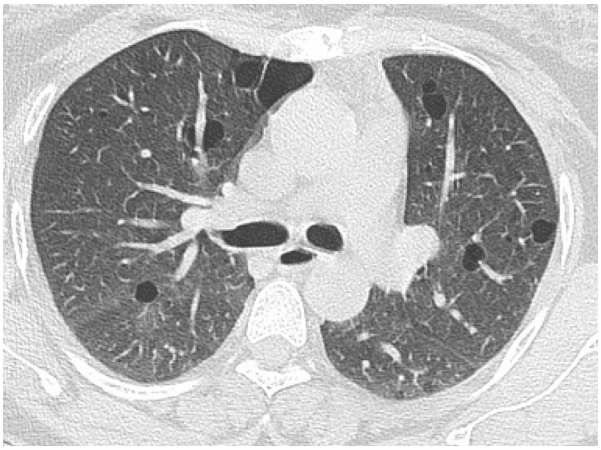

Figure 1. High resolution computed tomography of the thorax showing bilateral widespread lung cysts

were within normal limits and viral markers were negative. High-resolution computed tomography (HRCT) of the thorax was suggestive of the presence of bilateral widespread lung cysts, with imperceptible walls with lower zone predominance (Figure 1). Her spirometry was normal with ratio of forced expiratory voulme at the end of firts second (FEV_1) to forced vital capacity (FVC) being 77% . She was evaluated with skin biopsy of the axillary tag, which was suggestive of the presence of acrochordon (Figure 2). Ultrasonography of the abdomen was normal; magnetic resonance imaging (MRI) of the abdomen was suggestive of the presence of left-sided simple renal cyst (Figure 3). In view of the multisystemic involvement, a diagnosis of BHDS was suspected. Hence genetic analysis for the FLCN gene mutation was done, which was positive for the FLCN gene, showing germline mutation of cytosine residue at C_8 tract in exon 11. Hence in light of her clinico-radiological and genetic analysis, a diagnosis of BHDS was made and the patient was counseled accordingly. She was managed with pulmonary rehabilitation.

Case 2

A 61-year-old nonaddict man, with comorbidities in the form of ischemic heart disease and systemic hypertension, on medical management for the same presented with complaints of right-sided chest pain and exertional dyspnea of 10 months duration. On general examination, multiple skin tags were noted over bilateral axillary areas and on the neck. On examination of the respiratory system, his breath sounds were decreased in right inframammary, infraaxillary, lowerinterscapular and infrascapular areas. In

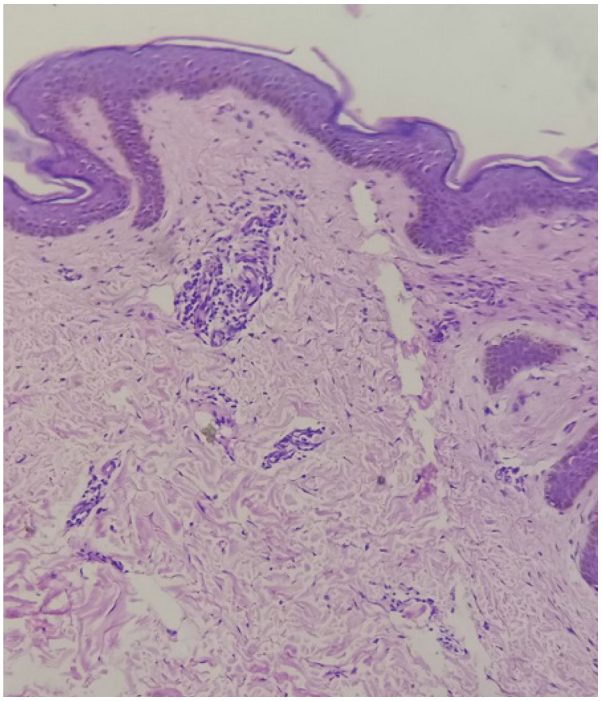

Figure 2. Histopathological skin biopsy image consistent with findings of acrocordon showing papillary dermis [H & E stain 10x power]

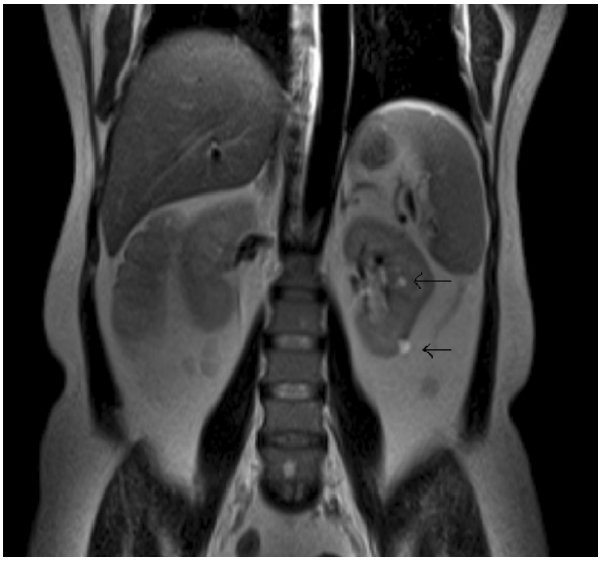

Figure 3. Magnetic resonance of the abdomen showing left-sided renal cyst

view of the above complaints, he was evaluated with chest X-ray suggestive of right-sided loculated pneumothorax. He was hospitalized on our side for a detailed evaluation. His baseline blood investigations were within normal limits and viral markers were negative. High-resolution computed tomography (HRCT) of the thorax was suggestive of bilateral diffuse thin-walled cysts of various

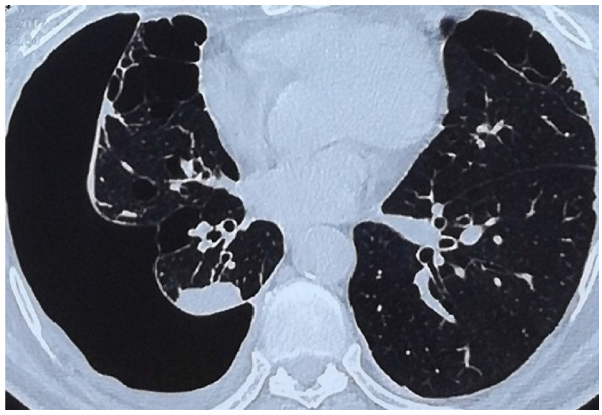

Figure 4. Computed tomography of the thorax showing right-sided loculated pneumothorax (lung window)

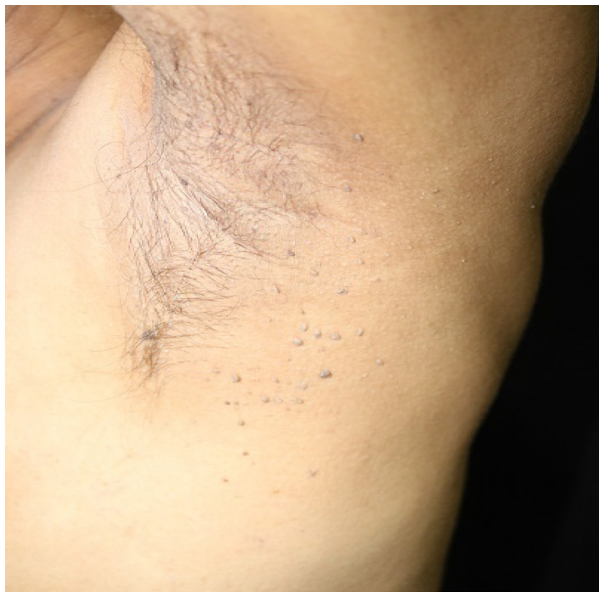

Figure 5. Skin tags in axillary area

size, predominantly in the upper lobe with partly loculated hydropneumothorax (Figure 4). Spirometry showed a restrictive abnormality with ratio of FEV^1/FVC being 72% and FVC of 52% predicted; two-dimensional echocardiography was suggestive of ischemic heart disease with concentric left ventricular hypertrophy showing increased global left ventricular wall thickness and pulmonary artery systolic pressure (PASP) by the tricuspid regurgitation (TR) velocity demonstrating normal findings. Dermatologist's opinion was taken for skin tags (Figure 5), which on skin biopsy was proven to be acrochordon. Hence on basis of clinico-radiological and skin biopsy reports, provisional diagnosis of Birt-Hogg-Dubé syndrome was made, and genetic analysis for the same was processed, the reports of which are awaited.

Discussion

Birt-Hogg-Dubé syndrome is a unique genetic condition, associated with multisystemic involvement in the form of benign skin lesions, lung cysts and an increased risk of benign kidney tumors. BHDS is a rare complex genetic skin disorder (genodermatosis), characterized by the development of skin papules generally located on the head, face and upper torso. These benign tumors (hamartomas) of the hair follicle are called fibrofolliculomas. Birt-Hogg-Dubé syndrome also predisposes individuals to the development of benign cysts in the lungs, repeated episodes of a collapsed lung (pneumothorax), and an increased risk for developing kidney neoplasia. It emanates from heterozygous loss-of-function mutations in the BHD tumor suppressor gene on chromosome 17p11.2, which encodes the novel protein folliculin. Fluorescent in situ hybridization of Birt-Hogg-Dubé mRNA has shown expression in many normal tissues, most commonly the skin and its appendages, the distal nephron of the kidney, stromal cells, and type 1 pneumocytes of the lung [1]. In 1977, Birt, Hogg, and Dubé reported a study of 70 members of three generations, 15 of whom exhibited multiple small skin-colored to grayish-white dome-shaped papules distributed over the face, neck, and the upper trunk. Histologic analysis revealed fibrofolliculomas, trichodiscomas, and acrochordons [2]. The triad of these lesions has been named "Birt-Hogg-Dubé syndrome", which exhibits an autosomal-dominant trait pattern of inheritance. The folliculin gene locus is within chromosome 17p11.2, in an unstable genomic region, which is associated with a number of diseases [3, 4].

Both cases presented with pulmonary and dermatological manifestations of BHDS with initial symptoms of progressive dyspnea.

Skin manifestations

The skin manifestations are the most conspicuous and often presenting features of the syndrome. They occur in the form of skin fibrofolliculomas and less commonly, trichodiscomas and acrochordons [3, 5–7]. Papules, varying in number from a few to several hundred, with a histological diagnosis of fibrofolliculoma, are the hallmark of the syndrome [2, 3]. They are asymptomatic and develop during the third or fourth decade of life, increasing in number and size as patients grow older. Our both cases were showing the presence of acrochordons proven on

skin biopsy reports, the first case presented with skin tags on the right axilla, while the second one had it on bilateral axilla and the neck.

Renal manifestations

Along with skin manifestations, patients with BHDS also have renal system affection in the form of renal tumors [3, 5, 7–9], ranging from benign oncocytomas to malignant renal carcinomas. Familial kidney tumors have bilateral predilection and multifocal involvement and are usually asymptomatic in the initial stages. It is therefore recommended that affected patients and family members undergo abdominal computed tomography and renal sonography screening for renal cancer [5, 7–9]. Our first case also had a renal cyst detected on her MRI of the abdomen, although her ultrasound of the abdomen was normal. Other systemic conditions associated with BHDS include colonic polyposis and ophthalmologic disorders, such as progressive flecked chorioretinopathy and chorioretinal scars [4].

Pulmonary manifestations

The pulmonary involvement in BHDS generally occurs in the form of lung cysts of varying sizes and incidentally picked up episodes of pneumothorax. The presence of lung cysts in association with Birt-Hogg-Dubé syndrome was first described by Toro *et al*. [7] in 1999 in a study of 152 individuals from 49 families with familial renal neoplasms syndromes. Among these patients, three of the 13 who had BHDS exhibited pulmonary cysts, and one of these three patients developed pneumothorax [5]. A few additional cases of lung cysts and spontaneous pneumothorax have subsequently been reported in the literature [3, 4, 6, 8, 9]. Bullous emphysema has also been described [3, 4]. The increased frequency of reports on pulmonary cystic abnormalities in these patients strongly suggests that they are manifestations of BHDS rather than chance associations. The location and profusion of the cysts may vary in individual cases. Our first patient had multiple scattered bilateral cysts with a lower zone predominance, while the second one had scattered lung cysts with upper lobe predilection and an incidentally detected loculated pneumothorax too.

Differential diagnosis

Before making diagnosis of BHDS, it is necessary to rule out the following differential diagnosis like *PTEN* hamartoma tumor syndrome (PHTS), which is a spectrum of disorders caused by mutations of the *PTEN* gene characterized by multiple hamartomas that can affect various areas of the body, tuberous sclerosis complex, including skin and lung hamartomas and angiomyolipomas of the kidney (and rare renal neoplasia) that are similar to BHD. Other differential diagnoses to BHD are other cystic lung diseases, such as Langerhans' cell histiocytosis, lymphangioleiomyomatosis (LAM), or other diseases with a high risk of secondary spontaneous pneumothorax, i.e. Marfan syndrome, chronic obstructive lung disease or emphysema.

Diagnosis

Diagnosis of BHDS is based on a combination of genetic analysis and the systemic manifestations. Major and minor criteria have been defined for the diagnosis [10]. The two major criteria include the presence of fibrofolliculoma, trichodiscoma or acrochordon, confirmed histologically on at least 5 cervical or facial areas and the folliculin gene mutation on DNA analysis [11]. The minor criteria include multiple lung cysts localized in the basal regions of no other identified etiology, with or without an evidence of pneumothorax, a history of renal cancer or renal cysts and a diagnosis of BHD syndrome in the first degree relatives. Diagnosis is confirmed by the presence of one of major criteria or two of minor criteria. Our first patient was a genetically proven case while the second one also satisfied the other required criteria whilst awaiting the genetic mutation report.

Prognosis

Prognosis of Birt-Hogg-Dubé syndrome depends on associated comorbid factors, particularly the occurance of renal cell carcinoma. It also depends on tumor histology, size, and metastatic spread. Of BHDS kidney cancers, 80–85% are slow growing with a low potential for metastasizing and a favorable prognosis. The typical dermatologic lesions are of benign etiology and could be relevant only from cosmetic concerns. Pulmonary component of the disease is not generally aggressive, and patients need to be kept under observation for the lung cysts and the occurance of spontaneous pneumothorax. A thorough counseling should be done pertaining to the benign nature of these cysts to avoid unwarranted surgeries and interventions. Genetic

counselling is advocated, considering autosomal trait of the syndrome.

Treatment

In the literature, no specific treatment for BHD syndrome is mentioned. The fibrofolliculomas can be resected surgically if bothersome from cosmetic angle. In patient with BHD syndrome with renal cancer, total or partial nephrectomy may be required [12]. Pleurodesis that may be offered for recurrent episodes of pneumothorax, can be either chemical or mechanical. Pleurodesis works by symphysis between parietal and visceral pleura by administration of sclerosing agents or mechanical process causing secretion of various mediators — most commonly used is talc (*magnesium silicate*). Chemical pleurodesis can be performed during surgery or via a chest tube.

Follow-up

Patients are kept under a regular follow-up from the perspective of early detection of complications. The renal and pulmonary systems are followed on the basis of clinical symptoms and with regular follow-up with the help of CT of the thorax, ultrasound of the abdomen, or MRIs of the kidneys annually. As MRI harbours a lesser risk of radiation complication than CT scans and is more sensitive than ultrasounds, it is the preferred method for observation of the kidneys in the patient with BHD.

Conclusions

It is crucial to keep BHDS as a differential diagnosis while evaluating a patient with cystic lung disease; and the key to the diagnosis of this uncommon syndrome is a due index of suspicion and a multidisciplinary workup.

Conflict of interest

None declared.

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Primary pleural synovial sarcoma: a rare cause of hemorrhagic pleural effusion

Abstract

Primary pleural synovial sarcoma (PPSS) is a rare malignant pleural tumor comprising < 1% of all primary lung malignancies. Primary pleural mesothelioma (PPM) has many similar features that may cause a diagnostic dilemma due to overlapping clinical and histopathological features. We present the case of a young male with recurrent hemorrhagic pleural effusion without any obvious lung mass who was diagnosed with PPSS. This rare entity must be considered with a high index of suspicion while evaluating pleural tumors.

Key words: hemorrhagic, immunohistochemistry, pleural effusion, sarcoma, synovial

Adv Respir Med. 2021; 89: 60–62

Introduction

Synovial sarcomas (SS) are rare entities predominantly affecting the deep soft tissue of the upper and lower extremities, with the trunk and head-neck region being uncommon sites [1]. Primary synovial sarcomas of the pleura are rare malignant pleural tumors comprising < 1% of all primary lung malignancies [2]. It usually presents as a localized solid tumor and, less commonly, as diffuse pleural thickening. Common presenting features include chest pain, breathlessness, and hemothorax. There have been a few cases that have presented with pleural effusion. Differentiating PPSS from primary pleural mesothelioma (PPM) can be a diagnostic challenge owing to PPM's clinical and histological resemblance to PPSS. Immunohistochemistry (IHC) and molecular genetics can help differentiate the two. We hereby report a case of Primary Pleural Synovial Sarcoma (PPSS) presenting with recurrent massive hemorrhagic pleural effusion in a young male.

Case report

A 26-year-old patient who was a non-smoking laborer presented with chief complaints of breathlessness, cough, fever, and left-sided chest pain for one month. He was diagnosed by another clinic as having a tuberculous pleural effusion and was initiated on anti-tuberculous treatment with no relief. At presentation, he had marked respiratory distress but was hemodynamically stable. Chest radiograph from a posteroanterior view (Figure 1A) revealed a massive left pleural effusion which was drained to relieve the distress. Pleural fluid was hemorrhagic in appearance and a lymphocytic exudate. Contrast-enhanced computed tomogram (CECT) of the thorax showed a gross left pleural effusion with multiple pleural-based heterogeneously-enhancing irregular lesions, necrotic mediastinal lymphadenopathy, and contralateral metastatic canon-ball opacities (Figure 1B).

Transthoracic fine needle aspiration from the pleural-based mass lesion was suggestive of a poorly differentiated malignant tumor. Fiberoptic bronchoscopy showed a narrowed lingular bronchus. Bronchoalveolar lavage and brush cytology were negative for malignant cells, as were three pleural fluid samples. Multiple septations and grape-like nodules studding the parietal pleura (predominantly at the base) were visualized on thoracoscopy (Figure 1C). Thoracoscopic pleural

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DOI: 10.5603/ARM.a2020.0147
Received: 11.06.2020

ISSN 2451–4934

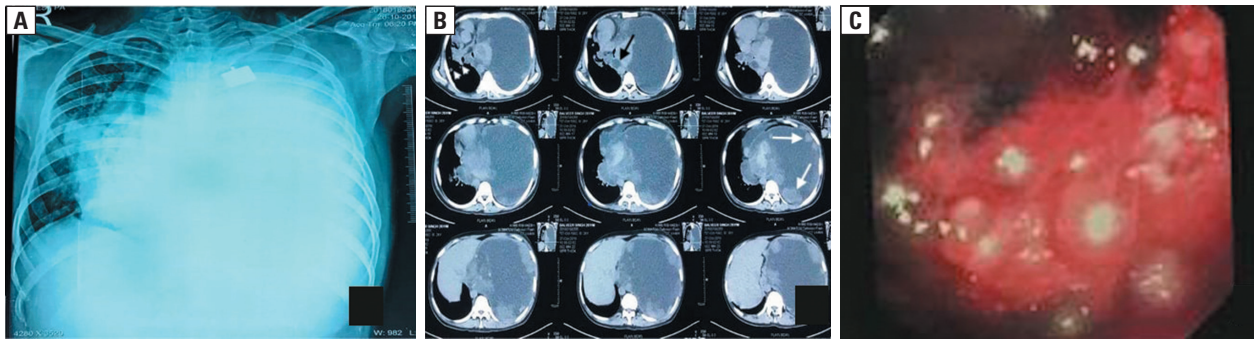

Figure 1. Chest X-ray (postero-anterior view) shows completely opaque left hemithorax with contralateral mediastinal shift (**A**). Contrast enhanced computed tomogram of thorax (**B**) shows gross left pleural effusion with multiple pleural-based irregular lesions (white arrows), necrotic mediastinal lymphadenopathy (black arrow) and contralateral metastatic canon-ball opacities (white arrowheads). Thoracoscopic image (**C**) showing multiple grape-like nodules studding parietal pleura

biopsy suggested a malignant small round cell tumor that was positive for TLE-1 (strong diffuse nuclear positive), CD-99 & Pan-CK (both strong diffuse membranous positive), and synaptophysin (mild diffuse membranous positive) on IHC, suggesting a final diagnosis of PPSS (Figure 2). A bone scan showed osteoblastic lesions suggestive of skeletal metastasis in the lower one-third of the sacrum, left femur, and lateral condyle of left tibia. The patient was started on palliative doxorubicin and palliative radiotherapy.

Discussion

Synovial sarcomas are uncommon mesenchymal tumors that arise from primitive pluripotent mesenchymal cells capable of synovial differentiation. Sarcomas involving the pleural cavity include chondrosarcoma, liposarcoma, osteosarcoma, malignant schwannoma, and synovial sarcoma [3]. PPSS is a rare variety with only a few cases reported in literature. It usually occurs in the age group of 30–50 years [4] and has equal predilection for males and females [5]. PPSS most commonly presents with chest pain, shortness of breath, hemothorax, and pleural effusion [2]. A case series of 19 PPSS cases indicated that the most common presentation was chest pain accompanied by breathlessness, while the least common presentation was pleural effusion [6]. Further, PPSSs are usually localised, solid pleural tumors but can, less commonly, present with diffuse pleural thickening [2]. Our patient presented with multiple pleural-based lesions with recurrent hemorrhagic pleural effusion.

Depending upon the type of cells, synovial sarcomas are classified histologically into monophasic, biphasic, and poorly differentiated subtypes. In the biphasic type, variable proportions of epithelial and spindle cell components are present. The monophasic type is predominantly composed of spindle cells. The poorly differentiated types show small round tumor cells. Most PPSSs are monophasic [2].

IHC studies reveal that expression of TLE-1 is a sensitive and specific marker for synovial sarcoma [7]. This was seen in our case as well which, along with CD99 and Pan-CK positivity, led to a final diagnosis of PPSS. Genetic analysis may be helpful in diagnosis when IHC is inconclusive. t(X;18) (p11.2;q11.2) is the most common chromosomal translocation found in more than 89% of synovial sarcomas regardless of its histological subtype. In our case, since IHC was confirmatory, genetic studies were not done.

The best treatment for synovial sarcoma is not yet clear. Though many treatment options are available, a multidisciplinary approach involving surgery, chemotherapy, and radiotherapy has been suggested. Radical resection is the first-line treatment, and adjuvant radiotherapy is recommended for cases with incomplete resection. The efficacy of chemotherapy as first line treatment is unclear, however, improvement in overall survival has been described with the use of doxorubicin and ifosfamide. Neoadjuvant chemotherapy could be beneficial for reducing tumor volume and treating micrometastatic disease. Radiofrequency thermal ablation may be considered as an alternative treatment for inoperable patients [8].

Conclusion

PPSS is a rare disease. Its clinical and histological resemblance to other primary pleural tumors, particularly mesothelioma, can pose a diagnostic challenge. The current case highlights the importance of maintaining a high clinical

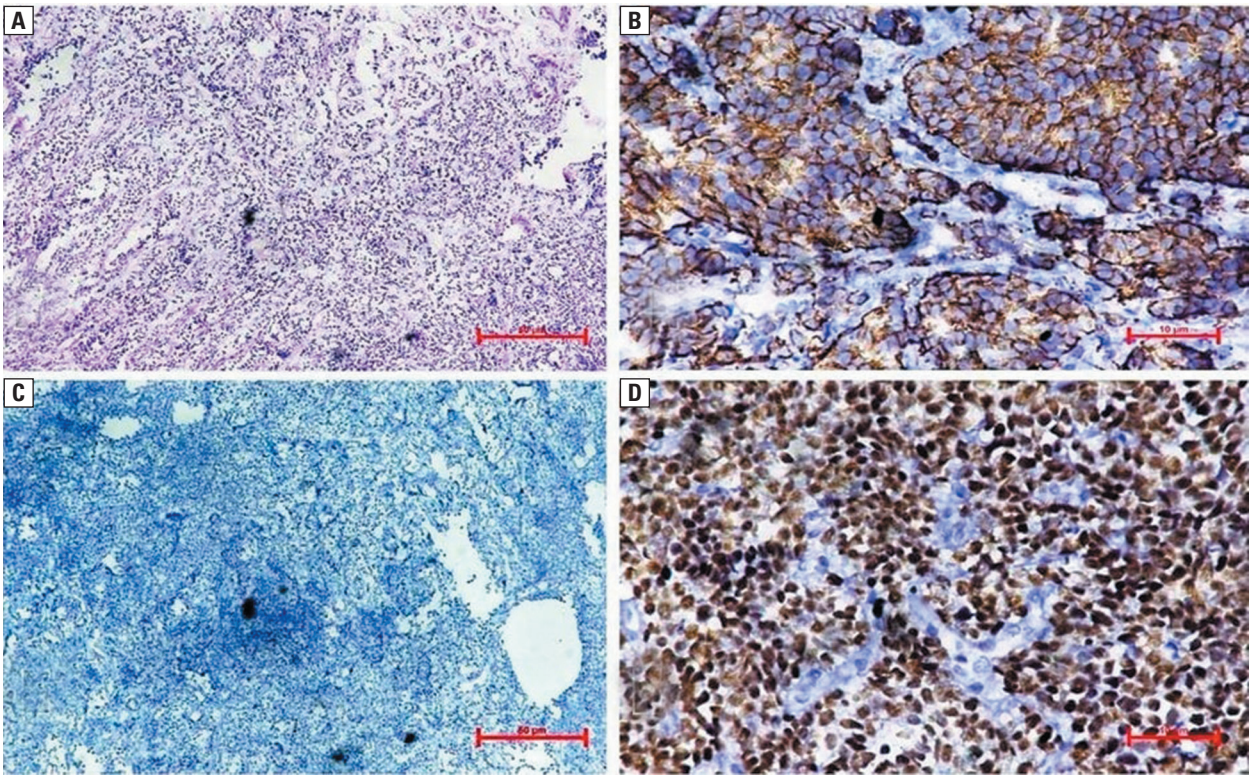

Figure 2. Section from pleural biopsy (H&E 10×) shows small round malignant cells (**A**). Immunohistochemistry shows nuclear positivity for TLE-1 and membranous positivity for pan-CK (**B, D** respectively). Tumor cells are negative for calretinin (**C**)

suspicion of this diagnosis when evaluating pleural tumors presenting with hemorrhagic pleural effusion.

Conflict of interest

None declared.

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Dyspnea in Takayasu arteritis — an ordinary cause with an extraordinary link

Abstract

Takayasu arteritis (TA) poses a diagnostic challenge as it may have a myriad of clinical presentations. Dyspnea, as an index presentation in TA, may be secondary to the involvement of the aorta, myocardium, and/or the pulmonary vessels, or can present as a manifestation of pulmonary infection with tuberculosis. Significant lymphadenopathy cannot be attributed to TA and serves to point towards a different diagnosis or concomitant infection. Tuberculosis has been associated with TA and has considerable pathogenic and therapeutic implications. We present a case of a young female with extensive intra-thoracic tubercular lymphadenopathy compressing the trachea and right main bronchus resulting in dyspnea. The patient was subsequently found to have active TA and improved after treatment with anti-tubercular therapy and steroids. We review the causes of dyspnea and mediastinal lymphadenopathy in a patient with TA.

Key words: Takayasu arteritis, extra-pulmonary tuberculosis, dyspnea

Adv Respir Med. 2021; 89: 63–67

Introduction

Takayasu arteritis (TA) is a large vessel vasculitis that preferentially affects young females of Asian origin. It classically presents with intermittent claudication and asymmetry in pulse volume between the limbs due to its predilection for the aorta and its branches. Dyspnea is uncommon and can be attributed to the involvement of the aorta, myocardium, and/or pulmonary vessels. It may also be caused by pulmonary infection with tuberculosis and, as in the present case, by extrinsic airway compression due to mediastinal lymphadenopathy.

Case

A 16-year-old girl presented with acute onset dyspnea on exertion (mMRC class III) along with a dry cough and low-grade fever for one week. There was no postural or diurnal variation in the dyspnea, no sputum production, and the patient did not have contact with a patient with tuberculosis. She had a history of intermittent claudication of both legs on walking more than 500 meters. On examination, the respiratory rate was 28/min and breath sounds were reduced on the right side without audible wheezes or crepitations. On percussion, resonance was noted on the right side. Peripheral pulses were not palpable in the upper limbs, and only feeble pulsations were felt in bilateral femoral and popliteal arteries. Correspondingly, blood pressure was not recordable in either upper limb and was asymmetric between the two lower limbs (80/40 mm Hg in the left *vs* 110/70 mm Hg in the right). Bruits were audible over the right brachial artery, abdominal aorta, and right femoral artery. There was no pedal edema or neck vein distention, and cardiac auscultation was normal.

The patient's feeble pulses and low blood pressure initiated emergency fluid resuscitation protocols. Laboratory investigations revealed anaemia (haemoglobin 10.3 g/dL), leukopenia (2380 cells/mm^3), and elevated inflammatory markers with an erythrocyte sedimentation rate of

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DOI: 10.5603/ARM.a2020.0175
Received: 01.07.2020

ISSN 2451–4934

60 mm/h and C-reactive protein levels of 13 mg/dL (normal < 5 mg/dL). For suspected vasculitis, we tested for rheumatoid factor, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, and antibodies to double-stranded DNA, along with serologies for HBV, HCV, syphilis, and HIV, which were all negative. Urinalysis was bland, without proteinuria, hematuria, or casts. Renal artery doppler screening ruled out significant renal artery stenosis. ECG and bedside echocardiographic examination ruled out left venticular (LV) systolic dysfunction, pulmonary hypertension, and stenosis.

A chest X-ray revealed bulky lymph nodes (Figure 1). A subsequent contrast-enhanced computed tomography (CECT) scan showed necrotic conglomerated and lobulated lymph nodes up to 7.5 cm in diameter, located in the subcarinal and paratracheal locations, with compression of the trachea and right main bronchus (Figure 2). A tubercular aetiology of these lymph nodes was suggested by the presence of tiny well-formed granulomas with necrosis on endobronchial-ultrasound-guided transbronchial node aspiration (EBUS TBNA). GeneXpert™ from the TBNA was positive for rifampicin-sensitive tuberculosis.

Magnetic resonance angiography (MRA) confirmed diffuse (60%) stenosis of the upper infrarenal abdominal aorta and occlusion of bilateral subclavian arteries with distal reformation suggestive of aortoarteritis (Figure 3). She fulfilled all six of the American College of Rheumatology (ACR) criteria and was thus diagnosed with TA. She was also diagnosed with extra-pulmonary tuberculosis. She was treated with a combination of corticosteroids (prednisone at 1 mg/kg for six weeks, followed by a slow taper over nine to twelve months) and anti-tubercular therapy (ATT, nine months). Repeat CT imaging at one year showed near resolution of lymph nodes (size 7.5 cm decreased to 1.5 cm), and an MRA confirmed reduction in disease activity with an increase in luminal patency. The patient is doing well at 1 year of follow-up without symptoms of claudication, cough, or dyspnea.

Discussion

Tuberculosis' association with TA is not only a medical curiosity, but is also thought to play a role in the immunopathogenesis of TA. A systematic review evaluating this association found a high prevalence of active tuberculosis (16%) and latent tuberculosis (59%) in patients with TA, far higher than the general population [1]. They hypothesized that a loss of tolerance against self-

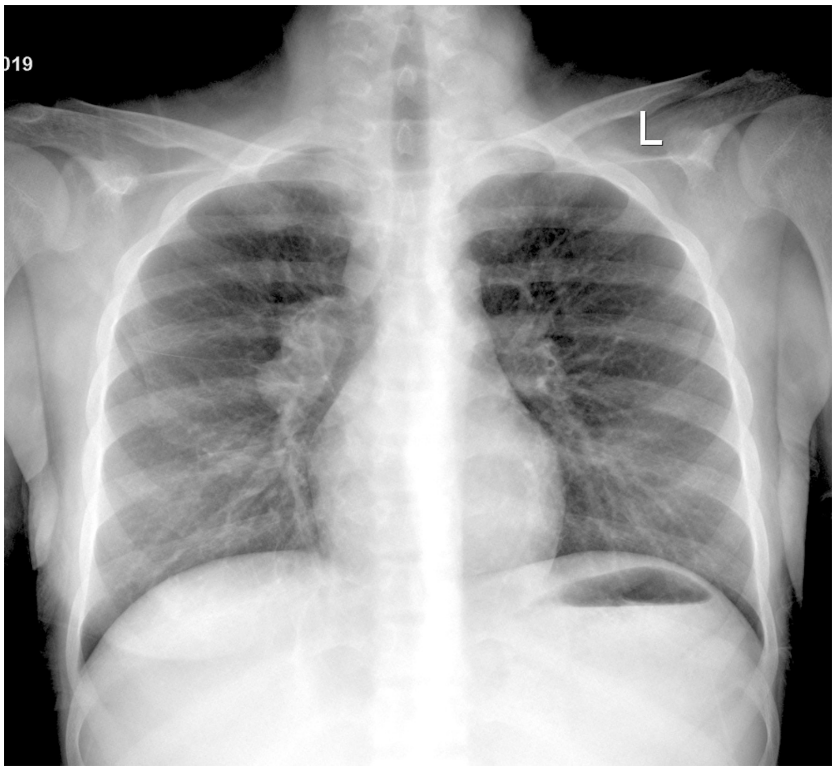

Figure 1. Chest X-ray posteroanterior view showing bulky hilum on the right side > left side with well defined enlarged lymph nodes, right paratracheal stripe thickening, and normal lung parenchyma. The right lower lobe bronchus appears to be narrowed without significant collapse

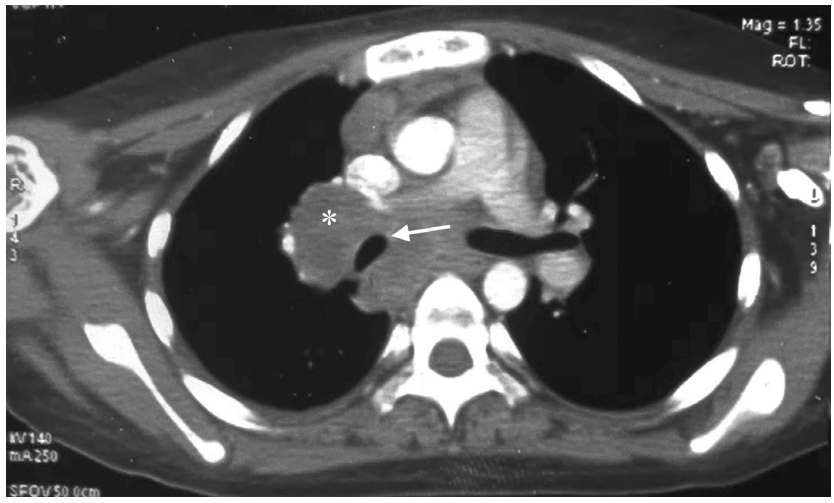

Figure 2. Contrast-enhanced computed tomography chest showed conglomerated lobulated lymph nodes with necrotic core in subcarinal and paratracheal location, the largest measuring 7.5 × 7.5 cm (asterisk), compressing the trachea and right main bronchus (arrow)

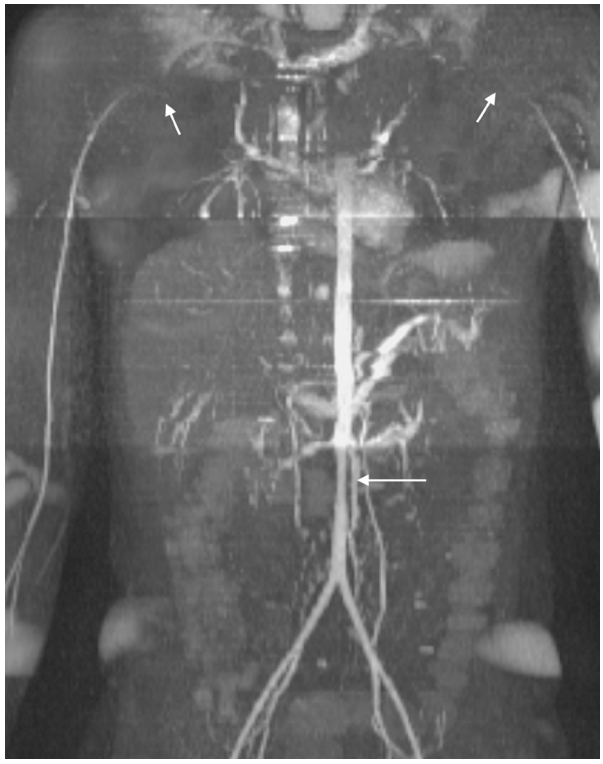

Figure 3. Magnetic resonance angiography revealed diffuse (60%) stenosis of the upper infrarenal abdominal aorta, occlusion of bilateral subclavian artery with distal reformation suggestive of aortoarteritis

stress proteins is the main pathogenic event in TA, and the extensive sequence homology between mycobacterial and human stress proteins leads to epiphenomenal cross-reactions.

Treating these conditions simultaneously with corticosteroids and ATT is effective. Use of corticosteroids does not increase the risk of microbiological failure of ATT in pulmonary tuberculosis [2]. TNFα inhibitors have been used in steroid-refractory TA with an extremely low risk of reactivation of latent tuberculosis (0.9%) similar to other rheumatic disorders [3]. This suggests that the association between TA and tuberculosis is predominantly epi-phenomenal, instead of a result of latent infection.

There are several mechanisms by which patients with TA can manifest dyspnea (Table 1). A previous case reported dyspnea as the index presentation which was attributed to the involvement of pulmonary arteries [4]. Pulmonary arterial involvement on pathological examination occurs in half of the cases but is rarely symptomatic. Since it presents with progressive dyspnea and angina, chronic thromboembolic pulmonary hypertension should be kept as a differential. Systolic cardiac failure resulting from dilated cardiomyopathy, with or without histological evidence of myocarditis, may be the first presentation of TA [5]. Other cardiovascular complications resulting in dyspnea include aortic regurgitation secondary to aortic root dilation [6] and acute myocardial infarction [7].

Lymphadenopathy cannot be attributed to TA alone. However, aortitis with concomitant lymphadenopathy narrows the list of differentials (Table 2). In patients with underlying TA, lymphadenopathy may be coincidental due to infections or malignancy, but the occurrence of tuberculosis is more likely. Lymph node involvement was present in 14% (16 out of 110) of adult cases of TA with active tuberculosis identified in the above-mentioned systematic review [1]. One must also consider that a distinct disease process resulted in the aortitis and lymphadenopathy exemplified by tubercular aortitis [8],

Table 1. Causes of dyspnea in patients with Takayasu arteritis

No.	Cause of dyspnea	Characteristics of dyspnea	Diagnosis	References
1	Pulmonary artery stenosis/ /pulmonary hypertension	Gradual onset, mild, exertional	CT or MRA, lung perfusion scan	[4]
2	Congestive heart failure (dilated cardiomyopathy, with or without myocarditis)	At rest or exertion, orthopnea, nocturnal; gradual or acute; crepitations, LV S3, pedal oedema	ECHO, rndomyocardial biopsy, pro-BNP/NT-pro BNP	[5]
3	Aortic insufficiency	Gradual, mild to severe, exertional; angina	Echocardiogram, cardiac CT or MRI scan	[6]
4	Acute myocardial infarction	Acute, at rest or exertion, orthopnea, nocturnal; crepitations, LV S3, pedal oedema	Cardiac troponins, ECG, angiography	[7]
5	Tuberculosis-pulmonary or extra-pulmonary	Gradual, exertional; wheeze or decreased air entry, cough, hemoptysis, fever, night sweats	Sputum examination, chest X-ray, HRCT chest	[1], present case

CT — computed tomography; ECG — electrocardiography; HRCT — high resolution computed tomography; MRA — magnetic resonance angiography; LV — left ventricular

Table 2. Causes of lymphadenopathy in a patient with aortitis

No.	Cause of lymphadenopathy	Characteristics	Diagnosis	References
1	Tuberculosis	Directly due to tubercular aortitis, or due to concomitant TA	Lymph node biopsy, ZN staining, CB-NAAT, liquid culture	[8]
2	IgG4 related disease	Thoracic: males, aortic arch, lymphoplasmacytic infiltrate, more severe. Inflammatory abdominal aortic aneurysms: less severe, lower IgG4 levels	Lymph node biopsy: HPE with staining for IgG4 + cells, serum IgG4 levels	[9]
3	Syphilis	Quaternary syphilis, often causes aortic root aneurysm, aortic regurgitation	Treponemal and non-treponemal serology	[10]
4	Sarcoidosis	Middle-aged, often with myocardial involvement	Lymph node biopsy, serum ACE levels, serum and urinary [Ca^{2+}] levels, Bronchoalveolar lavage (CD4: CD8 ratio)	[11]

ACE — angiotensin converting enzyme; TA — Takayasu arteritis; CB-NAAT — cartridge based nucleic acid amplification test; HPE — histopathological examination; ZN — Ziehl-Neelsen stain

IgG-4 disease-related periaortitis [9], syphilitic aortitis [10], and possibly sarcoidosis [11]. The visualization of necrotizing granulomas and AFB, or a positive GeneXpert™ from nodal tissue, as found in our case, establishes the diagnosis of tubercular lymphadenopathy.

Our patient presented with extrinsic airway compression by large mediastinal lymph nodes which was eventually attributed to tuberculosis. Further evaluation confirmed active TA necessitating appropriate treatment for both conditions with steroids and ATT. To the best of our knowledge, this unusual cause of dyspnea in TA is the first in literature.

Conclusions

Takayasu arteritis possibly results from an epi-phenomenal cross-reaction with tubercular and human stress proteins, and these patients often have active or latent tuberculosis at presentation. TA patients with dyspnea should be evaluated for cardiac, pulmonary, and vascular involvement, as well as pulmonary tuberculosis or mediastinal lymphadenopathy.

Conflict of interest

None declared.

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Streptomyces pneumonia in an immunocompetent adult — a rare isolate

Abstract

Streptomyces belongs to the *Actinomycetes* group of bacteria which are gram-positive non acid-fast bacilli, widely recognised for their potential to produce antimicrobials active against bacterial, mycobacterial, parasitic and fungal infections. They commonly cause cutaneous infections following traumatic inoculation. Visceral infections are relatively rare and limited to immunocompromised hosts. We describe a case of *Streptomyces* pneumonia in a healthy immunocompetent female, who when investigated for voluntary kidney donation, resulted in the isolation of *Streptomyces* species from bronchial wash cultures. *Streptomyces*, a potential pathogen in immunocompetent hosts is frequently underdiagnosed. Once isolated, both physicians and microbiologists should pay attention to differentiate true infection from contamination.

Key words: *Streptomyces*, pneumonia, immunocompetent, visceral infections

Adv Respir Med. 2020; 88: 68–71

Introduction

Streptomyces is an organism that is celebrated since time immemorial due to its great contribution to medicine in the form of many excellent antimicrobials. It is well known that *Streptomyces* causes superficial skin and soft tissue infections following traumatic inoculation, the most common of which being *Mycetoma* in the feet of farmers, a chronic suppurative infection of the skin and underlying soft tissue [1]. It rarely causes bacteremia, pneumonia, and other visceral infections in the backdrop of immunocompromised states. We herein report the occurrence of *Streptomyces* pneumonia in an immunocompetent adult and discuss its varied clinical manifestations, radiological features, diagnostic challenges, and treatment recommendations.

Case details

A 49-year-old non-smoking female visited our respiratory outpatient clinic to receive a fitness certificate in order to become a kidney donor. She wished to donate one of her kidneys to her brother. Detailed history revealed that she had a cough with purulent expectoration for 5 days. There was no history suggestive of pulmonary tuberculosis, chronic respiratory tract illness, or any immunocompromised state. She is a homemaker and there is no history of environmental or workplace exposure to dust or moldy hay. No previous significant medical history was noted. On examination, she was comfortable at rest. Her heart rate was 70 beats/min, blood pressure 110/70 mmHg, oxygen saturation 98% on room air, and respiratory rate 20 breaths/min. On chest auscultation, bilateral normal vesicular breath sounds were heard. Routine blood investigations were unremarkable. The chest radiograph was normal. However, high resolution computed tomography (HRCT) of the thorax showed bilateral tree-in-bud nodules in the right middle lobe and left lingula (Figure 1) which prompted us to investigate further for the cause of infection. Sputum pyogenic culture, acid-fast bacilli staining, and

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DOI: 10.5603/ARM.a2020.0171
Received: 06.07.2021

ISSN 2451–4934

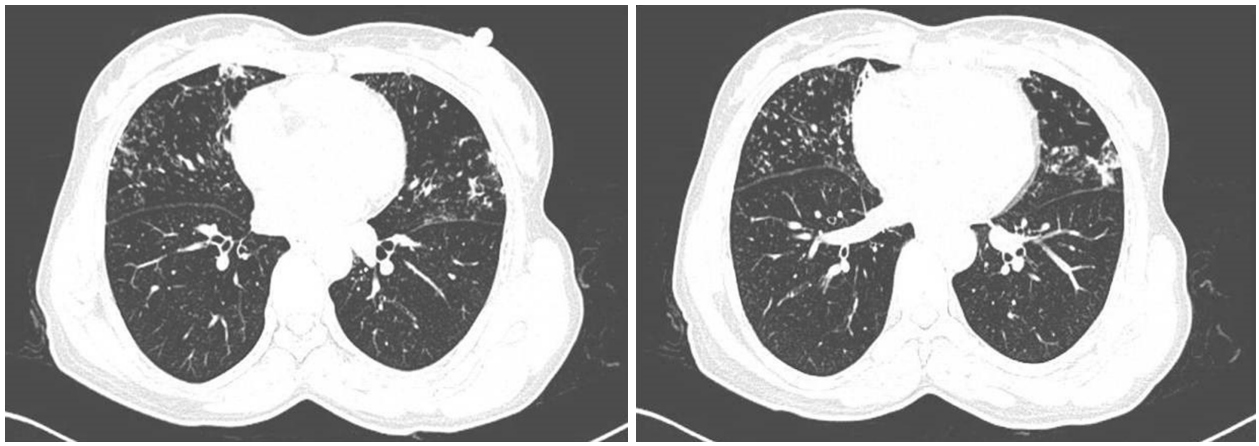

Figure 1. High resolution computed tomography of the thorax showing tree in bud nodules in right middle lobe and left lingula

a cartridge-based nucleic acid amplification test yielded negative results. She was treated with amoxicillin-clavulanic acid and azithromycin empirically for 5 days, but the symptoms persisted. Hence, fiberoptic bronchoscopy was completed. Bronchial washings grew *Streptomyces* species along with *Streptococcus pneumoniae*. Modified Ziehl-Neelsen staining showed thin, non acid-fast filaments of *Streptomyces* species (Figure 2), and blood agar showed non-hemolytic, dry, and whitish colonies of *Streptomyces* species (Figure 3). Bronchial wash mycobacterial culture and fungal culture yielded no other pathogen. She was treated with trimethoprim-sulfamethoxazole for *Streptomyces* infection based on antimicrobial sensitivity testing for 1 month. On follow-up, marked clinical and radiological resolution was observed.

Discussion

Streptomyces are aerobic, gram-positive, filamentous bacteria that are negative for acid-fast stain and classified under the order Actinomycetales [1]. The presence of extensive branched aerial hyphae with long chains of conidia gives them a characteristic appearance [1]. Once upon a time, these microorganisms were classified as fungi due to the presence of true aerial hyphae, but are now reclassified as bacteria. The natural habitat is soil as it supports the mycelial growth of the bacteria. The *Streptomyces* genus is widely known as the largest antimicrobial producing genus as it produces many antibacterials, antifungals, antiparasitic agents, immunosuppressants, and other bioactive compounds. Antimicrobial agents produced from the *Streptomyces* genus include Chloramphenicol, Streptomycin, Fosfomycin, Daptomycin, Lincomycin, Neomycin, Puromycin, Tetracyclines, and Clavulanic acid just to name a few [2]. More than 3,100 *Streptomyces* species are known so far [1].

Visceral infections are rare and commonly occur in immunocompromised states caused by cancer, chemotherapy, acquired immunodeficiency syndrome or human immunodeficiency virus infection, Crohn's disease, Cushing's syndrome, and exogenous steroid use. They can also occur due to the presence of foreign material like central venous catheters or prosthetic heart valves [4–6]. Our case is unusual as the microorganism was isolated from the bronchial wash of an immunocompetent adult. Very few cases of *Streptomyces* pneumonia in immunocompetent individuals have been reported in the literature to date [7].

Cases of *Streptomyces* pneumonia can present with complaints of fever, productive cough, hemoptysis, breathlessness, and pleuritic chest pain [8, 9]. It can also cause septicemia. Chest computed tomography (CT) features are varied and can include nodular infiltrates, abscesses, consolidations, interstitial infiltrates with interstitial thickening, hypersensitivity pneumonitis, pleural effusions, empyema, hilar adenopathy, and mediastinal lymphadenopathy [8, 9]. Our patient presented with cough with expectoration, a normal chest radiograph, and tree-in-bud nodules in chest CT imaging.

Streptomyces species have also been isolated in cases of lymphadenitis, pericarditis, endocarditis, monoarthritis, brain abscess, peritonitis, liver abscess, and dental caries. The outcome has been fairly good in the majority of these cases with resolution of infection [3]. However, *Streptomyces* species were not described as the principal pathogen in many of these reports. Hence, the role of *Streptomyces* becomes confusing and con-

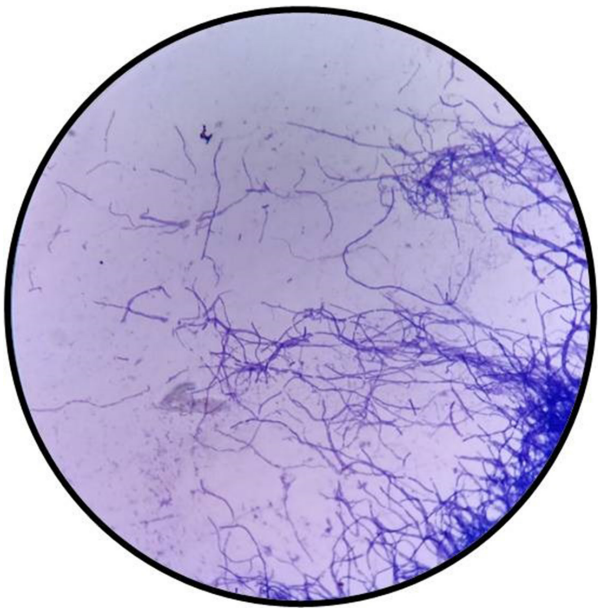

Figure 2. Modified Ziehl-Neelsen stain demonstrating thin non acid fast filaments of *Streptomyces* spp. (×1000)

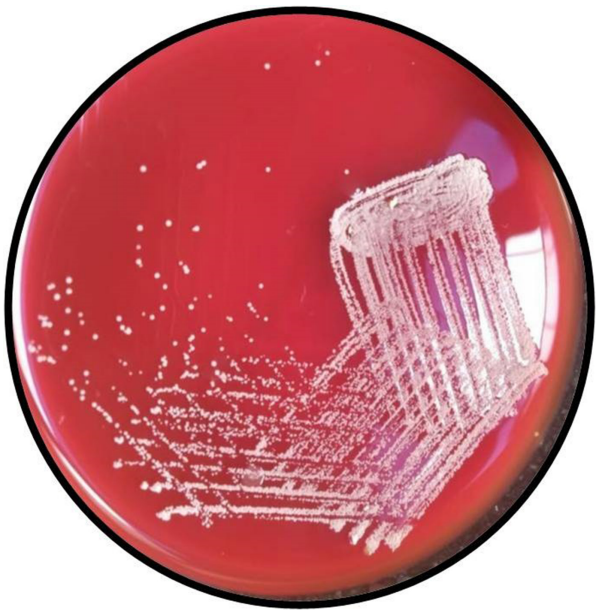

Figure 3. Blood agar showing non hemolytic, dry, whitish colony of *Streptomyces* spp.

troversial when isolated from visceral infections along with other primary pathogens. This makes isolation of organisms from sterile sources and the prevention of contamination of specimens important to diagnose the true infection. In our case, *Streptomyces* was isolated from bronchial wash ruling out the possibility of contamination. Although *Streptococcus pneumoniae* was isolated along with *Streptomyces,* there was no clinical or radiological improvement following empirical antibiotics. Hence, we assume *Streptomyces* to be the primary pathogen. In addition, there was clinical and radiological resolution following treatment with a sensitive antibiotic.

Streptomyces infection poses a diagnostic challenge. *Streptomyces* pneumonia was underdiagnosed in the past due to the diagnostic constraints and paucity of molecular methods. Diagnosis depends on clinical features and laboratory isolation of the bacteria. Diagnostic methods include pyogenic culture of sputum, bronchoalveolar lavage in cases of consolidation and lung abscess, pyogenic culture of pleural fluid, pleural biopsy in cases of pleural effusions, fine needle aspiration cytology or biopsy in the presence of peripheral nodules, and blood culture in the presence of septicemia [8]. The isolate is identified based on its colonial morphology and negative acid-fast staining. Histopathological examination may reveal the presence of granulomas associated with focal necrosis. This resemblance to mycobacteria makes it difficult to distinguish one from the other. Bacterial culture is used to confirm the diagnosis in such puzzling cases. Other features include sensitivity to lysozymes, a positive catalase test, positive gelatin, and hydrolysis of casein, tyrosine, and xanthine [7]. Recent advances in biotechnology helps in the identification of *Streptomyces* by sequence analysis of the 16S rRNA gene [10]. Isolation of the pathogen from sterile sources, direct microscopic identification of infected tissue, and exclusion of other causes are considered important. At least two of the above criteria is necessary to diagnose true infection [9].

Since there is a dearth of well-documented cases and treatment recommendations for visceral infections caused by *Streptomyces* species, treatment is based on in vitro antimicrobial susceptibility testing and analogous data from the management of Nocardia infections. *Kapadia et al.* illustrated that *Streptomyces* organisms were consistently susceptible to amikacin, frequently susceptible to imipenem, clarithromycin, erythromycin, minocycline, and trimethoprim-sulfamethoxazole, and infrequently susceptible to ciprofloxacin and ampicillin [8]. Kofteridis *et al.* reported that the most potent drugs were minocycline, imipenem, erythromycin, doxycycline, and an aminoglycoside, whereas a significant percentage were resistant to trimethoprim-sulfamethoxazole, ampicillin, and ciprofloxacin [7]. In the CDC evaluation of the antimicrobial susceptibility of *Streptomyces griseus*, the most potent

drugs were found to be minocycline, imipenem, erythromycin, and doxycycline with more than 80% of the strains susceptible to these drugs [1]. It is interesting to note that 29% of these strains were resistant to trimethoprim-sulfamethoxazole. Unlike *Streptomyces*, trimethoprim-sulfamethoxazole is considered to be the antimicrobial of choice for Nocardia, which belongs to the same class. These data provide valuable guidance and solutions for empiric management while awaiting a strain-specific susceptibility report. These also emphasize the importance of strain-specific susceptibility data for the optimal management of *Streptomyces* infections as antimicrobial resistance varies markedly among species.

Streptomyces usually demands a long treatment duration as they are slow-growing bacteria. A treatment duration of 6 to 24 weeks has been reported in the literature [9]. However, the host immunity, site of isolation, and chronicity of infection also play a central role in deciding treatment duration. *Streptomyces* infection generally carries a good prognosis.

Conclusion

Streptomyces pneumonia, though rare, should be considered in the differential diagnosis of interstitial pneumonia in immunocompetent adults. It is important to differentiate between contamination and true infection. *Streptomyces* infection usually warrants a longer treatment duration. Limited clinical experience thus far warrants further studies in order to improve knowledge of the genus *Streptomyces*, its natural history, and the course of these infections.

Conflict of interest

None declared.

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Transbronchial lung cryobiopsy (TBCB) performed in acute COVID-19 pneumonia: first report

Abstract

A COVID-19 diagnosis is usually based on PCR detection of viral RNA in airway specimens in a patient with typical clinical features. Histological features of the COVID-19 lung disease are reported from autopsies. Transbronchial cryobiopsy (TBCB) is an evolving technique usually performed in the diagnosis of interstitial lung disease.

We report a TBCB in a 76-year-old female patient who had repeatedly tested negative for SARS-CoV-2 infection. The pathological examination revealed the presence of interstitial pneumonia with lymphocytic infiltration. The qRT-PCR against SARS-CoV-2 from a pharyngeal swab was positive after performing the TBCB.

Key words: COVID-19; pneumonia; transbronchial lung cryobiopsy

Adv Respir Med. 2021; 89: 72–74

Introduction

Coronaviruses are known animal and human pathogens that have been getting more attention after the evolution of the novel coronavirus as an identified cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China [1]. On March 11, 2020, the WHO classified SARS-CoV-2, the causative agent of COVID-19, as a pandemic due to the rapid spread of the disease worldwide. At the time of writing, COVID-19 had spread to 184 countries [2].

Clinical and radiological features of COVID-19 have been described in many studies [3]China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV. However, pathological findings from postmortem studies are still insufficient. Only a few reports have been published that address the pathological features of the COVID-19 pneumonia and ARDS [4, 5]. To our knowledge, there are no reports of small biopsies from lung tissue because COVID-19 pneumonia itself is not an indication for transbronchial lung biopsy. In this report, we describe a transbronchial lung cryobiopsy (TBCB) as well as an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of an enlarged mediastinal lymph node in a patient with COVID-19 lung disease.

Case description

A 76-year-old female patient was referred to our center for further management. In February 2020, the patient suffered from flu-like symptoms which were partially relieved after 10 days of treatment with Amoxicillin und clavulanic acid. However, exertional dyspnea persisted. The patient was tested twice using nasopharyngeal swabs for qRT-PCR against SARS-CoV-2 and was negative both times (PCR-Platform of the BD Max System from Becton Dickinson with the VIASURE SARS-CoV-2 S gene Real Time PCR Detection from Certest). For further diagnosis, a chest CT (performed April 6th) revealed bilateral peripheral pulmonary consolidations. On admission, the patient was afebrile and acyanotic. Auscultation of the lungs revealed the presence of fine inspiratory crackles bilaterally. Following a multidisciplinary discussion, a decision was made to perform a bronchoscopy, specifically a transbronchial lung

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DOI: 10.5603/ARM.a2021.0032
Received: 18.07.2020

ISSN 2451–4934

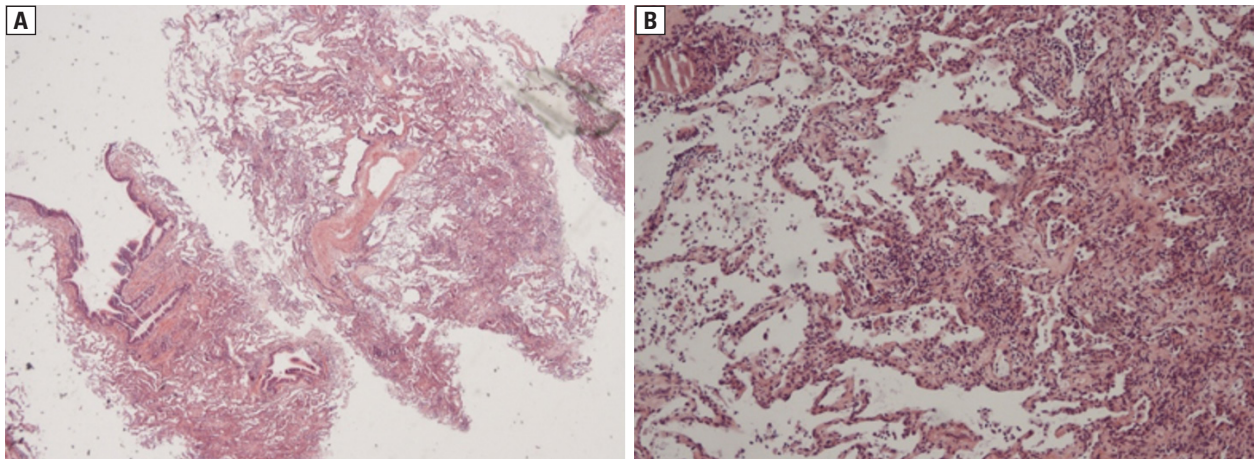

Figure 1. A. Overview with patchy peribronchial broadening of alveolar septa and interstitial inflammatory infiltrates (HE, 20×). **B.** A more detailed view with mixed interstitial inflammation, fibroblastic foci, and a protein precipitate (upper left) (HE, 100×)

cryobiopsy, in order to establish a diagnosis. Cryo-TBB was performed from the peripheral right lower lobe. Additionally, an EBUS-TBNA was performed from a subcarinal lymph node (Position 7, 10,3 mm). The histopathological results showed an interstitial pneumonia caused by an infiltration with lymphocytes. Subsequently, a swab was taken from the hypopharynx and qRT-PCR against SARS-CoV-2 was repeated for the third time, this time yielding a positive result and confirming the diagnosis of COVID-19 pneumonia.

After two further weeks, the patient was discharged after two negative COVID-19 tests without residual symptoms or an indication for oxygen supplementation.

Pathological findings

The cell block from the mediastinal lymph node showed small, complex, and bruised lymphatic tissues with macrophages and anthracotic pigments. The pathological examination of the Transbronchial Lung Cryobiopsy showed significant inflammatory changes with occasionally detectable spherical protein precipitates containing foreign bodies, activated pneumocytes, and moderate mixed inflammatory infiltrate such as T-lymphocytes, macrophages, and some neutrophils containing fibroblastic buds, which were partially septal and partially intra-alveolar in location. This finding indicates the presence of interstitial pneumonia (Figure 1, 2).

Discussion

The total number of confirmed COVID-19 cases exceeds 3,6 million worldwide at the time of the writing of this case report [6]. Despite that, the data about the disease, especially the histopathological data, is still growing. The lack of pathological information may be related to the sudden nature of the outbreak, the large number of affected patients that exceeds the capacity of health care facilities in many countries, and the fear of disease transmission during the invasive procedures when taking a biopsy [4].

The decision to take a biopsy from the lung was made in order to establish a diagnosis due to the suspicious ILD. This decision was made as a result of the CT imaging which showed an atypical pattern, as well as the atypical presentation of the patient (afebrile patient). Also, before the procedure, the qRT-PCR against SARS-CoV-2 was negative two times. Transbronchial lung cryobiopsy (TBCB) offers a higher diagnostic yield in parenchymal lung diseases compared to a regular transbronchial forceps biopsy due to larger sample sizes and reduced tissue artifacts [7]the resultant tissue samples are of high quality, and the lung parenchyma seen in the samples is adequate for a histological diagnosis in most cases. Bleeding after transbronchial biopsy is the most important procedure- associated complication and may be life threatening. This study addresses the risk of bleeding of transbronchial cryobiopsy. Methods: In this prospective, randomized, controlled multicentre study 359 patients with interstitial lung disease requiring diagnostic bronchoscopic tissue sampling were included. Both conventional transbronchial forceps biopsy and transbronchial cryobiopsy were undertaken in each patient. The sequence of the procedures was randomized. Bleeding severity was evaluated semi-quantitatively as \"no bleeding\", \"mild\" (suction alone. The

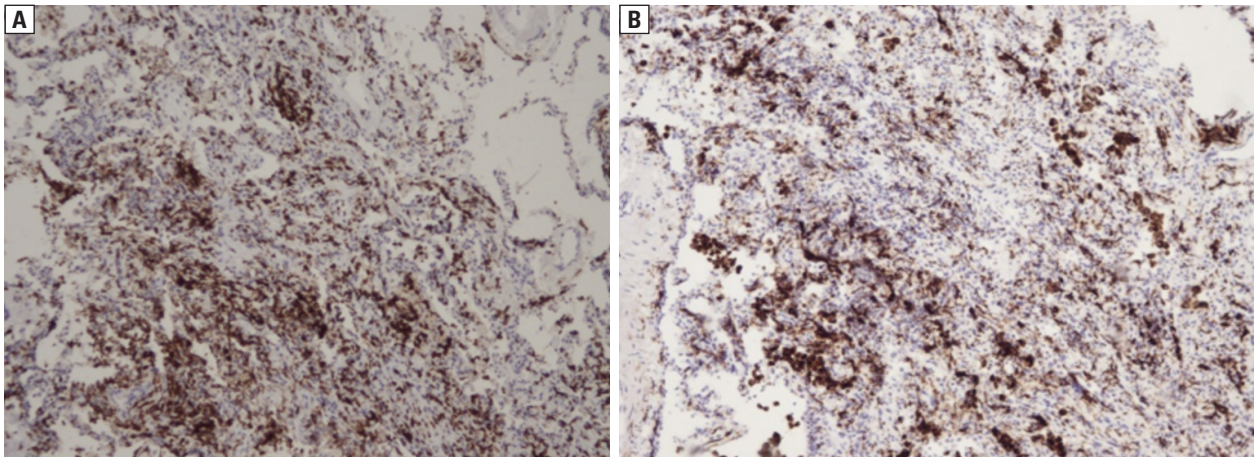

Figure 2. Immunohistological characterization of the inflammatory infiltrate with T-lymphocytes, macrophages, and nearly a complete absence of B-lymphocytes. **A.** Anti-CD3, 100×. **B.** Anti-CD68, 100×

pathological examination in our patient showed a complete picture of Acute Interstitial Pneumonia with significant lymphocytic infiltration. The patient suffered from exertional dyspnea and radiological imaging revealed bilateral consolidations.

The overall evaluation of the patient could be described as non-severe COVID-19 pneumonia. Those findings represent an early phase of the COVID-19 infection [8]. As a result of this, in our report we describe the pathological findings that could be found in early COVID-19 lung disease.

The clinical course of the COVID-19 infection can be classified as a mild form of the infection in the vast majority of the patients (80%), severe illness in about 14% of the patients, and critical illness (including severe ARDS, sepsis, and septic shock) in about 5% of the patients [9].

The difference in the clinical presentations is explained by the difference in the pathological findings that have been described in patients with COVID-19-ARDS in which features of diffuse alveolar damage (DAD) are present. These features include hyaline membrane formation, fibrin exudates, epithelial damage, and diffuse type II pneumocyte hyperplasia with features of bacterial superinfection [4]. The fibrotic changes are rare. Available pathological data is still limited and lung biopsies from surviving patients with non-severe disease have not yet been published. The DAD features were reported in postmortem studies in patients with severe ARDS [4, 5].

The pathological findings in COVID-19 pneumonia were described in one report describing two patients who underwent lobectomy for adenocarcinoma and were found to have COVID-19. The pathological examination revealed the presence of edema, pretentious exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells. The hyaline membrane was not prominent [4].

In our report, we describe novel pathological findings of non-severe COVID-19 pneumonia obtained by the innovative technique of transbronchial lung cryobiopsy (TBCB) that contribute to the overall limited available information about the pathology of the disease.

Conflict of interest

None declared.

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Systemic sclerosis-interstitial lung disease with coexistent subacute invasive pulmonary aspergillosis: a rare association

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A 55-year-old female complained of recurrent haemoptysis, low-grade fever, cough, and worsening dyspnoea for three months. She was a diagnosed case of systemic sclerosis-interstitial lung disease for which she was on tapering doses of prednisolone and Mycophenolate Mofetil for past 2 years. On admission, she was febrile, had tachycardia, tachypnoea and pallor was present. Bilateral fine velcro crepitations were present on auscultation of the chest. Arterial blood gas (ABG) revealed acute respiratory alkalosis and hypoxemic respiratory failure. Chest radiograph showed bilateral interstitial shadows and cavitation in right upper zone. Computerised tomography (CT) of the thorax revealed a fibrotic interstitial lung diseases (ILD) with multiple cavities, fungal ball, pericavitatory infiltrates, and pleural thickening (Figure 1). Transbronchial lung biopsy (TBLB) disclosed acute angled branching septate hyphae invading lung parenchyma with surrounding necrotic inflammation. Fungal culture grew *Aspergillus fumigatus*. *Aspergillus fumigatus*-specific IgG was elevated. She was labelled as subacute invasive aspergillosis (SAIA) and initiated on voriconazole 200mg twice a day. She responded to treatment and haemoptysis subsided. Oral voriconazole was continued and she was kept under close follow-up.

Pulmonary infections are the most common causes of morbidity and mortality in fibrotic ILD. Parenchymal fibrosis (cysts, traction bronchiectasis, and honeycombing) combined with immunosuppressive therapy predispose to chronic infections, such as tuberculosis and aspergillosis. Spectrum of aspergillus infections include pulmonary aspergilloma, chronic pulmonary aspergillosis (CPA), and invasive pulmonary aspergillosis (IPA).

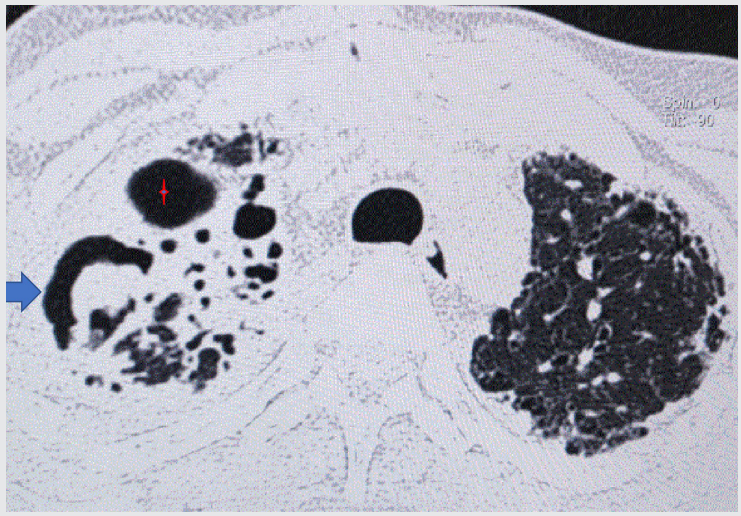

Figure 1. CT thorax lung window axial sections showing fungal ball with air crescent sign (blue arrow), cavity (red asterix), and pericavitatory infiltrates on background of fibrotic interstitial lung diseases

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DOI: 10.5603/ARM.a2020.0183
Received: 20.07.2020

ISSN 2451–4934
Conflict of interest: None declared

Table 1. Association of fibrotic ILD with pulmonary aspergillosis and their outcomes

Author	Type of study	Year	Fibrosing ILD	Aspergillus spectrum	Treatment	Outcome
Liu C, *et al.* [2]	Case report	2019	IPF	CNPA	Itraconazole	Progression
Mochizuki E, *et al.* [3]	Case report	2015	DM-ILD	CPA	Voriconazole	Responded
Nandi, *et al.* [4]	Case report	2015	Ssc-ILD	Aspergilloma	Itraconazole	Progression
Kurosaki F, *et al.* [5]	Retrospective study (15 cases out of 539 ILD had pulmonary aspergillosis)	2014	IPF, RA-ILD, PPFE	CPA-14 IPA-1	Itraconazole: 7 Voriconazole: 7 Micafungin: 1	Responded: 6 Progression: 8 No response: 1
Present case	Case report	2020	Ssc-ILD	SAIA	Voriconazole	Responded

DM — dermatomyositis; ILD — interstitial *lung diseases;* IPF — idiopathic pulmonary fibrosis; PPFE— pleuroparenchymal fibroelastosis; RA — rheumatoid arthritis

CPA can be either chronic cavitatory pulmonary aspergillosis (CCPA) or subacute invasive aspergillosis (SAIA). The diagnostic criteria of CPA include one or more cavities with or without a fungal ball or nodules on thoracic imaging, direct evidence of *Aspergillus* infection (microscopy or culture from biopsy) or an immunological response to *Aspergillus* spp. and exclusion of alternative diagnoses, all present for at least 3 months [1]. SAIA previously known as chronic necrotising pulmonary aspergillosis is a form of CPA occurring in mildly immunocompromised patients and has a rapid progression. Although aspergillus infection is usually seen in those with underlying lung diseases, their association with fibrotic ILD's is rare, limited to a single observational study and few case reports [2–5] (Table 1).

Management of CPA includes initiation of antifungal therapy, lowering doses of immunosuppression, intracavitary instillation of antifungal agents, surgical resection, and control of haemoptysis [1]. Itraconazole or voriconazole for a minimum of 4 to 6 months is preferred. Micafungin, caspofungin, amphotericin B lipid complex (ABLC) and posaconazole are used as salvage therapy. Surgery aids in improved control of infection and is curative in few cases. Indications for surgery include localised disease, life-threatening haemoptysis, and lack of response to medical therapy [1]. However, surgery is usually precluded by the lack of adequate pulmonary reserve in chronic fibrosing ILD. Finally, despite best management, prognosis of CPA is less favourable, especially in the background of ILD.

Our case report highlights this rare life-threatening complication of fibrotic ILD and alerts the clinician to the importance of early diagnosis and definitive management. SAIA is rapidly progressive and if not intervened timely, leads to morbidity and mortality.

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Thymic cancer superimposed opacity of the mediastinal anatomical structures

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Thymic cancer is a rare malignant neoplasm. Among epithelial thymic tumors, those in which thymocyte atypia is apparent, are classified as thymic cancers [1]. Thymic cancer is highly malignant and has a high frequency of distant organ metastasis. In addition, it tends to infiltrate the surrounding organs and often forms a large tumor at the time of detection. Therefore, the majority of patients can detect a large tumor by chest radiograph. We show herein a patient with thymic cancer, which was superimposed on the opacities of mediastinal structures.

A 72-year-old woman visited our hospital complaining about discomfort in the chest. She was diagnosed as having hypertension several years ago and treated with antihypertensive drugs. Echocardiography revealed pericardial fluid. Chest radiograph at this visit showed cardiomegaly, but this finding was not documented in chest radiograph taken half a year ago (Figure 1). No tumor shadow was detected in the lung field, pulmonary hilum or mediastinum. Chest computed tomography (CT) scan showed an irregularly shaped mass measuring 3 cm in diameter, which was superimposed on the opacity of mediastinal structures, in the left anterior mediastinum, and CT scan also revealed multiple liver masses, which were evaluated as liver metastases (Figure 2). Since obtaining sufficient tissue samples by transbronchial biopsy was assessed as difficult, video-assisted thoracic surgery (VATS) was performed. On macroscopic findings, the tumor was identified as mediastinal tumor. Specimens from the mediastinal mass obtained by VATS proved to be a squamous cell carcinoma.

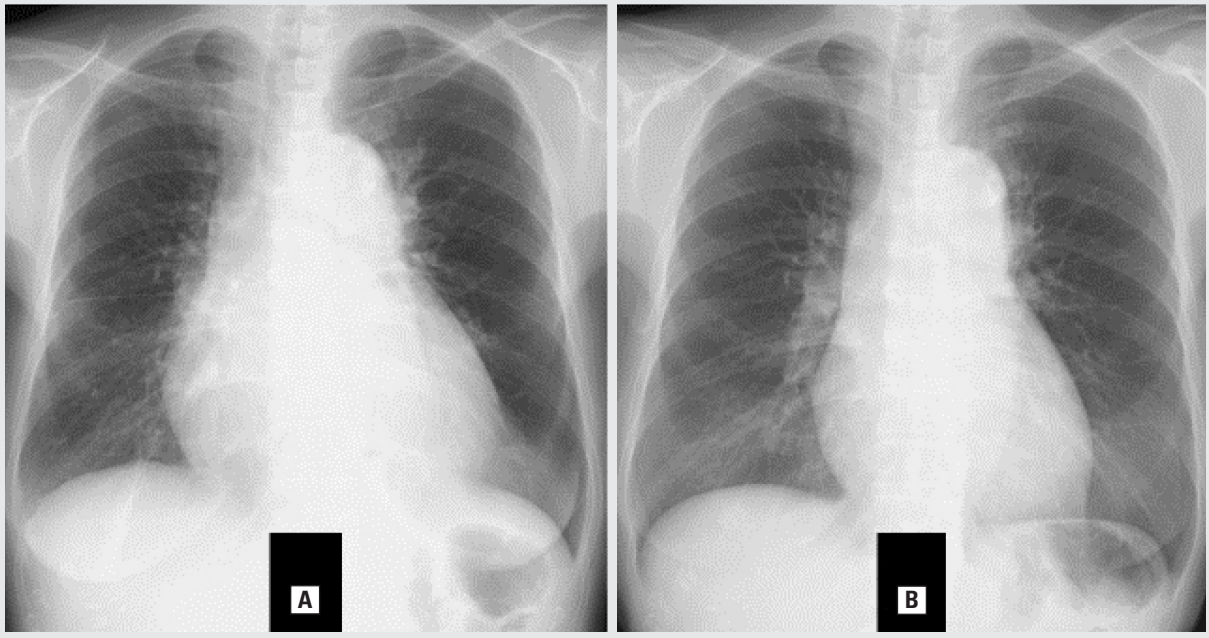

Figure 1. Chest radiograph at this visit showed cardiomegaly and abnormal separation of distance between the left hemidiaphragm and gastric air bubble (**A**), but this finding was not shown in chest radiograph taken half a year ago (**B**)

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DOI: 10.5603/ARM.a2020.0184
Received: 09.08.2020

ISSN 2451–4934
Conflict of interest: None declared

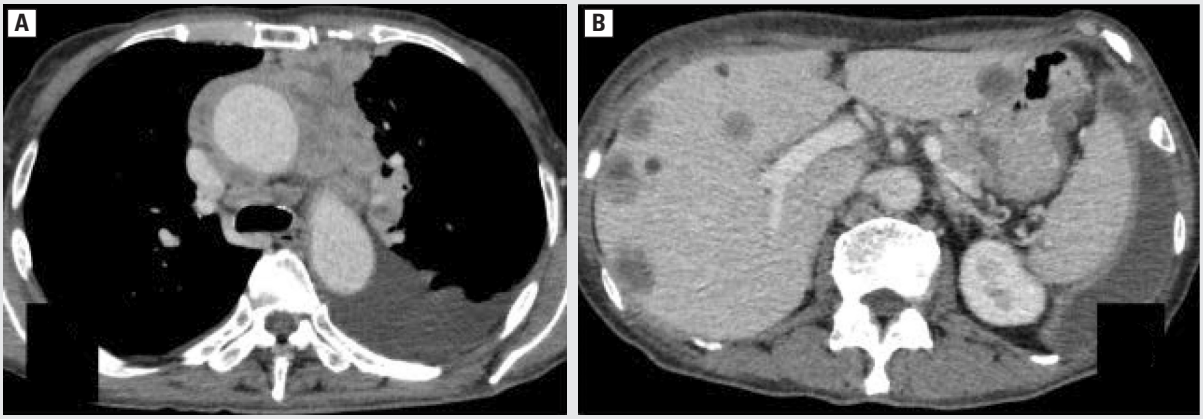

Figure 2. Chest CT scan showed an irregular-shaped mass measuring 3 cm in diameter, which was superimposed by the opacity of mediastinal structures, in the left anterior mediastinum (**A**). Abdominal CT scan revealed multiple liver masses, which were evaluated as metastatic liver tumors (**B**)

She was diagnosed as having thymic cancer with liver metastases, and received platinum-containing chemotherapy.

Although thymic cancer is a rare epithelial neoplasm, it tends to be aggressive and metastasizes widely. Many patients with thymic cancer already have distant organ metastases at the time of diagnosis. In addition, thymic cancers tend to invade surrounding organs, and often form large tumors. Therefore, the majority of thymic cancers can be easily detected as mediastinal masses on chest radiographs. The chest radiograph plays a pivotal role in the first-line imaging for initial detection of tumors originating from the thorax, although imaging for staging of most cancers is mainly based on CT scan. Regarding mediastinal tumors that could not be identified by chest radiograph, there were case reports on cardiac tumors [2, 3], esophageal submucosal tumor [4], and thymus-derived tumors [5, 6]. Thymolipoma is known as one of the superimposed thymus-derived tumors [5, 6]. Tindall *et al.* reported a patient with small thymolipoma which overlapped the mediastinum structures [5]. Mohan showed a patient with thymolipoma simulating cardiomegaly, an enlarged cardiac silhouette on chest radiograph. Chest CT revealed a giant anterior mediastinal non-contrast enhancing mass partially wrapping around the heart [6]. As far as we could search, however, there was no patient with thymic cancer, which was superimposed on mediastinal structures in chest radiograph. Although very rare, there are some mediastinal tumor patients with undetected primary lesion on chest radiograph. In such cases, chest CT is useful in confirming the exact extent of the mediastinal tumor, which is superimposed on opacities of mediastinal structures.

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A review of ciclesonide in the management of COVID-19. Still a long way to go

To the Editor

COVID-19 has spread throughout the world infecting 8,018,963 people and claiming 436,138 lives to date [1]. No definitive therapy is yet available. Numerous drugs and therapies are under investigation. One such drug is ciclesonide. It is an inhaled corticosteroid which is used in the management of bronchial asthma [2]. It has shown good anti-viral activity against SARS-CoV-2 in *in vitro* studies [3, 4]. It has been speculated that the anti-inflammatory and antiviral activity of Ciclesonide may play a beneficial role in mild to moderate cases of COVID-19.

The exact mechanism of the antiviral activity of ciclesonide is not yet known. Ciclesonide inhibits viral replication by targeting the viral endoribonuclease NSP15 [4]. Ciclesonide is a p21 activated kinase (PAK)-1 blocker and this may result in inhibition of SARS-CoV-2 replication. p21 activated kinases (PAK) are a family of 6 serine/threonine protein kinases involved in intracellular signalling by acting as downstream effectors of the small GTPases Cdc42 and Rac. They play a vital role in cell proliferation, survival, and motility. Several viruses are known to activate PAK so as to enter the cell and gain control over its biological machinery [5]. Certain viruses are also known to exploit PAK-mediated signalling to facilitate spread from one cell to another by formation of membrane nanotubes [6, 7]. SARS-CoV-2 has also been speculated to exploit PAK-1 signalling [8]. By blocking PAK-1, ciclesonide inhibits SARS-CoV-2 replication.

We searched PubMed using the terms "ciclesonide", "SARS-CoV-2", "COVID-19", and "corona virus" and found only one report describing the use of ciclesonide in three cases [9]. All three cases had pneumonia and required oxygen support at 1–2 L/min. All 3 cases improved clinically after starting ciclesonide. Fever resolved, oxygenation improved, and radiological improvement was seen in these patients. The dose used was 200 μg twice daily and was increased to 400 μg twice daily in one patient, and 400 μg thrice daily in two patients.

A search on *clinicaltrials.gov* and the World Health Organization-International Clinical Trial Registry Platform (WHO ICTRP) revealed 6 clinical trials (Table 1). The CONTAIN trial is a randomised, placebo-controlled trial in which the efficacy of inhaled and intranasal ciclesonide in patients with mild COVID-19 will be studied. Korean university Guro hospital will study the efficacy of ciclesonide alone or in combination with hydroxychloroquine for adults with mild COVID-19 in an open-labelled, randomized clinical trial. The dose of inhaled ciclesonide used will be 320 μg twice daily via a metered dose inhaler (MDI) for 14 days. The primary outcome studied will be the rate of SARS-CoV-2 eradication at day 14 from study enrolment. Covis pharma has initiated a phase 3, multi-center, randomized, double-blind, placebo-controlled trial. The dose of inhaled ciclesonide used is 320 μg twice daily via a metered dose inhaler (MDI) for 30 days. The primary outcome studied will be the percentage of patients requiring hospital admission or death by day 30. In the HALT COVID-19 study, patients will be randomized and allocated in a 1:1 ratio into ciclesonide 320 μg twice daily or standard of care groups. The primary outcome studied will be the duration of the requirement of supplemental

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DOI: 10.5603/ARM.a2020.0173
Received: 11.07.2020

ISSN 2451–4934

oxygen therapy. In an open label, randomised trial from India, the efficacy of hydroxychloroquine, ciclesonide, and ivermectin in the treatment of moderate COVID-19 illness will be assessed. The primary outcome studied will be the proportion of patients having a virologic cure on day 6 in each of the groups. The RACCO trial is a multi-center, open-label, randomized trial to evaluate the effi-

Table 1. Summary of clinical trials registered under the United States National Library of Medicine clinical trials registry and WHO International Clinical Trials Registry Platform on ciclesonide for COVID-19

Clinical trial identifier	Country	Title	Study design	Patient group	Intervention	Primary outcome measures	Recruitment status
NCT04435795	Canada	CONTAIN (CiclesOnide cliNical TriAl for COVID-19 treatmeNt)	Randomized, placebo controlled	Laboratory confirmed COVID-19 positive adults more than 18 years of age, within 5 days of laboratory diagnosis, not severely ill and who are at home on day 0	Intranasal ciclesonide to each nostril and inhaled cilcesonide *vs* normal saline intranasal BID and placebo MDI inhaled	Improvemet in dyspnea at day 7	Not yet recruiting
NCT04330586	Korea	A trial of ciclesonide alone or in combination with hydroxychloroquine for adults with mild COVID-19	Multi-center,open label randomized	Laboratory confirmed COVID-19 positive adults 18 to 80 years with mild COVID-19 (NEWS scoring system 0-4) and within 7 days from symptom onset or within 48 hours of laboratory diagnosis	Ciclesonide *vs* ciclesonide and hydroxychloroquine *vs* control	Rate of SARS-CoV-2 eradication at day 14	Not yet recruiting
NCT04377711	United States	A phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ciclesonide metered-dose inhaler in non-hospitalized patients 12 years of age and older with symptomatic COVID-19 infection	Multicenter, double-blind, randomized, placebo-controlled	Laboratory confirmed COVID-19 positive adults more than 12 years of age, within 72 hours of laboratory diagnosis, not hospitalized, but symptomatic with oxygen saturation > 93% and able to take MDI	Ciclesonide *vs* placebo	Percentage of patient's with hospital admission or death by day 30	Recruiting
NCT04381364	Sweden	Inhalation of ciclesonide for patients with COVID-19: A randomised open treatment study (HALT COVID-19)	Multicenter, double-blind randomized	Adults 18 to 85 years of age that are hospitalized and require oxygen therapy, within 48 hours of diagnosis by a physician based on clinical and radiological findings	Ciclesonide *vs* standard of care	Duration of supplemental oxygen therapy received	Not recruiting

CTRI/2020/04/ /024948	India	Efficacy of hydroxychloroquine, ciclesonide and ivermectin in treatment of moderate COVID-19 illness: an open-label randomised controlled study	Open-label, randomised	Laboratory confirmed COVID-19 positive adults ≥18 years with presence of moderate COVID-19 disease as defined by presence of pneumonia (clinical and radiological signs) with respiratory rate between 15 to 30/minute and/ /or SpO_2 90–94% on room air.	Hydroxychloroquine *vs* ciclesonide *vs* ivermectin *vs* standard of care	Proportion of patients having virologic cure on day 6	Not recruiting
jRCTs031190269	Japan	A multicenter, open-label, randomized trial to evaluate the efficacy and safety of inhaled ciclesonide for asymptomatic and mild patients with COVID-19 (RACCO trial)	Open-label, randomised	Laboratory confirmed COVID-19 positive adults more than 12 years of age, who have no apparent pneumonia due to COVID-19 on plain chest radiographs, who can be hospitalized, who can inhale using inhalation assist device	Ciclesonide *vs* standard of care	Pneumonia incidence on day 8 of ciclesonide inhalation	Recruiting

cacy and safety of inhaled ciclesonide for asymptomatic and mild patients. The primary outcome studied will be the incidence of pneumonia on day 8 of ciclesonide inhalation.

Thus, at present, the evidence regarding the role of ciclesonide in COVID-19 is limited to in-vitro studies and a case report. Results from randomised controlled trials are awaited. Though in-vitro studies have shown anti-SARS-CoV-2 activity of ciclesonide, it will be exciting to see if these translate into better clinical outcomes for patients with COVID-19.

Conflict of interest

None declared.

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Awake proning in COVID-19 — does CPAP make a difference?

To the Editor

Awake proning is being used as an adjunct to the current therapies for patients with cooronavirus disease 2019 (COVID-19) related hypoxemic respiratory failure. Although there is no universally accepted protocol, there is emerging data on the use of awake prone positioning [1, 2]. Although most studies have described patients on CPAP, high flow nasal cannula as well as standard oxygen therapies in different proportions, the response of prone positioning may likely be different among these as the application of positive end-expiratory pressure may lead to better recruitment, which is one of the major mechanism of the effect of prone positioning. Coppo *et al*., in a recent issue of The Lancet Respiratory Medicine, have reported results of a prospective study to assess the effects of awake proning in patients with COVID-19 [3]. This is the largest study till date regarding the utility of awake proning, in which the authors compared the characteristics of patients who responded to awake proning with those who did not and found the time between hospital admission and prone positioning to be the only variable significantly different between the groups. The one thing missing in the analysis in this study was whether the number of patients receiving continuous positive airway pressure (CPAP) and conventional oxygen therapy was similar between the groups. As CPAP might correct hypoxemia more than standard oxygen delivery, it will be interesting to know whether patients receiving CPAP therapy were more in the responders. On the literature review, we found only two other studies which have reported the use of awake proning in COVID-19 patients on continuous positive pressure ventilation, and both included patients on non-invasive positive pressure ventilation. Sartini *et al*. reported the use of prone positioning outside ICU in 15 patients on NIV and documented significant improvement in oxygenation, although absolute changes were not reported [4]. On the other hand, Golestanieraghi *et al*. reported results from 10 patients and had an increase in mean PO2 from 46.34 to 62.54 mmHg after proning [5]. Other studies have described the use of prone positioning in patients on conventional oxygen therapy or HFNC [6]. The effect of CPAP on oxygenation parameters during awake proning in patients with COVID-19-related ARDS is yet to be determined, and further studies are required to assess the same as this strategy may be a game changer for the ongoing COVID-19 pandemic.

Conflict of interest

None declared.

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DOI: 10.5603/ARM.a2020.0179
Received: 07.08.2020

ISSN 2451–4934

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Face shields for prevention of SARS-CoV-2 in community — need of the hour

To the Editor

Since the onset of the current pandemic of coronavirus disease-19 (COVID-19), the concerns regarding availability and cost of personal protective equipment (PPE) have been raised in all countries. Most of the governments have taken cognizance of this and have provided PPE to healthcare workers (HCWs) in the hospital. Community healthcare workers are one group which still suffer exposure to COVID-19 and needs to be protected in a better way. Recent news in the media highlighted that sample collection is done in some parts of India without the appropriate use of PPE [1]. This brings us to the main concern regarding how to protect the community HCWs. As there are concerns regarding airborne transmission, investigations have confirmed that as of now, community transmission rates are consistent with droplet and contact spread rather than airborne spread [2]. This leads to the conclusion that barriers to droplet transmission, along with hand hygiene, should remain a priority to prevent transmission. The two main barrier options for preventing droplet transmission include face masks and face shields. Face masks are being accepted and used regularly by the community HCWs; however, the use of face shields is not universal. In this regard, a recent prospective study was published in Journal of American Medical Association by Bhaskar *et al.* where the authors have presented their experience with the use of face shields in the community to prevent transmission to healthcare workers [3]. They have described the use of face shields in addition to 3-layered surgical masks, shoe covers as well as gloves in the community of health workers and found a marked reduction in transmission of SARS-CoV-2. Although face shields remain one of the essential components of personal protective equipment in the hospital, its use is less common in community settings. One main confounder of this assessment includes the behavioural change of healthcare workers, which ensues as one becomes more experienced as well as when one has peers who have suffered from the infection. The time spent in initial training for infection control practices may vary, and adherence to the same improves with time [4]. It is not feasible to measure the adherence to infection control measures, and it remains one of the major limitations in deriving the conclusion that face shields were the sole reason for the reduction in transmission. Nevertheless, face shields should continue to remain one cost-effective method of protecting the community HCWs as it prevents ocular transmission, and reduces mask, and face contamination as well.

Conflict of interest

None declared.

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DOI: 10.5603/ARM.a2020.0185
Received: 28.08.2020

ISSN 2451–4934

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New twist to an old problem: COVID-19 and idiopathic pulmonary fibrosis

Dear Editor

Pandemic of COVID-19 has brought a plethora of challenges throughout the world and has opened exposed gaps in already overburdened stressful health system. One of the most important one is diagnosis and monitoring of chronic lung diseases like idiopathic pulmonary fibrosis (IPF). IPF is the commonest type of idiopathic interstitial pneumonia (IIP) which is a spontaneously occurring progressive diffuse parenchymal lung disease. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing COVID-19 clinically manifests itself as mainly atypical pneumonia. Clinical profile of severe COVID-19 and acute exacerbation of IPF are quite similar as both affect the elderly, those with diabetes, ischemic heart disease or cigarette smoke exposure [1]. They are associated with significant hypoxemia, worsening pattern of diffuse lung involvement on high resolution computed tomography (HRCT).

Due to rapid spread of this pandemic, data regarding impact of COVID-19 on IPF disease is scarce, especially regarding the effect of antifibrotic therapy in this setting. COVID-19 has impacted on all the aspects of IPF, including diagnosis, treatment, and monitoring. Ideal multidisciplinary discussion (MDD) approach to the IPF diagnosis requires now several unique modifications. The goal should be to minimize contact with health care workers and at the same time speed up the diagnosis. In this scenario, artificial intelligence and machine learning can prove to be a boon by identifying the ones fitting the criteria to be screened on priority, coupled with final diagnosis on virtual MDD.

This should be complemented with blood work, preferably in an outpatient lab and quick online appointments. As spirometry (with diffusing capacity for carbon monoxide ($T_{L,CO}$) is the cornerstone of assessing lung physiology in these patients, it can be replaced with an easier alternative, 6-minute walk test. Pulmonary function test (PFT) should be avoided as it's an aerosol generating procedure, and previous dictum of starting anti-fibrotic therapy based on patients' forced vital capacity (FVC) % should be more relaxed now since benefit of these drugs have also been seen across various severities of IPF [2]. Diagnosing the ones with indefinite usual interstitial pneumonia (UIP) pattern in chest HRCT can prove to be the hornets' nest as these are the patients who would additionally require histopathological diagnosis. The usefulness of surgical lung biopsy should be weighed against the risks. Risk factors for adverse outcomes post biopsy are likely to get amplified due to COVID-19 [3]. Moreover, the emergence of nintedanib benefit in any progressive fibrotic interstitial lung disease has simplified the dilemma in the current scenario [4].

Acute exacerbations of IPF can also be virus-triggered, which has to be considered too, amplifying the need of COVID-19 Reverse transcription polymerase chain reaction (RT-PCR) in this setting, as early identification can help in better management of these patients [5]. Antifibrotic drugs, pirfenidone and nintedanib are currently being used for IPF treatment and are shown to

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DOI: 10.5603/ARM.a2020.0177
Received: 28.08.2020

ISSN 2451–4934

improve life expectancy and increase time to first exacerbation [6]. Both these drugs per se are not immunosuppressive; hence there is no rationale of stopping them during COVID-19 pandemic for the scare of increased exacerbation risk. In the INPULSIS II study, nintedanib has also shown the benefit of reducing exacerbations incidence. The use of these drugs now is restricted to only non-intubated, as only oral form is available, though inhaled form of pirfenidone is under evaluation [7]. Side effects of these medications have considerable overlap with COVID-19 symptoms (like diarrhea) too, and that can interfere with early diagnosis of COVID-19. Renal and hepatic dysfunction during severe illness of COVID-19 should be considered while continuing antifibrotics. Nintedanib is theoretically associated with increased bleeding risk and can be avoided in severe COVID-19 and concomitant coagulopathy, as these patients may be on full therapeutic anticoagulation [8, 9]. Apart from pharmacological therapy in IPF during this pandemic, physical distancing, routine hygiene measures, smoking cessation and virtual social support means should be advised and encouraged in IPF patients.

Conflict of interest

None declared.

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Cardiology and COVID-19: A bidirectional association!

To the Editor

The novel corona virus pandemic has the world in its grip and infection with COVID-19 has proven to be beyond a pulmonary disease. There are pre-existing cardiac conditions predisposing to it and the cardiological manifestations of the disease are being increasingly recognised.

The previous viral pandemics and epidemics have shown that viral infections are more likely to occur in patients with underlying cardiovascular disease [1]. Viral myocarditis is a prominent infectious-inflammatory disease reported with the previous corona virus epidemics [2, 3]. Even long-term follow up of the survivors of the previous viral epidemics has documented cardiovascular and metabolic abnormalities [4].

The published medical literature on COVID-19 relevant to cardiology is summarised in Table 1. There is mounting evidence that underlying cardiovascular conditions lead to a higher likelihood of infection, more severe disease progression, and a greater risk for mortality from COVID-19. Also, studies evaluating patients with COVID-19 presenting with cardiac injury show that they have a poorer outcome. It is important for physicians to realise the importance of cardiac disease as a risk factor and potential complication of the disease because this might help in improving the management and treatment of infected patients.

Early measurement of cardiac biomarkers (troponin and NT-pro BNP) of a suspected infected patient can help identify cardiac injury. However, it is important to realise that biomarkers of cardiac injury often rise in hospitalized patients and that its interpretation and actionability would require careful consideration. Electrocardiography (ECG) is instrumental in assessing for arrhythmia, and echocardiography (ECHO) is a convenient bedside test to assess for cardiac systolic and diastolic function. The other test for assessing cardiac function is a cardiac MRI. CT and Doppler may assist in detecting the thrombotic complications in a patient.

It is still not clear whether the cardiac manifestations are because the cardiac myocytes are the primary target or secondary bystander. Minimally invasive autopsies from lung, heart, and other sites of COVID-19 patients have shown that, while the virus does have a predilection for the lungs, the infection also results in damage to the heart, vessels, liver, kidney, and other organs [5]. Cardiac manifestations are likely due to a multifactorial aetiology; the myocardial damage could be related to the direct effect of the virus or may occur indirectly with increased oxygen demands due to tachycardia and fever, and reduced oxygen delivery due to hypotension and hypoxemia. Another possibility is that the enhanced inflammatory state can induce vascular inflammation, myocarditis, and cardiac arrhythmias [6]. The resulting cytokine storm can elicit activation of cells within pre-existing atherosclerotic lesions thus augmenting thrombotic risk and risk of ischemic syndromes. Moreover, microvascular activation by cytokines can cause myocardial injury along with harm to other organ systems [7]. Besides these causes, the possible impacts of the drugs currently used to treat COVID-19 cannot be ignored. Some of the drugs that are frequently used to manage these cases are known to prolong the QT interval and can have a proarrhythmic propensity resulting in cardiac complications [8, 9].

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DOI: 10.5603/ARM.a2020.0169
Received: 22.06.2020

ISSN 2451–4934

Table 1. Summary of the medical literature on COVID-19 and cardiology

Author, country	Type of article	Number of patients	Cardiology relevant findings	Implications/conclusions
Aghagoli *et al.* [10], all trials are from China	Meta-analysis	Six studies* with 1527 patients	**Pre-existing conditions:** Hypertension — 17 %, cardia-cerebrovascular disease — 16.4%, diabetes — 9.7% **Cardiac complications:** At least 8.0% suffered from acute cardiac injury 13 folds higher in ICU/severe patients compared with the non-ICU/severe patients	Patients with previous cardiovascular metabolic diseases may face a greater risk of developing the severe condition
Shi *et al*. [11], China	Cohort study	416 patients	**Cardiac complications:** Cardiac injury — 19.7% Patient with cardiac injury were older and had more co-morbidities	Deaths were more common in patients with cardiac injury than those without
Zhou F *et al.* [12], China	Retrospective, multicentre cohort study	191 patients (137 discharged and 54 died)	**Pre-existing conditions:** Hypertension — 30%, diabetes — 19%, coronary heart disease — 8% Increasing odds of in-hospital death associated with elevated d-dimer on admission.	d-dimer could help clinicians to identify patients with a poor prognosis at an early stage
Deng Y *et al.* [13], China	Retrospective study	225 patients (109 died and 116 recovered)	**Pre-existing conditions:** **A. Hypertension:** Death group — 36.7%, recovered group — 15.5% **B. Diabetes:** Death group — 11.9%, recovered group — 3.4% **C. Cardiac complications:** Acute cardiac injury Death group — 59.6%, recovered group — 0.8% Disseminated intravascular coagulation Death group — 6.4%, recovered group — 0%	More patients in the death groups had complications such as acute cardiac injury, shock, and DIC
Chen T *et al.* [14], China	Retrospective case series	274 cases (113 died and 161 recovered)	**Pre-existing conditions:** **A. Chronic hypertension:** Death group — 48%, recovered group — 24% **B. Other cardiovascular comorbidities:** Death group — 14%, recovered group — 4% Concentrations of creatine kinase, cardiac troponin I, N-terminal pro-brain natriuretic peptide, and D-dimer were markedly higher in deceased patients than in recovered patients **Common cardiac complications:** Acute cardiac injury — 77%, heart failure — 49%	Patients with cardiovascular comorbidities were more likely to develop cardiac complications Regardless of history of cardiovascular disease, acute cardiac injury and heart failure were more common in deceased patients
Du Y *et al*. [15], China	Retrospective chart review	85 fatal cases	**Pre-existing conditions:** Hypertension — 37.6%, diabetes — 22.4%, CAD — 11.8% **Complications:** Respiratory failure — 94.1%, shock — 81.2%, ARDS — 74.1%, arrhythmia — 60.0%, acute myocardial injury — 44.7%, acute liver injury — 35.3%, sepsis — 32.9%	The majority of the patients died of multiple organ failure

Li *et al*. [16], China	Retrospectively enrolled and followed up	548 patients (269 severe and 279 non-severe)	**Mortality:** 1.1% in non-severe patients 32.5% in severe cases Elder age, underlying hypertension, high cytokine levels and high LDH level were associated with severe disease **Factors associated with seath:** Cardiac injury, high LDH, hyperglycemia, high-dose corticosteroid	Elderly patients with hypertension and high LDH levels need careful observation and early intervention
Klok FA *et al.* [17], Netherlands	Prospective study	184 ICU patients	CTPA and/or ultrasonography confirmed VTE in 27% and arterial thrombotic events in 3.7%	Recommend strict application of pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU
Richardson S *et al.* [18], USA	Prospective	5700 patients	**Pre-existing condition:** Hypertension — 56.6%, obesity — 41.7%, diabetes — 33.8%, coronary artery disease — 11.1%, congestive heart failure — 6.9% Troponin above the test specific upper limit was seen in 22.6% of those tested. Of the patients who died, those with hypertension were **less likely** to have received invasive mechanical ventilation or care in the ICU compared with those without hypertension. Mortality rates for patients with hypertension not taking an ACEI or ARB, taking an ACEI, and taking an ARB were 26.7%, 32.7%, and 30.6%, respectively	This study reported mortality rates only for patients with definite outcomes (discharge or death) The case series design cannot address the speculation about the possible adverse, protective, or biphasic effects of treatment with ACEI
Zeng JH *et al.* [19], China	Case report	A 63-year-old male	An elevated troponin I (Trop I) level (up to 11.37 g/L) and diffuse myocardial dyskinesia along with a decreased LVEF on echocardiography. Patient improved with antiviral therapy and mechanical life support. However, died of aggravation of secondary infection on the 33rd day of hospitalization	This is the first report of COVID-19 complicated by fulminant myocarditis
Inciardi *et al.* [20], Italy	Case report	53-year-old patient	Acute myopericarditis with systolic dysfunction confirmed on cardiac magnetic resonance imaging — showed increased wall thickness with diffuse biventricular hypokinesis, especially in the apical segments, and severe left ventricular dysfunction The condition developed a week after onset of fever and dry cough due to COVID-19	The patient did not show any respiratory involvement during the clinical course. Treated with dobutamine, antiviral drugs (lopinavir/ritonavir), steroids, chloroquine, and medical treatment for heart failure
Cui *et al*. [21], China	Case report	55-day-old patient	Abnormal myocardial zymogram on admission and increased troponin I on hospital day 4 indicated myocardial injury The patient also had lung and liver injury	Children with COVID-19 can also present with multi-organ damage and rapid disease changes
Bemtgen X *et al*. [22], Germany	Case report	A 52-year-old patient	COVID-19 patient presenting with ARDS plus refractory combined cardiogenic and vasoplegic shock Successfully stabilized after implantation of pVAD plus an ECMO	ECMO and VAD is a labour and resource intensive technique; not always suitable for crowded and burdened ICU

*These 6 studies have not been included separately in the table

ACEI — angiotensin-converting enzyme inhibitors; ARDS — acute respiratory distress syndrome; ARB — angiotensin receptor blockers; CAD — coronary artery disease; CTPA — computed tomography pulmonary angiograph; DIC — disseminated intravascular coagulation; ECMO — extracorporeal membrane oxygenation; ICU — *intensive care unit; LDH — venous thromboembolism;* LVEF — *left ventricular ejection fraction;* pVAD — percutaneous ventricular assist devices; VTE — *venous thromboembolism*

As the pandemic progresses, our knowledge on this novel infection will evolve. We have sufficient evidence of an increased severity of COVID-19 infection in patients with cardiac diseases and more mortality in patients with COVID-19 related cardiac failure and myocarditis. It is important to alert clinicians of this because it would aid in the timely diagnosis of the cardiac complications. It is also important to acknowledge our poor understanding of the exact pathogenesis because currently, the possible role of angiotensin receptors and the possible long-term effects of this virus are still to be assessed. Trials proving an optimal management strategy have not yet been completed, therefore, the best management that can currently be offered is of a supportive nature. Thus, constant physician vigilance of the clinical presentation of such patients can help in reducing morbidity and mortality until further evidence surfaces.

Conflict of interest

None declared.

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Risk assessment and prognostic aspect of coagulopathy in COVID-19

To the Editor

Coronavirus disease 2019 (COVID-19) primarily being considered as a respiratory illness has been showing a highly diverse and anomalous array of symptoms since its origin in December 2019. The death toll has already surpassed 545,481 with more than 11.87 million confirmed cases worldwide [1], while the pathophysiology of COVID-19 is still obscure. At present, concerns are mounting over the increasing reports of blood coagulation accompanied by organ dysfunction among the COVID-19 patients. The disease tends to cause a hyper- and rapid coagulable state allegedly leading to pulmonary embolism and deep vein thrombosis, especially among the severe cases of COVID-19 [2]. However, predisposition to both venous and arterial thromboembolism causing acute pulmonary embolism (PE), deep vein thrombosis (DVT), ischemic stroke, myocardial infarction and systemic arterial embolism has also been reported. So, the experts are claiming that COVID-19 causes an eminent change in coagulation function, which is directly associated with disease severity [3]. Even a study showed that 71.4% of COVID-19 non-survivors meet the diagnostic criteria for disseminated intravascular coagulation (DIC) compared to only 0.6% of the survivors [4].

However, that study also reported an elevated level of D-dimer protein among COVID-19 cases, which is produced as the result of fibrinolysis following a thrombotic event and associated with the risk of Acute Respiratory Distress Syndrome (ARDS) [5]. Besides, D-dimer protein was reported significantly higher among the severe cases and the patients requiring intensive care compared to those with mild symptoms [6]. A meta-analysis on 1015 cases showed a notable difference in D-dimer level along with prothrombin time between severe and mild cases, but not in case of platelet count (PLT) and activated partial thromboplastin time (aPTT) [3]. Most importantly, the level of D-dimer and other fibrin degradation protein of non-survivor cases significantly differ from survivors [4] and is considered the major cause of mortality. Therefore, the spike in the level of D- dimer protein provides evidence of abnormal coagulation with the prognostic value, which can be used to evaluate the severity and adverse outcome among patients with community-acquired pneumonia as well as COVID-19 [7]. Moreover, the level of D-dimer has been reported to be dependent on the ethnic groups, which may explain the differential racial susceptibility to COVID-19 severity evident across the world [8].

However, the patients' immobilization during treatment, presence of cardiovascular disease and damage of endothelial cells by viral infection/mechanical procedure has been reported to cause a higher incidence of venous thromboembolism among hospitalized subjects [9], which is even more threatening to COVID-19 susceptible individuals with underlying comorbidities, including cardiovascular diseases. Because COVID-19 patients with pre-existing comorbidities have higher risk of developing disease severity leading to hospitalization, which may result in hospital-induced thrombotic complications and vice versa [10].

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DOI: 10.5603/ARM.a2020.0191
Received: 09.07.2020

ISSN 2451–4934

So, the differences in coagulopathy, especially D-dimer level among severe and non-severe cases surely urge immediate attention to the current diagnosis and treatment strategy. Besides, both thrombotic complications of COVID-19 and its risk factors need to be addressed to adapt a more effective management strategy.

Acknowledgments

The corresponding author extends her gratitude to the University Grants Commission (UGC), Bangladesh for funding.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Young and exhausted

Introduction

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a complex, multisystem and often debilitating disorder of unknown aetiology [1]. It is a complicated disease characterised by at least six months (in paediatrics 3 months) of extreme fatigue that is not alleviated by rest and a group of other symptoms that are constant for a period of time [1].

Post-exertional malaise (PEM) and delayed recovery are core symptoms and the most useful when making a diagnosis [3]. PEM involves a constellation of substantially disabling signs and symptoms that occur in response to physical, mental, emotional, and spiritual overexertion [2]. In many people with chronic fatigue syndrome, the disorder begins suddenly, often after a flu-like infection or after an episode of physical or mental trauma. The diagnosis of CFS/ME relies on the typical clinical presentation and the exclusion of other causes of fatigue. A diagnosis can be made by taking a thorough history, examining the patient, and using blood tests to screen for other causes of fatigue [3]. Up until now there was no test to confirm the diagnosis of CFS/ME. The two-day cardiopulmonary exercise testing (CPET) is becoming a new diagnostic method that can be used in case of suspicion of CFS/ME in attempt to evaluate the presence of PEM [5]. CPET provides a wealth of data on the dynamic function and coordination of the heart, lungs and muscles, as well as on the efficiency of gas exchange between mitochondria and the surrounding air, even in patients complaining about PEM. In the last 2 years, there has been a boom in using CPET as a diagnostic tool for PEM as a core symptom of CFS. Results of this testing, used in centres for patients with CFS/ME, in small cohorts of adults, have been published. One study, applying single one-day CPET in patients with CFS/ME in paediatrics, was published in 2007 [7]. None of these reports and studies highlighted breathing pattern disturbances as a possible cause of the chronic fatigue itself, nor did they mention the occurrence of dysfunctional breathing in patients with CFS. Dysfunctional breathing (DB) is highly prevalent and is overlooked mainly in adolescents and often attributed to behavioural changes during adolescence [6]. Chronic fatigue might be a symptom of DB in adolescents. We present a case study supporting this claim.

Case report

In the case report, we present a 13-year-old patient with chronic debilitating fatigue who meets the criteria for CFS/ME. The patient and patient's parents reported 6 months of fatigue, which was not improved even after an adequate period of sleep and very low physical performance. According to the parents, the patient has difficulty concentrating, is morose most of the day and reports limb twitching and paraesthesia. The patient was examined in detail by a paediatrician (anamnestic unclear cause, resting tachycardia in the physical examination, laboratory tests within normal limits, serum minerals within normal limits), endocrinologist (normal hormonal profile for a given age, Tanner stage 3), infectologist (serology for typical viruses negative), psychologist (normal cognitive functions). For a history of resting tachycardia, the patient was examined by a cardiologist, where no cardiogenic cause

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DOI: 10.5603/ARM.a2020.0196
Received: 05.08.2020

ISSN 2451–4934

Table 1. CPET data obtained on day 1, day 2 of the examination and after 3 months of rehabilitation

	CPET on day 1	CPET on day 2	CPET after 3 months
Exercise duration [min]	6:32	7:00	7:50
VO_2 peak [mL/kg/min]	34.5	36.5	36.7
WR peak [W/kg]	3.26	3.68	3.8
HR peak [1/min]	187	197	199
WR at anaerobic threshold [AT] [W/kg]	0.72	1.5	1.68
VO_2 at AT [ml/kg/min]	19.0	23.0	22.3
VE/VCO_2 [1]	34.1	34.6	27.3
Max Vt [mL]	1.18	1.33	2.15
Max respiratory rate [1/min]	72	81	41
EtCO2 resting [mm Hg]	25	23	36

CPET — cardiopulmonary exercise testing; VE — minute ventilation; WR — work rate; HR — heart rate; VT — tidal volume; EtCO2 — end-tidal carbon dioxide; VO_2peak — peak oxygen consumption; VE/VCO_2 — minute ventilation/carbon dioxide production

of fatigue was demonstrated, sinus tachycardia was present, and the patient was recommended head-up-tilt test, which showed the presence of postural orthostatic tachycardia. Due to the idiopathic nature of the difficulties and the excluded secondary cause, a two-day protocol examination by cardiopulmonary exercise testing was indicated. Written consent was taken and documented. Before the examination, we performed resting spirometry (FEV1 106% of predicted, FVC 101% of predicted), resting ECG (sinus tachycardia) and a shortened Schellong test with a tachycardic response to orthostasis immediately after standing up and after 3 minutes of standing. Subsequently, standard CPET using treadmill (Itam, Poland) with individualised protocol with progressive increase in workload until exhaustion and breath-by-breath analysis of exhaled gases (Geratherm, Germany) was performed. On the first day, basal values were determined, the patient subjectively tolerated the examination well, the exercise ended prematurely due to subjective fatigue and a feeling of lack of air. On the second day, under the same conditions, the CPET was repeated, during which the patient also terminated the exercise prematurely but a half minute later than on the first day. Using this methodology, the patient did not meet diagnostic criteria for PEM and subsequently CFS/ME (decrease in monitored values on the second day of the examinations) (Table 1, Figure 1G). On both days, during exercise, a bizarre pattern of respiration with malposition of the respiratory act to the large airways was observed by noticing the flow-volume loop. Analysis of the respiratory pattern identified an erratic respiratory pattern (Figure 1A) with low resting EtCO2 (Table 1) and tachypnoea at maximal workload with dominant ventilation of dead space (Figure 1B, 1C). The consequence of this pattern of respiration is a chronic state of hypocapnia and respiratory alkalosis, which is metabolically compensated in the patient. Fatigue and increased heart rate are expected clinical manifestations. Respiratory rehabilitation was recommended to the patient in order to fixate the correct breathing patterns (diaphragmatic breathing) and psychological guidance. The patient was subsequently retested 3 months after the start of physiotherapy and psychotherapy at the request of the parents. Retesting showed significant improvements in the monitored parameters (Table 1, Figure 1G) as well as in the clinical condition of the patient.

We observed changes in breathing pattern and subsequent normalisation of observed cardiopulmonary parameters during resting capnography and exercise test. The patient increased tidal volumes (Vt) with preserved inspiration capacity (IC) during exercise. Resting ETCO2 tracing showed normal values. The patient's overall fitness increased, an adequate resting respiratory pattern was present (Figure 1D), ventilatory efficiency was adjusted (VE/VCO2 in Table 1, Figure 1G), and the patient reported a subjective increase in energy. Prior to the examination, we performed the Schellong test on the patient, in which there were no signs of postural orthostatic tachycardia.

Discussion

Dysfunctional breathing is a condition of the airways characterised by an irregular breathing pattern and changes in the airways that cannot be

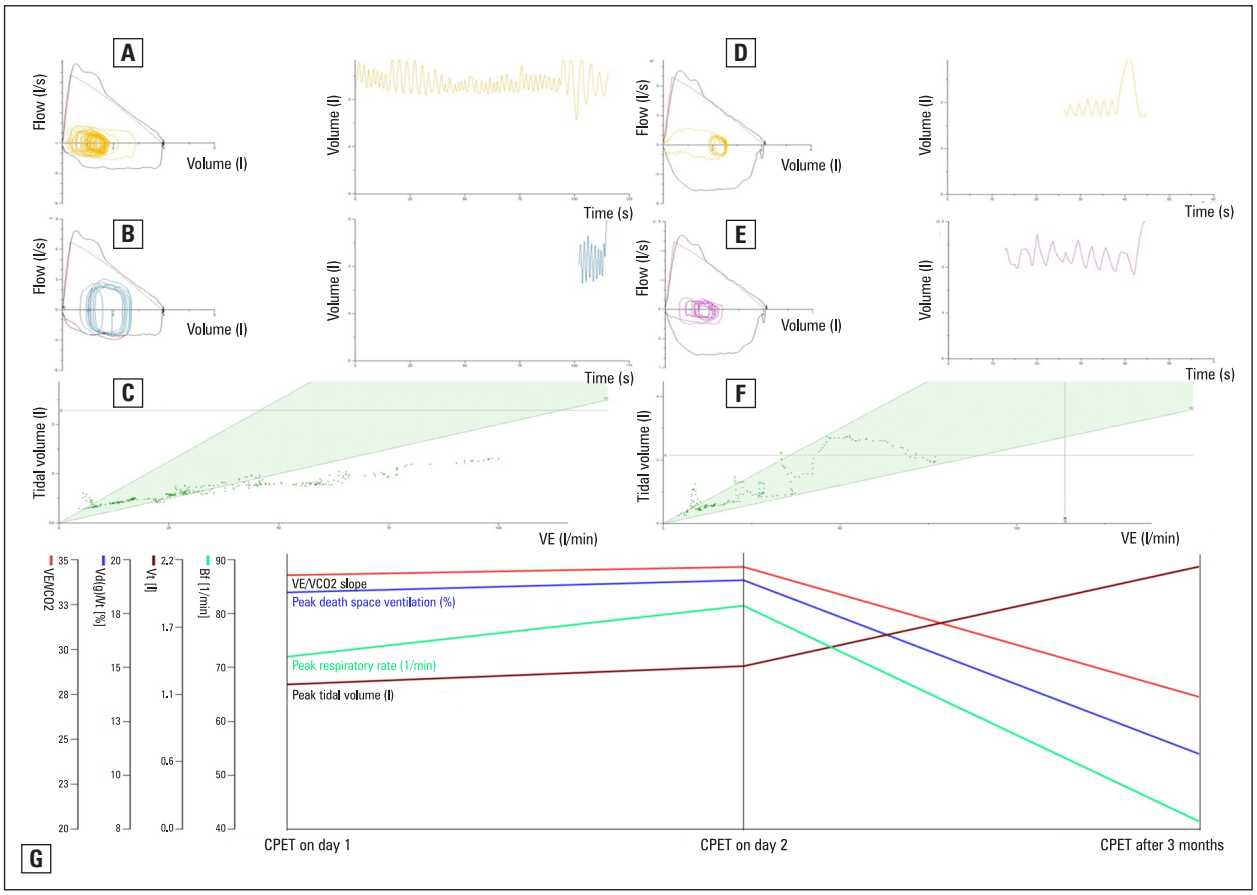

Figure 1. A. Resting flow volume loop, first day of examination. **B.** Flow volume loop at the top of exertion, first day of examination. **C.** Breathing pattern, first day of examination. **D.** Resting flow volume loop, examination after 3 months. **E.** Flow volume loop at the top of exertion, examination after 3 months. **F.** Breathing pattern, examination after 3 months

attributed to a specific diagnosis and that cause respiratory and non-respiratory problems [4]. It is not a disease process, but rather changes in respiratory patterns that disrupt normal respiratory processes. However, DB can coexist with diseases such as bronchial asthma or heart disease. The main symptom is shortness of breath or air hunger, associated with non-respiratory symptoms such as dizziness, palpitations, cervical spine pain or fatigue [6]. It also plays a role in chronic fatigue, neck and back pain, fibromyalgia, and some aspects of anxiety and depression [6].

The most common type of DB is hyperventilation syndrome, which is defined as respiration exceeding metabolic requirements, reducing blood carbon dioxide concentrations below normal values [4]. This changes the pH of the blood, increases the alkalinity and thus triggers a number of adaptive changes that cause symptoms. These conditions are non-somatic in nature and their treatment consists of respiratory rehabilitation with various techniques (diaphragmatic breathing, Feldenkrais method, Buteyko method, Pilates) and psychotherapy in order to control impulsive changes in the respiratory pattern in various situations [6]. Rehabilitation and physiotherapy seem to be efficient enough and should be encouraged in patients with DB.

Conclusions

CPET confirmed the presence of DB in the patient based on the low resting value of EtCO2, the existence of a chaotic pattern of respiration during resting and exercise with the presence of tachypnoea (with very low ventilatory efficiency) in maximal exertion. Diagnosis of DB using CPET is one of the methods of DB diagnostics. Proper respiratory rehabilitation and psychological guidance resulted in the patient fixing the respiratory pattern and subsequently eliminating the primary cause of the examination — chronic fatigue. Patients with CFS/ME are a common paediatric problem. The current possibilities of diagnostics are enriched by the possibility of performing CPET, which can be a benefit in differential diag-

nostics as well as in confirming the diagnosis. Patients with CFS/ME and/or postural orthostatic tachycardia should be checked for the presence of DB as a treatable cause of clinical symptoms.

Conflict of interest

No conflict of interest to declare.

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COVID-19 pandemic — did we sign up for "this"?

To the Editor

Since the beginning of the pandemic, there is an increasing pressure on our healthcare systems to cope with the increasing workload. As the expansion of hospital beds and equipment was taken up by governments readily, the predominant problem in the system remains to be the scarcity of trained workforce such as doctors, nurses, and supporting staff. As we have a wide range of medical and surgical specialties, not every doctor is equally capable of handling Coronavirus disease 19 (COVID-19) patients who present with respiratory failure. This has led to a sense of incompleteness in many resident doctors working in various COVID care hospitals.

In a recent article by Gallagher *et al*. in the New England Journal of Medicine, the authors have detailed the role of medical students and residents in the COVID-19 pandemic and how it has affected their training [1]. The authors have given a vivid account of the emotions and liabilities that medical students have experienced during the pandemic. The authors have elaborated in detail about the concerns and sense of responsibility among Internal Medicine, Pulmonary Medicine, and Critical Care residents and fellows. The authors have mentioned that the involvement of residents varies by specialty but that they have not addressed the concerns of resident doctors from other specialties. This aspect is crucial to the current scenario of the pandemic in India. Residents who are not from Internal Medicine are also being deployed to the COVID areas and their involvement varies depending upon their expertise. It has led to a paradigmal shift in the work of these residents. For example, residents who were once operating on abdominal tumours are now managing the Intensive Care Unit. The training in the primary specialty is also compromised as this pandemic is still growing in our country [2, 3]. Did these residents sign up for "this" or "that" or "both"? These are questions to ponder upon for all of us. Encouragement and training of residents working in COVID areas and using simulator-based training in surgical specialties can help to reduce the gap between "this" and "that".

Conflict of interest

None declared.

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DOI: 10.5603/ARM.a2021.0030
Received: 27.08.2020

ISSN 2451–4934

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Suction above cuff endotracheal tube can reduce ventilator-associated pneumonia in COVID-19 patients

To the Editor

Ventilator-associated pneumonia (VAP) is a type of pneumonia classified as a nosocomial infection associated with mechanical ventilation which occurs 48-72 hours after endotracheal intubation [1]. VAP is the second most common infectious complication of hospitalization accounting for approximately 10% to 25% of patients who require invasive mechanical ventilation for over 24 hours [2, 3]. It is characterized by a mortality rate of 40%, but in patients whose etiological factor was a moisture-resistant microorganism, the mortality rate may be as high as 70%. VAP is mainly the result of the mechanical transfer of microorganisms from the upper respiratory tract to the bronchi during intubation, mechanical damage to the mucosa of the respiratory tract, and translocation of bacterial flora from the nasopharynx and stomach.

Under normal conditions, the human body prevents various infections through the cough reflex, bronchial secretions, and/or humoral and cellular immunity. In COVID-19 patients, humoral and cellular immunity is significantly reduced. In addition, an intubated and flaccid patient cannot perform a bronchial tree toilet due to suppressed natural defense reflexes. After just a few hours, a bacterial filter is formed on the surface of the cuff sealing the endotracheal tube which, each time an over-intubation or inadequate ventilation occurs, reaches the bronchial tree and then the patient's lungs. The use of classic tidal volumes (10–12 mL/kg) and standard peak pressures (35–45 cm H_2O) leads to ventilatory-induced lung injury, which favors the development of VAP. Considering the above risk factors, it is important to use a fixed suction above endotracheal tube cuff which may reduce the risk of bacteria that accumulate there being transferred to the bronchi. Suction above cuff endotracheal tubes (SACETT) are available on the market and are used in intensive care conditions. However, in patients with suspected or confirmed COVID-19, this type of endotracheal tube should be considered at the pre-hospital stage if the patient's condition requires respiratory device protection. Then, the risk of over-intubating the patient by SACETT will be minimized. Tubes with suction above the cuff allow for the intermittent aspiration of these secretions with high pressure or continuously with pressures up to 20 mm Hg. They maintain the space above the cuff free of secretions and reduce the occurrence of microaspirations.

According to the Yuzkat and Demir studies [4], the use of SACETT reduces the incidence of PIV as well as the incidence of agitation, sore throat, and difficulty swallowing. The advantage of SACETT over the standard endotracheal tube is also shown in studies by other authors, including Jena *et al.* [5]. In turn, Kelley *et al.* [6] calculated that it is necessary to use tubes with suction above the cuff in 33 patients to prevent one episode of VAP, which shows that this protocol would be cost effective.

However, as with standard low-lumen catheters, the use of SACETT with a single suction

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DOI: 10.5603/ARM.a2021.0025
Received: 14.11.2020

ISSN 2451–4934

Figure 1. Example of a multiple suction port in the NeVap aspire subglottic suction endotracheal tube

port may clog the opening and make it difficult or impossible to perform above cuff suction. Due to the above, it seems reasonable to use intubation tubes equipped with multiple suction ports. An example of such a tube is the NeVap Aspire Subglottic Suction Endotracheal Tube (Nevap Inc., San Jose, CA, USA; Figure 1). Thanks to the use of the multiple suction port, it is possible to distribute the suction pressure over a larger area thus reducing the risk of damage to the surrounding tissues and reducing the risk of port obstruction, therefore making the suction of secretions more effective.

Conflict of interest

None declared.

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Proper respirators use is crucial for protecting both emergency first aid responder and casualty from COVID-19 and airborne-transmitted infections

To the Editor

We read with great interest the paper by Barycka *et al.* [1] in which the authors argue that healthcare workers (HCWs) should use filtering facepiece masks (FFP) with exhaust valve, when performing procedures such as cardiopulmonary resuscitation (CRP), to reduce the adverse effects of using FFP without valve, including high discomfort, low performance and thermal stress.

Their letter, however, addresses numerous prevention problems and deserves some clarification. The literature agrees on the greater effectiveness of filter masks compared to surgical ones in protecting HCWs against microorganisms; however, it is known that filter masks do not offer absolute safety against coronaviruses and prevention must be based on the simultaneous adoption of many measures [2].

There is also a broad consensus that wearing a mask for the entire work shift during a pandemic can cause numerous symptoms in workers [3]. These problems, whose pathogenesis is due to a combination of ergonomic and psychosocial factors, require a careful choice of this Personal Protective Equipment (PPE), with the participatory contribution of workers, as indicated by the European Directives on health and safety at workplace.

However, we believe that the example chosen by the authors to illustrate their claim is not appropriate. Cardiopulmonary resuscitation (CPR) is not an exclusively hospital procedure, because it must be performed in prehospital setting, including when needed at workplace. In addition, no HCW carries out this activity for the entire work shift. Consequently, extrapolating the conditions of the long-time occupational mask user to the rescuer doing CPR in the workplace can be misleading.

During first aid, indeed, rescuer and casualty come into close contact, especially during CRP. Mouth-to-mouth resuscitation poses, therefore, the greatest risk of COVID-19 infection not only to rescuer, but also to the casualty. For this reason, ERC guidelines suggest that appropriate PPEs, such as gloves, masks and visor eye protection should we worn by rescuers, whereas the casualty should wear surgical mask. FFP masks, furthermore, must be made of filter material, cover the nose and mouth, and possibly also the chin (semi-mask) [4].

It is possible, indeed, that lay or medical first aid responders who are asymptomatic carriers can transmit the SARS-CoV-2 virus to casualty, if they use respirators with EV [5]. It is well known that HCWs are at high risk of infection and can be a source of infection [6, 7]. Asymptomatic or presymptomatic HCWs acting as potential "superspreaders" were cited as responsible of COVID-19 hospital outbreaks [8]. At the same time, casualty can be particularly "vulnerable" to COVID-19 infection [8].

SARS-CoV-2 is a highly contagious virus and facial respirators could be insufficient to prevent the infection, because the "minimal infective dose" of the virus responsible for COVID-19 infection is unknown [4, 9]. Therefore, adverse

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DOI: 10.5603/ARM.a2021.0028
Received: 22.01.2021

ISSN 2451–4934

effects in HCWs caused by using respirators without EV should be carefully assessed and balanced with the risk of SARS-CoV-2 transmission to casualty.

In this evaluation, it should be noted that hospital HCWs wearing PPEs against COVID-19 (i.e., masks, respirators, gloves, and in hospitals where the contact with the infected and confirmed patient is direct, also gowns or body covers) can have many troubles to change their mask when it comes to perform lifesaving maneuvers. The level of protection, indeed, depends much on the ability to use the masks correctly, including if the rescuer has passed fit testing [4].

Physical fatigue and discomfort in people performing CRP should be prevented with organizational measures. Rescuers should be encouraged to interchange after 2 minutes of CPR delivery. Team leaders must be instructed to arrange changes in advance, without waiting for rescuers to report fatigue. Early defibrillation, finally, remains the major key to a successful outcome [10].

In conclusion, we believe it is more prudent that in case of emergency, both lay and medical rescuers use respirators without EV, except when hospital HCWs assist patients with highly suspected or confirmed COVID-19 infection. Educational efforts, implementing fit testing and seal checking of masks, organizational measures as well as using appropriate PPEs are needed to offer safe emergency interventions to rescuer and casualty for this and other airborne-transmitted diseases.

Conflict of interest

None declared.

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