Year 2020 | Vol. 88 | No. 5 | September–October | ISSN 2451–4934

Advances in Respiratory Medicine 2020, vol. 88, no 5, pages 369–476

Advances in Respiratory Medicine

Formerly Pneumonologia i Alergologia Polska
Edited since 1926

ORIGINAL RESEARCHES

REVIEW ARTICLES

The Journal is indexed in the following databases: Index Medicus/Medline, EMBASE, EBSCO, Emerging Sources Citation Index (ESCI), Scopus, Index Copernicus 121,38 (2019), MNiSW 2019 (20 points)

www.journals.viamedica.pl

VIA MEDICA

Advances in Respiratory Medicine

www.journals.viamedica.pl

Formerly Pneumonologia i Alergologia Polska

www.ptchp.org

Editor-in-Chief:
Wojciech J. Piotrowski — Łódź
wojciech.piotrowski@pneumonologia.viamedica.pl

Vice Editor-In-Chief:
Claudio Pedone — Rome
claudio.pedone@gmail.com

Contributing Editors:
Katarzyna Górska — Warsaw
drkgorska@gmail.com
Maciej Kupczyk — Łódź
maciej.kupczyk@pneumonologia.viamedica.pl
Sebastian Majewski — Łódź
sebastian.majewski@pneumonologia.viamedica.pl
Sonu Sahni — New York
sahni.sonu@gmail.com

Statistical Editor:
Agnieszka Skoczylas — Warsaw
Michał Poznański — Łódź
Łukasz Mokros — Łódź

Managing Editor:
Anna Młynarczyk

Editorial Advisory Board:
Nicolino Ambrosino — Pavia, Italy
Adam Antczak — Łódź, Poland
Ewa Augustynowicz-Kopeć — Warsaw, Poland
Halina Batura-Gabryel — Poznań, Poland
Andrey Belevskiy — Moscow, Russia
Wojciech Biernacki — London, Great Britain
Anna Brębborowicz — Poznań, Poland
Otto Burghuber — Vienna, Austria
Ryszarda Chazan — Warsaw, Poland
Ivane Chkhaidze — Tbilisi, Georgia
Joanna Chorostowska-Wynimko — Warsaw, Poland
Elżbieta Chyczewska — Białystok, Poland
Enrico Maria Clini — Modena, Italy
Brendan Cooper — Birmingham, Great Britain
Sven-Erik Dahlén — Solna, Sweden
Wilfried De Backer — Antwerp, Belgium
Anna Doboszyńska — Olsztyn, Poland
Antonio M. Esquinas — Murcia, Spain
Dorota Górecka — Warsaw, Poland
Paweł Górski — Łódź, Poland
Sylwia Hartl — Vienna, Austria
Raffaele Antonelli Incalzi — Rome, Italy
Renata Jankowska — Wrocław, Poland
Sabina Janciauskiene — Hannover, Germany
Christer Janson — Uppsala, Sweden
Ewa Jassem — Gdańsk, Poland
Kozui Kida — Tokyo, Japan
Jerzy Kozielski — Zabrze, Poland
Piotr Kuna — Łódź, Poland
Jan Kuś — Warsaw, Poland
Henryk Mazurek — Rabka, Poland
Florin Mihaltan — Bucharest, Romania
Janusz Milanowski — Lublin, Poland
Tadeusz Orłowski — Warsaw, Poland
Bernard Panaszek — Wrocław, Poland
Władysław Pierzchała — Katowice, Poland
Tadeusz Płusa — Warsaw, Poland
Venerino Poletti — Forli, Italy
Michał Poznański — Lodz, Poland
Stephen Rennard — Omaha, United States
Kazimierz Roszkowski — Warsaw, Poland
Monika Szturmowicz — Warsaw, Poland
Paweł Śliwiński — Warsaw, Poland
Branislava Savic — Belgrade, Serbia
Nikos Siafakas — Heraclion, Greece
Dragan Subotic — Belgrad, Serbia
Adam Torbicki — Otwock, Poland
Michał Unger — Philadelphia, United States
Arunas Valiulis — Vilnius, Lithuania
Martina Vašáková — Praque, Czech Republic
Jadwiga Wędzicha — London, Great Britain
Elżbieta Wiatr — Warsaw, Poland
Dariusz Ziora — Zabrze, Poland
Zofia Zwolska — Warsaw, Poland

Past Editors-in-Chief (most recent first)
Monika Szturmowicz — Warsaw
Dorota Górecka — Warsaw
Elżbieta Wiatr — Warsaw
Tadeusz Płusa — Warsaw

Opinions presented in the articles not necessarily represent the opinions of the Editors
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
http://www.viamedica.pl
project manager: weronika.kordyka@viamedica.pl
Editorial Address: Biuro ZG PTChP, ul. Wronia 45, lok. 132, Warszawa, Poland
Subscription Rates: Paper subscription, 6 issues incl. package and postage individual 60E
Paper subscription, 6 issues incl. package and postage institutional 90E.
Payment should be made to: Fortis Bank Polska SA, Gdańsk, Poland, Acc.: PL 15 1600 1303 0004 1007 1035 9001; SWIFT: PPABPLPK.
Single issues, subscriptions orders and requests for sample copies should be send
to e-mail: prenumerata@viamedica.pl
Electronic orders option available at: https://journals.viamedica.pl/advances_in_respiratory_medicine/about/subscriptions
Advertising: For details on media opportunities within this journal please contact the advertising sales department, ul. Świętokrzyska 73, 80–180 Gdańsk, Poland, phone: +48 58 320 94 94; e-mail: dsk@viamedica.pl
The Editors accept no responsibility for the advertisement contents.

All rights reserved, including translation into foreign languages. No part of this periodical, either text or illustration, may be used in any form whatsoever. It is particularly forbidden for any part of this material to be copied or translated into a mechanical or electronic language and also to be recorded in whatever form, stored in any kind of retrieval system or transmitted, whether in an electronic or mechanical form or with the aid of photocopying, microfilm, recording, scanning or in any other form, without the prior written permission of the publisher. The rights of the publisher are protected by national copyright laws and by international conventions, and their violation will be punishable by penal sanctions.

Editorial policy and information for authors available on https://journals.viamedica.pl/public/journals/30/0B_ARM_2017_1_zasady1.pdf.
Polish Ministry of Science and Higher Education score: 20 pts.

19-0179.014.001

VIA MEDICA Copyright © 2020 PTChP

Advances in Respiratory Medicine

www.journals.viamedica.pl

Formerly Pneumonologia i Alergologia Polska

www.ptchp.org

Contents

ORIGINAL RESEARCHES

PRELIMINARY REPORT

REVIEW ARTICLES

CASE REPORTS

CLINICAL VIGNETTES

LETTERS TO THE EDITOR

Mitsuhiro Abe[1], Kenji Tsushima[2], Keiichiro Yoshioka[1], Masashi Sakayori, Kenichi Suzuki[1], Yasutaka Hirasawa[1], Takeshi Kawasaki[1], Jun Ikari[1], Jiro Terada[1], Koichiro Tatsumi[1]

[1]Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan
[2]Department of Pulmonary Medicine, International University of Health and Welfare, School of Medicine, Chiba, Japan

The Gender–Age–Physiology system as a prognostic model in patients with idiopathic pulmonary fibrosis treated with nintedanib: a longitudinal cohort study

Abstract

Introduction: The Gender-Age-Physiology (GAP) system is a tool for predicting prognosis in patients with idiopathic pulmonary fibrosis (IPF). Yet, to date, the GAP system has not been evaluated in patients with IPF who received nintedanib.

Material and methods: This single-center retrospective study included 89 patients with IPF who received nintedanib for at least 3 months. All-cause mortality was set as the end point. Clinical parameters, including the GAP stage, were statistically analyzed for risk factors leading to mortality using the Cox proportional hazard model.

Results: The median follow-up was 16.4 months (range 3.7–37.4 months), during which 23 patients died. Univariate analysis revealed that the GAP stage (hazard ratio [HR] 3.00, 95% confidence interval [CI] 1.52–5.92, $p = 0.0014$) and PaO_2 (HR 0.95, 95% CI 0.92–0.98, $p = 0.0063$) were significant prognostic factors. Multivariate analysis revealed that the GAP stage was a significant prognostic factor (HR 2.26, 95% CI 1.07–4.78, $p = 0.031$). Log-rank analysis revealed that there were no significant differences in "Gender" ($p = 0.47$) and "Age" ($p = 0.18$) factors. However, there were significant differences in "Physiology" factors (% of forced vital capacity, $p = 0.018$; % of diffusing capacity of lung carbon monoxide, $p < 0.001$). The cumulative incidences of mortality at 1 and 2 years were as follows: GAP I: 5.1% and 6.8%; GAP II: 9.5% and 29.3%; and GAP III: 18.9% and 84.2%.

Conclusions: The GAP system is useful as a prognostic tool in patients with IPF who have been treated with nintedanib.

Key words: diffusing capacity of lung carbon monoxide, forced vital capacity, GAP stage, idiopathic pulmonary fibrosis, nintedanib

Adv Respir Med. 2020; 88: 369–376

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia [1]. IPF exhibits a poor prognosis similar to many types of cancers, with an average survival time of 2–3 years after diagnosis [2–4]. Pulmonary function tests are important in the evaluation of the severity of IPF [1, 4]. In pulmonary function testing, the forced vital capacity (FVC) and the diffusion capacity of lung carbon monoxide (D_{LCO}) have been identified as important prognostic factors in patients with IPF [2, 5, 6].

Nintedanib is a tyrosine-kinase inhibitor that targets vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptors [7, 8]. In the most recent international clinical practice guidelines, nintedanib received a conditional recommendation for the treatment of IPF [9]. It should be noted that although nintedanib was useful in patients with severe IPF who did not meet the eligibility criteria for clinical trials of nintedanib (INPULSIS-1/2 trial [10]), we previously reported that the prognosis of these patients was worse [11].

An accurate evaluation of a patient's clinical severity combined with a theory regarding prognosis are both very important clinical issues in determining appropriate treatment. Several prognostic

Address for correspondence: Mitsuhiro Abe, Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan; e-mail: mthrsgnm@chiba-u.jp
DOI: 10.5603/ARM.a2020.0137
Received: 13.02.2020
Copyright © 2020 PTChP
ISSN 2451–4934

factors for IPF have been reported including male gender [12], elderly age [13], %FVC at baseline [13–15], and $\%D_{LCO}$ at baseline [14]. In addition, serum biomarkers (surfactant proteins A and D [16], C-C motif chemokine ligand 18 [15], and matrix metalloproteinase collagen fragments [17]) and gene polymorphisms (*MUC5B* promoter polymorphism [18]) have been reported as prognostic factors. However, as these biomarkers are difficult to measure in general hospitals, they are not always used as prognostic factors in clinical practice.

The Gender-Age-Physiology (GAP) system has been reported as a simple and useful tool for the prediction of prognosis in patients with IPF in several nationwide IPF registries (e.g., Germany, Australia, and South Korea) [19–22]. However, these registries include many patients who were registered prior to the increased use of antifibrotic drugs. Since 2015, antifibrotic agents (e.g., pirfenidone and nintedanib) have been recommended as treatments for IPF [9].

Recently, the GAP system was evaluated as a prognostic model in patients with IPF treated with pirfenidone [23–25]. However, to date, the GAP system has not been evaluated in patients with IPF who received other recommended antifibrotic agents such as nintedanib. Therefore, in this study, we retrospectively examined whether the GAP system is useful as a prognostic model in patients with IPF who have received nintedanib.

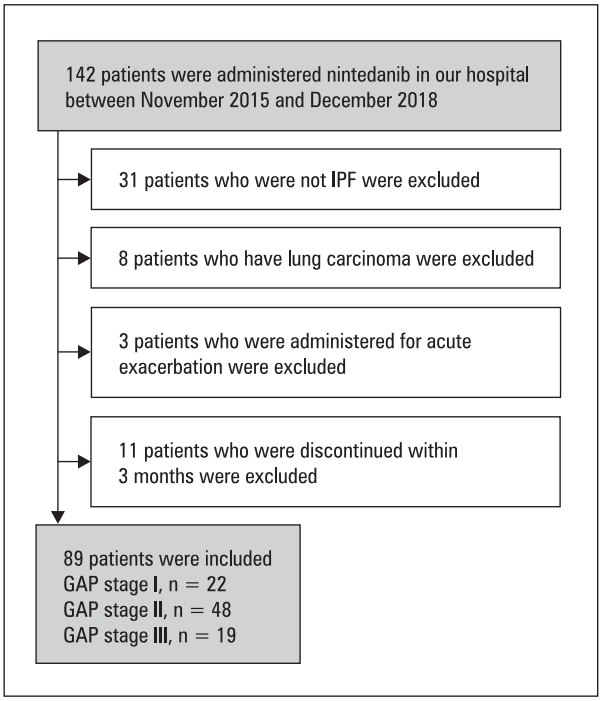

Figure 1. Study flow chart. In total, 124 patients received nintedanib in our hospital between November 2015 and December 2018. Patients who did not have IPF (n = 26), with lung cancer at the start of nintedanib treatment (n = 6), and who received nintedanib for acute exacerbation stage (n = 3) were excluded. Of the remaining 92 patients, 12 were excluded because they discontinued treatment within 3 months of nintedanib administration. Ultimately, 82 patients with IPF were enrolled (GAP stage I, n = 20; GAP stage II, n = 45; GAP stage III, n = 17). GAP — Gender-Age-Physiology stage; IPF — idiopathic pulmonary fibrosis

Materials and methods

This single-center, retrospective study was performed in accordance with the amended Declaration of Helsinki. The research protocol was approved by the Human Ethics Committee of Chiba University Hospital (approval number: 3481). We obtained informed consent with an option to opt out.

Patients

Overall, 142 consecutive patients received nintedanib in the Chiba University Hospital between November 2015 and December 2018. Patients who did not have IPF (n = 31), patients with lung cancer at the start of nintedanib (n = 8), and patients who received nintedanib for acute exacerbations (n = 3) were excluded. Of the remaining 100 patients, 11 patients were excluded because they discontinued treatment within 3 months of starting therapy with nintedanib. Ultimately, 89 patients with IPF were enrolled (Figure 1). IPF was diagnosed based on the American Thoracic Society/European Respiratory Society Thoracic Association/Japanese Respiratory Society (JRS)/Latin American Thoracic Association IPF guidelines from 2018 [26].

GAP system

The GAP score was calculated according to the report by Ley *et al.* [19]: gender (female, 0 points; male, 1 point), age (≤ 60 years, 0 points; 61–65 years, 1 point; > 65, 2 points), %FVC (> 75%, 0 points; 50–75, 1 point; < 50, 2 points), and $\%D_{LCO}$ (> 55%, 0; 36–55, 1 point; ≤ 35, 2 points; cannot obtain D_{LCO}, 3 points). The GAP stage was determined based on the total GAP score: stage I (0–3 points), stage II (4–5 points), and stage III (6–8 points).

JRS severity staging system

The JRS severity staging system consists of the combination of two known prognostic variables which are resting arterial partial pressure of oxygen (PaO_2) and peripheral capillary oxygen saturation (SpO_2) in the 6-minute walk test (6MWT)

[27]. The present severity staging system for IPF defines $PaO_2 \geq 80$ Torr at rest as stage I, 70–79 Torr as stage II, 60–69 Torr as stage III, and < 60 Torr as stage IV. If the SpO_2 at the end of 6MWT is < 90%, then the severity should be increased by one stage for patients with stage II or III.

Statistical analysis

The clinical data regarding continuous variables are expressed as the mean ± standard deviation. The categorical variables are given as percentages. The Cox proportional hazard model analysis was used to identify significant factors for predicting patient mortality. Kaplan-Meier survival curves and log-rank tests were used to compare patient survival according to GAP stages. The level of significance [p value (p) < 0.05] was adopted as statistically significant. All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [28] and the graphical user interface for R (R version 3.2.0, The R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the included patients (GAP I, n = 22; GAP II, n = 48; GAP III, n = 19) are shown in Table 1. The median duration of follow-up time, which started following 3 months of treatment, was 16.4 months (range 3.7–37.4 months). Twenty-three deaths (25%) were observed during the follow-up time (GAP I, n = 2 [9%]; GAP II, n = 11 [22%]; GAP III, n = 10 [52%]). The causes of death are shown in Table 2. Ten patients died of chronic pulmonary failure and eight patients died due to an acute exacerbation of disease.

The log-rank test result revealed a significant difference in mortality among the three groups (GAP I, II, and III; p = 0.0013; Figure 2). The cumulative incidences of mortality at 1 and 2 years were as follows: GAP I, 5.1 % and 6.8 %; GAP II, 9.5 % and 29.3 %; and GAP III, 18.9 % and 84.2 %.

The survival curves drawn for each of the four factors comprising the GAP system (gender, age, %FVC, and $\%D_{LCO}$) are shown in Figures 3–6. There were no significant differences between male and female patients (p = 0.47; Figure 3), or among the three age groups (p = 0.18; Figure 4). There was a significant difference among the three groups in %FVC (p = 0.018; Figure 5) and $\%D_{LCO}$ (p < 0.001; Figure 6).

The log-rank test result also revealed a significant difference in the survival of patients who were not admitted for hospital care among the

Table 1. Baseline characteristics of 89 included patients

	Total (n = 89)	GAP I (n = 22)	GAP II (n = 48)	GAP III (n = 19)
Age	71.3 ± 6.2	70.3 ± 5.4	71.6 ± 7.0	71.5 ± 4.6
Male, n (%)	68 (76%)	15 (68%)	39 (81%)	14 (73%)
Smoker, n (%)	68 (76%)	15 (68%)	38 (79%)	15 (78%)
BMI (kg/m^2)	23.8 ± 4.0	23.9 ± 4.0	23.9 ± 4.1	23.4 ± 3.7
Severity staging system in JRS (I/II/III/IV)	29 / 4 / 26 / 30	13 / 1 / 5 / 3	14 / 2 / 17 / 15	2 / 1 / 4 / 12
UIP pattern in HRCT	66 (74%)	13 (59%)	37 (77%)	16 (84%)
Pre-treatment with PFD	32 (35%)	4 (18%)	15 (31%)	13 (68%)
Long-term home oxygen therapy	23 (25%)	3 (13%)	9 (18%)	11 (57%)
PaO_2 (mm Hg)	73 ± 13	81 ± 13	73 ± 12	63 ± 11
Minimum SpO_2 by 6MWT (%)	80 ± 9	83 ± 10	80 ± 7	75 ± 12
KL-6 (U/mL)	1421 ± 1114	1252 ± 953	1323 ± 1106	1889 ± 1242
FVC (mL)	2172 ± 802	2735 ± 833	2129 ± 706	1601 ± 544
%FVC (%)	67 ± 19	86 ± 17	64 ± 14	50 ± 11
$\%_{DLCO}$ (%)	56 ± 21	71 ± 9	54 ± 22	32 ± 7
Follow-up duration, median [range] (month)	16.4 [3.7–37.4]	16.5 [4.5–33.9]	18.1 [3.7–37.4]	12.5 [4.0–36.0]
Death, n (%)	23 (25%)	2 (9%)	11 (22%)	10 (52%)

6MWT — 6 minutes walk test; BMI — body mass index; D_{LCO} — diffusing capacity of the lungs for carbon monoxide; FVC — forced vital capacity; GAP — Gender Age-Physiology; HRCT — high-resolution computed tomography; JRS — Japan respiratory society; KL-6 — Krebs von den Lungen-6; PFD — pirfenidone; UIP — usual interstitial pneumonia

Table 2. Cause of death

	Total (n = 89)	GAP I (n = 22)	GAP II (n =4 8)	GAP III (n = 19)
Death, n (%)	23 (25%)	2 (9%)	11 (22%)	10 (52%)
Chronic pulmonary failure	10	0	6	4
Acute exacerbation	8	0	4	4
Lung cancer	2	1	1	0
Pneumonia	3	1	0	2

GAP — Gender-Age-Physiology

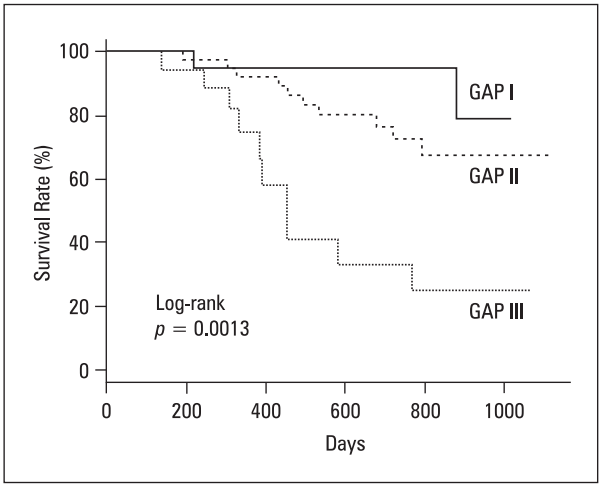

Figure 2. Survival curves of GAP stages I, II, and III. The log-rank test result reveals a significant difference in mortality among the three groups (GAP I, II, and III) (p = 0.0013). GAP — Gender-Age-Physiology stage.

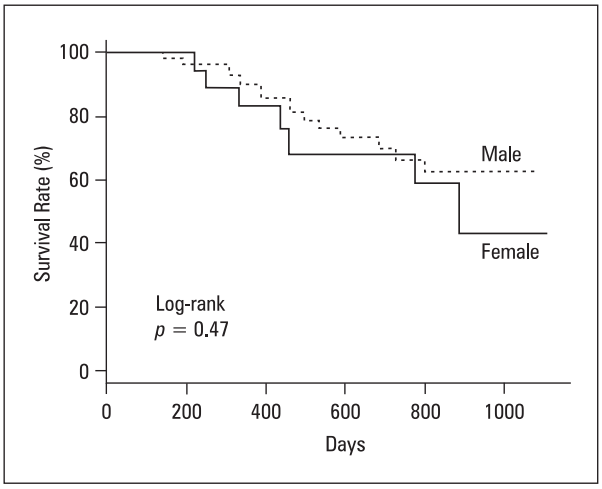

Figure 3. Survival curves between male and female patients. The log-rank test result reveals no significant difference between male and female patients (p = 0.40)

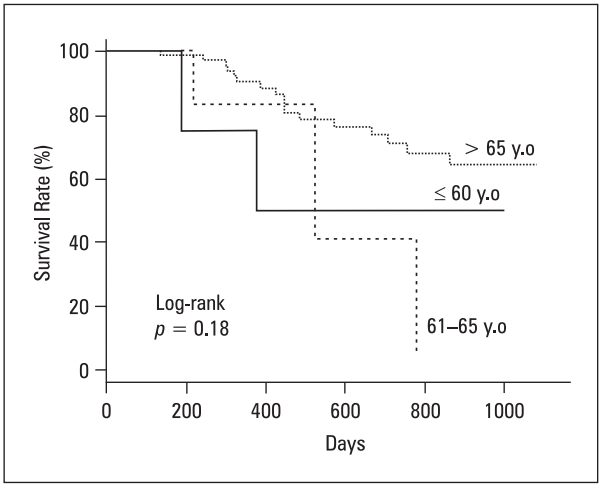

Figure 4. Survival curves of the three age groups. The log-rank test result reveals no significant difference among the three age groups (p = 0.14). Y.o. — years old

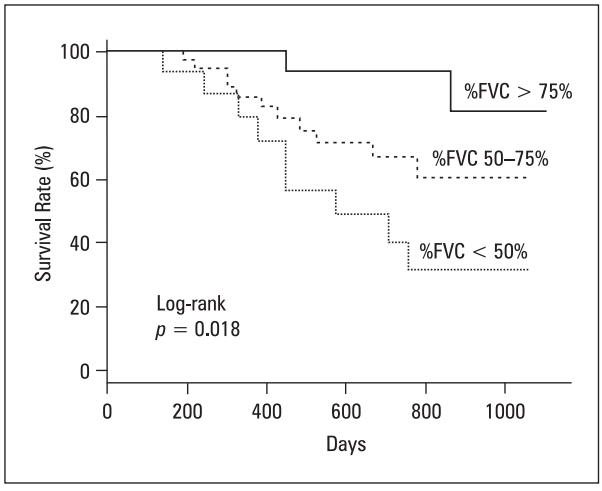

Figure 5. Survival curves of the three groups of %FVC. The log-rank test result reveals a significant difference among the three groups of %FVC (p = 0.015). %FVC — percentage of forced vital capacity

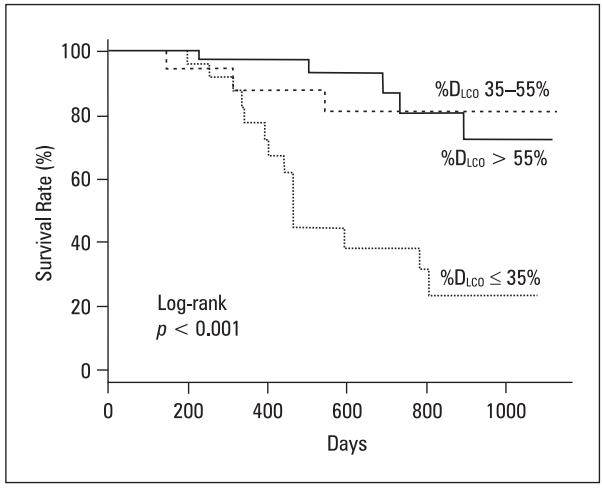

Figure 6. Survival curves of the three groups of %D_{LCO}. The log-rank test result reveals a significant difference among the three groups of %D_{LCO} ($p < 0.001$). %D_{LCO}, diffusing capacity of lung carbon monoxide

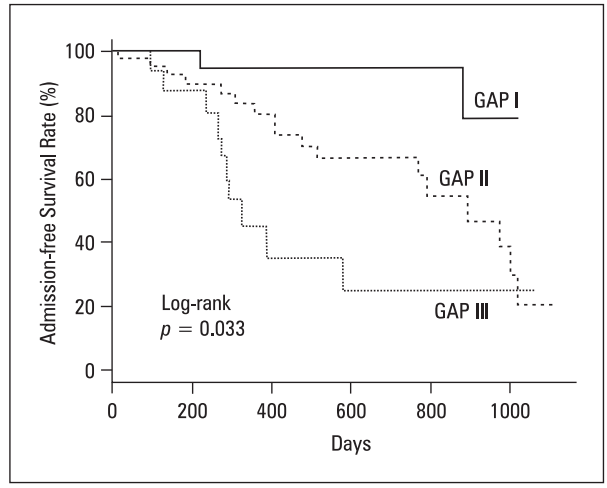

Figure 7. Admission-free survival curves of GAP stages I, II, and III. The log-rank test result reveals a significant difference in admission free survival time among the three groups (GAP I, II, and III) ($p = 0.033$). GAP — Gender-Age-Physiology stage

three groups (GAP I, II, and III; p = 0.033; Figure 7). The cumulative incidence of admission or death at 1 and 2 years were as follows: GAP I, 5.1% and 6.8%; GAP II, 14.9% and 34.6%; and GAP III, 46.8% and 91.5%.

Univariate analysis revealed that the GAP stage [hazard ratio (HR) 3.00, 95% confidence interval (CI) 1.52–5.92, p = 0.0014], PaO_2 (HR 0.95, 95% CI 0.92–0.98, p = 0.0063), and long-term home oxygen therapy (HR 2.72, 95% CI 1.17–6.28, p = 0.018) were significant risk factors (Table 3). Additionally, the %FVC (HR 0.96, 95% CI 0.93–0.98, p = 0.0042) and the %D_{LCO} (HR 0.93, 95% CI 0.90–0.97, p < 0.001), which constitute the GAP stage, were demonstrated as significant risk factors. Multivariate analysis with the GAP stage, PaO_2, and body mass index (BMI), which had low p-values in the univariate analysis, showed that the GAP stage (HR 2.26, 95% CI 1.07–4.78, p = 0.031) and BMI (HR 0.89, 95% CI 0.80–0.99, p = 0.048) were significant prognostic factors (Table 3).

Discussion

To the best of our knowledge, this is the first study to demonstrate that the GAP system, which is a prognostic model for patients with IPF, also has prognostic value in patients with IPF that had been treated with the antifibrotic agent nintedanib (Figure 2). In Japan, the JRS severity system is a classification system based on PaO_2 and the lowest SpO_2 in the 6MWT. In the present study, we found that while PaO_2 was a significant prognostic factor in univariate analysis, the JRS severity system was not (Table 3). Moreover, multivariate analysis revealed that the GAP system and BMI were also significant prognostic factors. The GAP system has been reported as a simple and useful tool for the prediction of prognosis in patients with IPF [19], However, the use of the GAP system as a prognostic model was proposed before the widespread use of antifibrotic drugs for IPF treatment. Therefore, it was potentially less useful in the context of antifibrotic drug treatment. Recently, the GAP system has been validated as a prognostic model for patients with IPF receiving the antifibrotic drug pirfenidone [23–25]. Our current results confirm these findings and suggest that the GAP system is also an appropriate prognostic model for patients with IPF receiving the antifibrotic drug nintedanib.

In this study, %FVC was the strongest prognostic factor among the four items evaluated in the GAP system. The effects of age and gender were weaker than those of %FVC and %D_{LCO} (Figures 3–6). We found no significant differences in sex (HR 0.72, 95% CI 0.29–1.76, p = 0.47) in the univariate analysis, although male patients tended to have a better prognosis (Figure 3). In the original report of the GAP system by Ley *et al.* [19], sex had a lower impact on prognosis compared with other factors. Although mortality due to IPF was initially reported to be higher in men [12], a recent study by Song *et al.* [29] found that among 380 patients with IPF, survival time was nearly equivalent between male (46.6 months) and female (45.0 months) patients (Chi-squared

Table 3. Univariate and multivariate analysis of survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.98	0.93–1.04	0.63			
Male	0.72	0.29–1.76	0.47			
Smoker	0.96	0.35–2.60	0.94			
BMI	0.90	0.82–1.00	0.056	0.89	0.80–0.99	0.048
Severity staging system in JRS	1.37	0.95–1.99	0.091			
GAP stage	3.00	1.52–5.92	0.0014	2.26	1.07–4.78	0.031
UIP pattern in HRCT	2.30	0.68–7.77	0.17			
Pre-treatment with PFD	1.47	0.88–2.45	0.13			
Long-term home oxygen therapy	2.50	1.10–5.68	0.027			
PaO_2	0.95	0.92–0.98	0.0063	0.97	0.93–1.00	0.11
Minimum SpO_2 by 6MWT	0.96	0.93–1.00	0.061			
KL-6	1.00	0.99–1.00	0.91			
FVC	0.50	0.27–0.90	0.022			
%FVC	0.96	0.93–0.98	0.0042			
$\%D_{LCO}$	0.95	0.92–0.98	0.0023			

6MWT — 6 minutes walk test; BMI — body mass index; CI — confidence interval; D_{LCO} — diffusing capacity of the lungs for carbon monoxide; FVC — forced vital capacity; GAP — Gender-Age-Physiology; HR — hazard ratio; HRCT — high-resolution computed tomography; JRS — Japan Respiratory Society; KL-6 — Krebs von den Lungen-6, UIP — usual interstitial pneumonia; PFD — pirfenidone

test, p = 0.887). These findings are consistent with the outcome of our study and together suggest that the administration of nintedanib does not affect the relationship between gender and prognosis.

In the present study, elderly people (> 65 years) did not have a worse prognosis than young people (≤ 60 years). While Song *et al.* [29] reported that younger patients (< 50 years) tended to have a good prognosis compared to that of elderly patients (> 75 years), the difference was not significant (Kolmogorov-Smirnov test, p = 0.268). One potential reason for this difference is due to nintedanib's high frequency of side effects (e.g., diarrhea, anorexia, liver injury) [10]. Elderly patients with a poor general condition might not have received nintedanib due to their attending physician's preferences. This may have affected the assessment of differences in prognosis by age.

In this study, the cumulative incidences of mortality at 1 and 2 years were as follows: GAP I, 5.1% and 6.8%; GAP II, 9.5% and 29.3%; and GAP III, 18.9% and 84.2%, respectively. These results are similar to those reported by Harari *et al.* [25] in their study of patients who received pirfenidone (GAP I, 8.4% and 17.2%; GAP II, 17.6% and 34.2%; and GAP III 28.3% and 51.2%, respectively) thus indicating the validity of the present study. Together, these findings also suggest that the therapeutic effects obtained by nintedanib and pirfenidone might be similar.

Notably, our results showed that patients with GAP stage III have an extremely poor prognosis. Therefore, it is desirable to start treatment of these patients immediately. However, our results indicate that for patients with IPF with GAP stage I/II, it is also important to start early treatment with antifibrotic drugs. In the original report of the GAP system by Ley *et al.*, [19] the cumulative incidences of mortality at 1 and 2 years were as follows: GAP I, 5.6% and 10.9%; GAP II, 16.2% and 29.9%; and GAP III 39.2% and 62.8%. Although obtaining a direct comparison between the studies is difficult due to differences in patient background, the overall mortality rate in the present study tended to be better than that reported by Ley *et al.* [19]. However, it should be noted that the 2-year mortality rate for GAP III patients was higher in the present study. The long-term effects of nintedanib in patients with advanced IPF are unknown and should be clarified in further studies.

Our study revealed that the GAP system is not only a prognostic model, but also an appropriate predictive model of survival in non-admitted pa-

tients with IPF who were receiving the antifibrotic drug nintedanib (Figure 7).

This study had some limitations. Firstly, the study had a retrospective, single-center design with a small sample size. Secondly, the median follow-up duration was short. Therefore, in the future, it will be necessary to demonstrate the usefulness of the GAP system in patients receiving antifibrotic drugs in a large-scale, nationwide, prospective study.

Conclusions

The GAP stage is useful as a prognostic tool in patients with IPF who have been treated with nintedanib. The physiological parameters of the GAP system (%FVC and $\%D_{LCO}$) are of particular importance with regard to patient prognosis.

Acknowledgements

We would like to thank Editage (*www.editage.jp*) for English language editing.

Authors' contributions

MA and KTs analyzed and interpreted the patient data regarding idiopathic pulmonary fibrosis treated with nintedanib. MA was a major contributor to the writing of the manuscript. All authors read and approved the final manuscript.

Competing interests

MA, KTs, and KTa report receipt of personal fees from Boehringer Ingelheim Japan.

Funding

This work was supported by the Japanese Society for the Promotion of Science KAKENHI (Grant Number JP19K20727).

References:

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011; 183(6): 788–824, doi: 10.1164/rccm.2009-040GL, indexed in Pubmed: 21471066.
2. Vancheri C, Failla M, Crimi N, et al. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J. 2010; 35(3): 496–504, doi: 10.1183/09031936.00077309, indexed in Pubmed: 20190329.
3. Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med. 2007; 176(3): 277–284, doi: 10.1164/rccm.200701-044OC, indexed in Pubmed: 17478620.
4. Natsuizaka M, Chiba H, Kuronuma K, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014; 190(7): 773–779, doi: 10.1164/rccm.201403-0566OC, indexed in Pubmed: 25162152.
5. du Bois RM, Nathan SD, Richeldi L, et al. Idiopathic pulmonary fibrosis: lung function is a clinically meaningful endpoint for phase III trials. Am J Respir Crit Care Med. 2012; 186(8): 712–715, doi: 10.1164/rccm.201206-1010PP, indexed in Pubmed: 22798316.
6. Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib. N Engl J Med. 2015; 372(13): 1189–1191, doi: 10.1056/NEJMp1500526, indexed in Pubmed: 25806913.
7. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008; 68(12): 4774–4782, doi: 10.1158/0008-5472.CAN-07-6307, indexed in Pubmed: 18559524.
8. Wollin L, Wex E, Pautsch A, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J. 2015; 45(5): 1434–1445, doi: 10.1183/09031936.00174914, indexed in Pubmed: 25745043.
9. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015; 192(2): e3–19, doi: 10.1164/rccm.201506-1063ST, indexed in Pubmed: 26177183.
10. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370(22): 2071–2082, doi: 10.1056/NEJMoa1402584, indexed in Pubmed: 24836310.
11. Abe M, Tsushima K, Tatsumi K, et al. Utility of nintedanib for severe idiopathic pulmonary fibrosis: a single-center retrospective study. Drug Des Devel Ther. 2018; 12: 3369–3375, doi: 10.2147/DDDT.S179427, indexed in Pubmed: 30349191.
12. Johnston I, Britton J, Kinnear W, et al. Rising mortality from cryptogenic fibrosing alveolitis. BMJ. 1990; 301(6759): 1017–1021, doi: 10.1136/bmj.301.6759.1017, indexed in Pubmed: 2249048.
13. King TE, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001; 164(7): 1171–1181, doi: 10.1164/ajrccm.164.7.2003140, indexed in Pubmed: 11673205.
14. Nathan SD, Shlobin OA, Weir N, et al. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest. 2011; 140(1): 221–229, doi: 10.1378/chest.10-2572, indexed in Pubmed: 21729893.
15. Neighbors M, Cabanski CR, Ramalingam TR, et al. Prognostic and predictive biomarkers for patients with idiopathic pulmonary fibrosis treated with pirfenidone: post-hoc assessment of the CAPACITY and ASCEND trials. Lancet Respir Med. 2018; 6(8): 615–626, doi: 10.1016/S2213-2600(18)30185-1, indexed in Pubmed: 30072107.
16. Wang K, Ju Q, Cao J, et al. Impact of serum SP-A and SP-D levels on comparison and prognosis of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Medicine (Baltimore). 2017; 96(23): e7083, doi: 10.1097/MD.0000000000007083, indexed in Pubmed: 28591049.
17. Jenkins RG, Simpson JK, Saini G, et al. Longitudinal change in collagen degradation biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicentre PROFILE study. Lancet Respir Med. 2015; 3(6): 462–472, doi: 10.1016/S2213-2600(15)00048-X, indexed in Pubmed: 25770676.
18. Peljto AL, Zhang Y, Fingerlin TE, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA. 2013; 309(21): 2232–2239, doi: 10.1001/jama.2013.5827, indexed in Pubmed: 23695349.
19. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012; 156(10): 684–691, doi: 10.7326/0003-4819-156-10-201205150-00004, indexed in Pubmed: 22586007.
20. Kreuter M, Swigris J, Pittrow D, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. Eur Respir J. 2015; 46(1): 186–196, doi: 10.1183/09031936.00217614, indexed in Pubmed: 25837040.
21. Jo HE, Glaspole I, Grainge C, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian

Idiopathic Pulmonary Fibrosis Registry. Eur Respir J. 2017; 49(2), doi: 10.1183/13993003.01592-2016, indexed in Pubmed: 28232409.
22. Lee SH, Park JS, Kim SY, et al. Comparison of CPI and GAP models in patients with idiopathic pulmonary fibrosis: a nationwide cohort study. Sci Rep. 2018; 8(1): 4784, doi: 10.1038/s41598-018-23073-3, indexed in Pubmed: 29555917.
23. Albera C, Costabel U, Fagan EA, et al. Efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with more preserved lung function. Eur Respir J. 2016; 48(3): 843–851, doi: 10.1183/13993003.01966-2015, indexed in Pubmed: 27471208.
24. Hosein K, Le J, Mura M. Assessing the therapeutic response to pirfenidone in idiopathic pulmonary fibrosis: can we do better than with forced vital capacity alone? Lung. 2017; 195(1): 101–105, doi: 10.1007/s00408-016-9963-3, indexed in Pubmed: 27858160.
25. Harari S, Caminati A, Confalonieri M, et al. The prognostic role of Gender-Age-Physiology system in idiopathic pulmonary fibrosis patients treated with pirfenidone. Clin Respir J. 2019; 13(3): 166–173, doi: 10.1111/crj.12999, indexed in Pubmed: 30675755.
26. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018; 198(5): e44–e68, doi: 10.1164/rccm.201807-1255ST, indexed in Pubmed: 30168753.
27. Nukiwa T, Abe T, Yaekashiwa M. A revised clinical staging classification of idiopathic interstitial pneumonia. The Annual Report by Study Group of Ministry of Health and Welfare for Diffuse Lung Disease. Diffuse Lung Disease Research Group from the Ministry of Health, Labor and Welfare of Japanese Government. 1999: 36–41.
28. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013; 48(3): 452–458, doi: 10.1038/bmt.2012.244, indexed in Pubmed: 23208313.
29. Song H, Sun D, Ban C, et al. Independent clinical factors relevant to prognosis of patients with idiopathic pulmonary fibrosis. Med Sci Monit. 2019; 25: 4193–4201, doi: 10.12659/MSM.914725, indexed in Pubmed: 31166938.

Mohammad Ali Zohal[1], Sima Rafiei[1, 2], Nafise Rastgoo[1], Sanaz Jamshidi[1]

[1]Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran
[2]Social Determinants of Health Research Center, Qazvin University of Medical Sciences, Qazvin, Iran

Exposure to stressful life events among patients with chronic obstructive pulmonary disease: a prospective study

Abstract

Introduction: Although depression and anxiety have been widely investigated among patients with chronic obstructive pulmonary disease (COPD), experiencing stressful life events and its effect on increasing risk of exacerbations was rarely assessed. This study aimed to clarify the association between facing with stressful events among COPD patients and their disease severity leading to hospitalization.

Material and methods: A prospective study was conducted among 128 COPD patients from the population of Qazvin, a northwest, industrialized city of Iran from December 2017 to December 2018. Patients were followed up for one-year and their related measures were gathered. To compare variables among patients stratified by reporting stressful life conditions, Pearson's chi-square and Fisher's exact tests were used. Furthermore, to assess the effect of several covariates on the response variable, a logistic regression modelling was applied. Results were reported in form of odds ratios and their 95% confidence intervals.

Results: Study findings affirmed that patients who had experienced stressful situation had lower BMI, were retired, experienced more frequent exacerbations, and reported higher levels of anxiety/ depression. Moreover, those with stressful conditions were among current or former smokers ($p < 0.05$). Logistic regression analysis revealed that facing with stressful situations was significantly associated with the severity of COPD disease (OR 1.9; 95% CI 2.5 to 5.6), smoking habit (OR 2.8; 95% CI 1.6 to 4.2; OR 1.5; 95% CI 1.4 to 2.2), and hospitalization during one-year follow up (OR 1.2; 95% CI 1 to 3.3).

Conclusions: To improve health outcomes of COPD patients, close attention should be given to their psychological disorder and appropriate strategies should be applied to reduce patients' exposure to stressful life events and subsequent anxieties.

Key words: anxiety, depression, stressful life event, chronic obstructive pulmonary disease, severity

Adv Respir Med. 2020; 88: 377–382

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease leading to reduced air flow in pulmonary function, and shortness of breath which is largely due to an exposure to irritants like air pollution, noxious particles or tobacco smoking [1, 2]. It is anticipated that the disease will have become the fourth prominent death cause and the seventh prominent factor of disability worldwide by 2030. High blood pressure, diabetes mellitus, lung cancer, ischemic heart disease, anxiety disorder, and depression are among important comorbidities for advanced COPD. Literature has affirmed that COPD patients who suffer from comorbidities are more likely to be hospitalized in a frequent manner [3]. Psychological issues like anxiety and depression are key factors which cause significant burden of mortality, and morbidity, among patients [4].

Indeed, patients with symptoms of depression experience more frequent hospitalization, failure in smoking cessation, and worse prognosis of the disease. Furthermore, such mental disorders might lead to desperateness, and distress among patients which subsequently would lead to a defective cycle that perpetuates anxiety and depression [5, 6]. Thus, addressing psychological disorders in

Address for correspondence: Sima Rafiei, Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Qazvin, Iran; e-mail: sima.rafie@gmail.com
DOI: 10.5603/ARM.a2020.0122
Received: 13.03.2020
Copyright © 2020 PTChP
ISSN 2451–4934

the clinical management of COPD has got a great importance, though still little is known about the diagnosis and management strategies of such disorders and their impact on COPD patients' health status. In a study conducted by Gianjoppe-Santos to compare anxiety and depression symptoms between patients in stable and post-exacerbated groups, findings revealed that the latter group of patients experienced more anxiety symptoms compared to the former one [7]. Furthermore, some of the studies have surveyed the potential relationships between psychological distress, and COPD exacerbation. Almost all the studies affirmed that patients with depression or potential anxiety faced with more exacerbations and subsequent hospitalization [8–10]. Similarly, Laurin *et al.* found that patients with anxiety and depressive disorders were at higher risk of exacerbation [11].

Identification of these influencing factors empowers policy makers to develop more effective strategies for the disease management. Although depression and anxiety have been widely investigated in patients with chronic obstructive pulmonary disease, experiencing stressful life events and its effect on increasing risk of exacerbations or death was rarely assessed [12, 13]. Due to lack of evidence about the impact of stressful life events on patient health outcomes in cohort studies, mainly in Iran, this study aimed to clarify the association between facing with stressful events among COPD patients and their disease severity leading to hospitalization.

Material and methods

Study design, participants and ethics

This was a prospective study conducted among 128 patients with COPD who referred to an outpatient pulmonary clinic in Qazvin, Iran between December and June 2018. Patients aged over 40 years old, with a COPD diagnosis according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were included in the study (n = 146); among which 18 patients excluded from the research due to having concurrent pulmonary disease, or taking drugs other than those for COPD. Finally, 128 patients (78.1% male, mean age 65.3 ± 11.9) were enrolled. The patients were followed up for a year and their related measures were gathered and recorded during this period of time.

Ethics statement

The ethics committee of Qazvin University of Medical Sciences approved the study, and written informed consent was obtained from each of the participants.

Measurements

Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety/ depression among patients. The 7-item subscale with a score scale ranging from 0 to 21 has been previously used in several studies and was proved to have validity and reliability [8, 14]. According to defined cut-off points, those who got score under 11, were regarded to have low level of anxiety, while patients with 11 to 14 score were mentioned in moderate and those with 15 to 21 score were categorized in severe anxiety group.

Besides assessing patients' anxiety, researchers asked a number of questions to assess stressful situations which patients faced with during 1-year follow up. The questions were mainly about the issues including losing a family member, patient's disability due to severe illness, lack of adequate support from relatives and friends, financial difficulties, retirement, and divorce. They also asked the patients to try to recall the date/month/year of the occurrence of the events.

Statistical analysis

Statistical analysis was conducted using Stata software, version 12.0. Patients' characteristics including their age, BMI, educational level, profession, and living situation, also their mean HADS score comprised of depression and anxiety were calculated for each of the patients based on their exposure to stressful life situations. Furthermore, for each patient who had at least one distressful situation during 1-year period of follow-up time, number of exacerbations was calculated. To compare variables among patients stratified by reporting stressful life conditions, Pearson's chi-square and Fisher's exact tests were used.

Finally, using a logistic regression modelling, the impact of exposure to stressful situations on some of the measures including disease severity, smoking behavior, and hospitalization was assessed. For all analyses, $P < 0.05$ was considered statistically significant.

Results

This study included and followed 128 patients for a year. Table 1 depicts the characteristics of study participants based on their hospitalization during the follow-up period. Results

affirmed that the mean age of patients who were hospitalized was slightly higher (65.5 ± 11.3 versus 62.4 ± 12.6). In relation to smoking, 30% of patients who continued smoking at the time of study experienced at least one hospitalization. Furthermore, 12.64% of patients with severe COPD and 14.2% with comorbidity faced with the disease exacerbation leading to hospitalization. Average score of anxiety and depression among patients who reported hospitalization during 1-year period was respectively 18.7 ± 10.2 and 17.1 ± 8 confirming higher levels of psychological disorder among these patients ($p < 0.05$).

In the second step, stressful conditions which patients were facing during the follow up period of time, were assessed. Table 2 shows patients' characteristics based on their report of stressful life events. Overall, seventy percent of patients declared that they had encountered with at least one stressful and distressing situation during the last year. Those who had experienced stressful situation had lower BMI, were retired, lived alone, experienced more frequent exacerbations, and reported higher levels of anxiety/ depression. Moreover, those with stressful conditions were among current or former smokers ($p < 0.05$).

Table 1. Patients' characteristics based on reporting stressful situations

Characteristics		Encountered with stressful situation		p-value
		Yes	No	
Age, mean [SD]		63 (10.7)	62.7 (18.5)	0.21
BMI, mean [SD]		25.2 (12.5)	24.9 (9.8)	0.04
Education, n [%]	Diploma	27 (30)	26 (70)	0.15
	University degree	63 (70)	12 (30)	
Smoking status, n [%]	Smoker	20 (22)	7 (18)	< 0.001
	Former smoker	64 (71.7)	24 (64)	
	Non-smoker	6 (6.3)	7 (18)	
Living condition, n [%]	Alone	67 (25)	10 (25)	0.12
	With family	23 (75)	28 (75)	
Occupation, n [%]	Employed	18 (20)	6 (15)	0.01
	Un-employed	13 (15)	—	
	Retired	59 (65)	32 (85)	
Number of exacerbations, n [%]	0	20 (22.3)	18 (47.9)	< 0.001
	≥ 1	70 (77.7)	20 (52.1)	
HADS anxiety, mean [SD]		12.2 (7.7)	10.7 (6.9)	< 0.001
HADS depression, mean [SD]		14.5 (6.5)	11.1 (5.7)	< 0.001

BMI — body mass index; HADS — Hospital Anxiety and Depression Scale

Table 2. Patients' health outcomes and behavior based on reporting stressful situations

Patients' characteristics	Stressful life event reported (baseline to follow-up)	Mean (95% CI)	p-value
Number of hospitalization	Yes	0.8 (0.5–1.1)	< 0.001
	No	0.7 (0.4–0.9)	
Cigarette use (number per day)	Yes	5.2 (4.5–7.7)	< 0.001
	No	3.5 (2.8–4.6)	
HADS anxiety	Yes	12.2 (10.6–14.2)	< 0.001
	No	10.7 (9.2–11.6)	
HADS depression	Yes	14.5 (10.2–18.7)	< 0.001
	No	11.1 (9.7–13.5)	

HADS — Hospital Anxiety and Depression Scale

Table 3. Univariate analysis to compare patients experiencing hospitalization during one-year follow-up

Characteristics		Hospitalization				
Categorical variables		**No**	**Yes**	**P**	**OR**	**95% CI**
Gender, n [%]	Male	91 (91)	9 (9)	0.11	1.2	0.83–2.6
Marital status, n [%]	Married	112 (92.6)	9 (7.4)	0.25	1.1	0.92–4.4
Educational level, n [%]	University degree	6 (85.8)	1 (14.2)	0.26	0.8	0.77–2.02
Current smoker, n [%]		21 (70)	9 (30)	< 0.001	2.9	2.1–5.7
COPD grade, n [%]	Moderate	62 (48.4)	4 (3.12)	0.06	1.1	0.87–3.08
	Severe	32 (25)	4 (3.12)	0.001	1.2	1.12–5.3
	Very severe	3 (2.34)	12 (9.25)	< 0.001	1.5	1.38–3.1
Comorbidity, n [%]		36 (85.8)	6 (14.2)	< 0.001	1.3	1.17–2.2
Experiencing stressful life event, n [%]	Yes	79 (87.7)	11 (12.3)	0.52	1.07	9.02–2.4
Continuous variables		Mean (SD)	Mean (SD)	P	OR	95% CI
Age		62.4 (12.6)	65.5 (11.3)	0.07	1.12	0.77–1.36
BMI		25.5 (4.9)	23.3 (3.8)	0.05	0.95	0.87–1.0
HADS anxiety		7 (2.1)	18.7 (10.2)	< 0.001	1.17	1.01–4.8
HADS depression		10.2 (4.5)	17.1 (8)	< 0.001	1.21	1.12–3.7

BMI — body mass index; COPD — chronic obstructive pulmonary disease; HADS — Hospital Anxiety and Depression Scale

Then the impact of exposure to stressful situations on some of the measures including disease severity (FEV_1 GOLD measure) was analyzed. Data are reported in Table 3.

Logistic regression analysis revealed that facing with stressful situations was significantly associated with the severity of COPD disease (OR 1.9; 95% CI 2.5 to 5.6), smoking habit (OR 2.8; 95% CI 1.6 to 4.2; OR 1.5; 95% CI 1.4 to 2.2), and hospitalization during one-year follow up (OR 1.2; 95% CI 1 to 3.3).

Finally, we adjusted the model for age, gender, educational level, occupation, income, and smoking history and assessed the impact of stressful conditions on the risk of COPD exacerbation among study patients. Results are shown in Table 4.

After adjusting the model for mentioned variables, results revealed that patients who faced with stressful situations were 2.8 times more likely to be hospitalized due to exacerbation (OR 2.28; 95% CI 1.04 to 2.84).

Discussion

In our study, we found that experiencing stressful life events is associated with COPD exacerbation. This finding emphasizes on the importance of psychological factors in COPD patients which has been similarly confirmed in several studies. Literature highlights that patients with psychological stress may reveal unhealthier behaviors which ultimately worsens their health condition and increases the risk of COPD exacerbation [15]. In a survey conducted by Yohannes *et al.*, results revealed higher rate of hospitalization among depressed patients [16]. Similar studies also affirmed significant associations between psychological disorder and exacerbation leading to disease-related hospitalizations. This suggests that COPD patients are more in danger when experiencing stressful events [11, 17].

Regarding this issue, Xu *et al.* reported that after one-year follow up, patients with some degrees of anxiety and depression encountered significantly more exacerbations and subsequent hospitalizations [18]. These findings were in line with Laurin *et al.* report emphasizing on a significant association between psychological distress and higher rates of exacerbations [11]. However, Fan and colleagues stated that using various types of cut-off scores through the Beck Depression Inventory leads to different findings. In fact, analysis of depressive symptoms as continuous predictors is not going to be associated with hospitalizations. While, using quantile measurements approves the relationship between depressive symptoms and higher risk of COPD-re-

Table 4. Multivariate models of risk factors for hospitalization of COPD patients

Variables		P	OR	95% CI	
				Lower	Upper
COPD grade 5.6	Severe	< 0.001	1.19	1.11	5.6
Current smoker		< 0.001	2.8	1.6	4.2
Comorbidity		0.001	1.34	1.005	2.8
Depression		0.005	2.28	1.04	2.8

COPD — chronic obstructive pulmonary disease

lated hospitalizations [19]. In a study conducted by Yu *et al.* results disclosed that stressful life events were significantly related to symptoms of depression and anxiety among patients. Otherwise, stressful life events were not associated with COPD exacerbations which reported to be due to the small sample size of study or short time frame of follow-up [8]. Similarly, some of the researches highlighted that after adjusting the model for covariates namely gender, disease severity, oxygen use, history of COPD hospitalization, and comorbidity the association between psychological distress and hospitalizations became non-significant. Such uneven results also highpoint the effect of differences in analysis methods and use of varying cutoffs.

Our findings also affirmed that facing with stressful conditions reinforces the smoking behavior as a risk factor for severity of COPD, hospitalization and restriction for daily activities which could also increase the risk of depression or anxiety in patients. In agreement with these results, several studies have shown that anxiety and depression are associated with feelings of desperateness and lack of self-confidence which will consequently lead to poor health behaviors namely smoking or physical inactivity [16, 20]. Andrenas *et al.* ascertained that most of the patients evaluated their stressful situation as a threat, and challenging issue which inversely affects their coping skills with distressful disorders [21]. They also believed that such worrying conditions have a harmful effect on patients' mental health and their quality of life [22–24]. Literature also revealed that deterioration in the immune system of patients with anxiety and depression is more likely which eventually weakens their resistance toward pathogens [25–27].

Despite several studies conducted to explore the relationship between the experience of stressful situations and increased risk of COPD exacerbation, our research tried to obtain more robust findings through applying a prospective study design and choosing shorter time frame for asking patients to recall their stressful life experiences. In our study, stressful situations were asked monthly from patients and documented through a prospective approach. Otherwise, there are some limitations regarding the current study. First, we were dependent on a self-reported scale which identified exposure to stressful conditions based on patients' perception.

Conclusions

In conclusion, our study found that experiencing stressful conditions was connected with more anxious and depressing signs among COPD patients which ultimately worsened the disease severity. Thus, to improve health outcomes of COPD patients, close attention should be given to their psychological disorder and appropriate strategies should be applied to reduce patients' exposure to stressful life events and subsequent anxieties.

Conflict of interest

None declared.

References:

1. Pauwels RA, Buist AS, Calverley PM, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001; 163(5): 1256–1276, doi: 10.1164/ajrccm.163.5.2101039, indexed in Pubmed: 11316667.
2. National Heart, Lung, and Blood Institute. COPD essentials for health professionals. NIH Publication No. 07-5845. December 2006. Bethesda, MD. Available at: www.nhlbi.nih.gov/health/public/lung/copd/campaign-materials/pub/provider-card.pdf. [Last accessed at: 13.07.2020].
3. Wagena EJ, Huibers MJ, van Schayck CP. Antidepressants in the treatment of patients with COPD: possible associations between smoking cigarettes, COPD and depression. Thorax. 2001; 56(8): 587–588, doi: 10.1136/thorax.56.8.587a, indexed in Pubmed: 11462058.
4. Pace TWW, Mletzko TC, Alagbe O, *et al.* Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006; 163(9): 1630–1633, doi: 10.1176/ajp.2006.163.9.1630,

indexed in Pubmed: 16946190.
5. Cohen S, Janicki-Deverts D, Miller G. Psychological stress and disease. JAMA. 2007; 298(14): 1685, doi: 10.1001/jama.298.14.1685.
6. Tosevski DL, Milovancevic MP. Stressful life events and physical health. Curr Opin Psychiatry. 2006; 19(2): 184–189, doi: 10.1097/01.yco.0000214346.44625.57, indexed in Pubmed: 16612201.
7. Gianjoppe-Santos J, Sentanin A, Barusso M, *et al.* Impact of exacerbation of COPD on anxiety and depression symptoms and dyspnea in the activities of daily living. 9.2 Physiotherapists. 2015, doi: 10.1183/13993003.congress-2015.pa3306.
8. Yu T, Frei A, Ter Riet G, *et al.* Impact of stressful life events on patients with chronic obstructive pulmonary disease. Respiration. 2018; 95(2): 73–79, doi: 10.1159/000481714, indexed in Pubmed: 29156451.
9. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010; 363(12): 1128–1138, doi: 10.1056/NEJMoa0909883, indexed in Pubmed: 20843247.
10. Bruce ML, Seeman TE, Merrill SS, *et al.* The impact of depressive symptomatology on physical disability: MacArthur Studies of Successful Aging. Am J Public Health. 1994; 84(11): 1796–1799, doi: 10.2105/ajph.84.11.1796, indexed in Pubmed: 7977920.
11. Laurin C, Labrecque M, Dupuis G, *et al.* Chronic obstructive pulmonary disease patients with psychiatric disorders are at greater risk of exacerbations. Psychosom Med. 2009; 71(6): 667–674, doi: 10.1097/PSY.0b013e3181a82849, indexed in Pubmed: 19561164.
12. Marin MF, Lord C, Andrews J, *et al.* Chronic stress, cognitive functioning and mental health. Neurobiol Learn Mem. 2011; 96(4): 583–595, doi: 10.1016/j.nlm.2011.02.016, indexed in Pubmed: 21376129.
13. Colby JP, Linsky AS, Straus MA. Social stress and state-to-state differences in smoking and smoking related mortality in the United States. Soc Sci Med. 1994; 38(2): 373–381, doi: 10.1016/0277-9536(94)90407-3, indexed in Pubmed: 8140464.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6): 361–370, doi: 10.1111/j.1600-0447.1983.tb09716.x, indexed in Pubmed: 6880820.
15. Sarafino EP, Smith TW. Health psychology: biopsychosocial interactions. Ed. 8. John Wiley & Sons, 2014.
16. Yohannes AM, Baldwin RC, Connolly MJ, *et al.* Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: prevalence, and validation of the BASDEC screening questionnaire. Int J Geriatr Psychiatry. 2000; 15(12): 1090–1096, doi: 10.1002/1099-1166(200012)15:12<1090::aid-gps249>3.0.co;2-l, indexed in Pubmed: 11180464.
17. Dahlén I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. Chest. 2002; 122(5): 1633–1637, doi: 10.1378/chest.122.5.1633, indexed in Pubmed: 12426264.
18. Pumar MI, Gray CR, Walsh JR, *et al.* Anxiety and depression. Important psychological comorbidities of COPD. J Thorac Dis. 2014; 6(11): 1615–1631, doi: 10.3978/j.issn.2072-1439.2014.09.28, indexed in Pubmed: 25478202.
19. Omachi TA, Katz PP, Yelin EH, *et al.* Depression and health-related quality of life in chronic obstructive pulmonary disease. Am J Med. 2009; 122(8): 778.e9–778.15, doi: 10.1016/j.amjmed.2009.01.036, indexed in Pubmed: 19635280.
20. Schneider C, Jick SS, Bothner U, *et al.* COPD and the risk of depression. Chest. 2010; 137(2): 341–347, doi: 10.1378/chest.09-0614, indexed in Pubmed: 19801582.
21. Xu W, Collet JP, Shapiro S, *et al.* Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. Am J Respir Crit Care Med. 2008; 178(9): 913–920, doi: 10.1164/rccm.200804-619OC, indexed in Pubmed: 18755925.
22. MC J, G P, MJ R, *et al.* Chronic obstructive pulmonary disease and anxiety and depression disorders: prospective cohort study in primary care. Insights in Chest Diseases. 2016; 01(03), doi: 10.21767/2577-0578.10027.
23. Cao Z, Ong KC, Eng P, *et al.* Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. Respirology. 2006; 11(2): 188–195, doi: 10.1111/j.1440-1843.2006.00819.x, indexed in Pubmed: 16548905.
24. Ng TP, Niti M, Tan WC, *et al.* Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med. 2007; 167(1): 60–67, doi: 10.1001/archinte.167.1.60, indexed in Pubmed: 17210879.
25. Fan VS, Ramsey SD, Giardino ND, *et al.* Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. Arch Intern Med. 2007; 167(21): 2345–2353, doi: 10.1001/archinte.167.21.2345, indexed in Pubmed: 18039994.
26. Atlantis E, Fahey P, Cochrane B, *et al.* Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. Chest. 2013; 144(3): 766–777, doi: 10.1378/chest.12-1911, indexed in Pubmed: 23429910.
27. Yohannes AM, Alexopoulos GS. Depression and anxiety in patients with COPD. Eur Respir Rev. 2014; 23(133): 345–349, doi: 10.1183/09059180.00007813, indexed in Pubmed: 25176970.
28. Burgess A, Kunik ME, Stanley MA. Chronic obstructive pulmonary disease: assessing and treating psychological issues in patients with COPD. Geriatrics. 2005; 60(12): 18–21, indexed in Pubmed: 16343032.
29. Andenaes R, Kalfoss MH, Wahl AK, *et al.* Psychological distress and quality of life in hospitalized patients with chronic obstructive pulmonary disease. J Adv Nurs. 2004; 46(5): 523–530, doi: 10.1111/j.1365-2648.2004.03026.x, indexed in Pubmed: 15139941.
30. McSweeny A. Life quality of patients with chronic obstructive pulmonary disease. Archives of Internal Medicine. 1982; 142(3): 473, doi: 10.1001/archinte.1982.00340160057014.
31. Kim HF, Kunik ME, Molinari VA, *et al.* Functional impairment in COPD patients: the impact of anxiety and depression. Psychosomatics. 2000; 41(6): 465–471, doi: 10.1176/appi.psy.41.6.465, indexed in Pubmed: 11110109.
32. Kunik ME, Veazey C, Cully JA, *et al.* A 2-item screen for depression in rehabilitation inpatients. Arch Phys Med Rehabil. 2005; 86(3): 469–472, doi: 10.1016/j.apmr.2004.04.042, indexed in Pubmed: 15759230.
33. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004; 130(4): 601–630, doi: 10.1037/0033-2909.130.4.601, indexed in Pubmed: 15250815.
34. Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. The Lancet. 1995; 345(8942): 99–103, doi: 10.1016/s0140-6736(95)90066-7.
35. Andersen BL, Farrar WB, Golden-Kreutz D, *et al.* Stress and immune responses after surgical treatment for regional breast cancer. J Natl Cancer Inst. 1998; 90(1): 30–36, doi: 10.1093/jnci/90.1.30, indexed in Pubmed: 9428780.
36. Basiony OL. Anxiety-depressive symptoms in patients with chronic obstructive pulmonary disease (COPD) and impact on outcome. Journal of Depression and Anxiety. 2015; 04(02), doi: 10.4172/2167-1044.1000181.
37. Witusik A, Mokros Ł, Kuna P, *et al.* Type a behavior pattern, impulsiveness, risk propensity, and empathy as predictors of dyspnea and number of infections in men with chronic obstructive pulmonary disease: a cross-sectional study. Med Sci Monit. 2018; 24: 3832–3839, doi: 10.12659/MSM.907742, indexed in Pubmed: 29874681.
38. Topp M, Vestbo J, Mortensen EL. Personality traits and mental symptoms are associated with impact of chronic obstructive pulmonary disease on patients' daily life. COPD. 2016; 13(6): 773–778, doi: 10.3109/15412555.2016.1168793, indexed in Pubmed: 27089450.
39. Benzo RP, Kirsch JL, Dulohery MM, *et al.* Emotional intelligence: a novel outcome associated with wellbeing and self-management in chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2016; 13(1): 10–16, doi: 10.1513/AnnalsATS.201508-490OC, indexed in Pubmed: 26501370.

Homa Serpoosh[1, 2], Yadollah Hamidi[1], Payman Eini[3], Younes Mohammadi[4, 5]

[1]Department of Health Economy and Management, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
[2]Students Research Committee, Hamadan University of Medical Sciences, Hamadan, Iran
[3]Department of Infectious Disease, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran
[4]Social Determinants of Health Research Center, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
[5]Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

Association of smoking and drug abuse with treatment failure in individuals with tuberculosis: a case-control study

Abstract

Introduction: Treatment failure in tuberculosis (defined as a positive sputum smear 5 months after the initiation of anti-TB treatment) is a major threat to the control over TB. This study aimed to investigate the association of smoking and drug abuse with treatment failure among individuals with TB.

Material and methods: Out of 286 TB patients with available data registered by the health system of Hamadan Provinces in western Iran, 24 TB patients with treatment failure (positive sputum smear, 5 months after initiation of anti-TB treatment) and 262 patients without treatment failure (negative sputum smear, five months after initiation of anti-TB treatment) were selected as case and control groups, respectively. These two groups were compared to each other in terms of demographic status which include age, sex, job, residence, and risk factors such as smoking and drug abuse status. An odds ratio (OR) with a 95% confidence interval was used as a measure of association. The Bonferroni correction was used to counteract multiple comparisons, therefore, a p-value of less than 0.004 was statistically significant.

Results: No significant association was found between treatment failure and age, residence, comorbidity, education level, job status, sex, smoking, and method of drug abuse ($P > 0.004$). However, a significant association was found between duration of smoking, number of cigarettes per day, and drug abuse with treatment failure in univariate analysis ($P < 0.004$). In multivariate analysis, only an association with drug abuse was significantly associated with treatment failure ($P = 0.047$).

Conclusion: Drug abuse substantially increases the risk of treatment failure. Therefore, in order to control TB, it is suggested that preventive programs are designed in order to decrease drug abuse among TB patients before starting treatment.

Key words: tuberculosis, smoking, drug abuse, treatment outcome

Adv Respir Med. 2020; 88: 383–388

Introduction

Tuberculosis (TB) is a contagious and airborne disease caused mainly by Mycobacterium tuberculosis, but also rarely by Mycobacterium bovis and africanum [1]. Many of the health and medical interventions used to control TB have resulted in a remarkable reduction of the disease over recent decades [2]. Despite this substantial progress against TB, it has remained as one of ten major causes of death in the world. Based on the global tuberculosis report of 2018 conducted by the World Health Organization (WHO), 10 million people developed TB disease and 1.3 million people died from TB [3, 4]. In addition, the report reveals that 90% of cases of TB and deaths due to the disease occur in developing countries [5]. Moreover, the studies report that nearly one-third of the world's population is infected with tuberculosis [6, 7].

Many risk factors have been identified that increase the risk of developing TB. Poverty, HIV infection, substance abuse, alcohol consumption, silicosis, diabetes mellitus, severe kidney disease,

Address for correspondence: Younes Mohammadi, Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran; e-mail: u.mohammadi@umsha.ac.ir
DOI: 10.5603/ARM.a2020.0138
Received: 04.04.2020
Copyright © 2020 PTChP
ISSN 2451–4934

low body weight, organ transplants, and head and neck cancers are examples of risk factors that are confirmed to increase the risk of being infected with TB [8–11]. Therefore, preventing and removing these risk factors may decrease the prevalence of TB remarkably.

The WHO's recommended strategy for controlling TB is via treatment of patients using the DOTS (Directly Observed Treatment, Short-course) program [12]. As the WHO claims, "the most cost-effective way to stop the spread of TB in communities with a high incidence is by curing it" [13]. This strategy has five elements that include government commitment, case detection, treatment regimen, standardized recording, and a structured reporting system. The major threat to this strategy is treatment failure of TB [14]. Treatment failure occurs in patients who, five months after initiation of anti-TB treatment, have positive sputum smears [15]. Treatment failure increases the probability of drug resistance and may result in the spread of TB. Several factors contribute to treatment failure such as age, sex, education level, alcohol consumption, HIV, and weight loss [16-19]. Another two suspected risk factors that may have a role in treatment failure are smoking and drug abuse. However, findings on these two risk factors are not clarified well, and results are contradictory. While some studies confirm existence of an association between smoking and drug abuse with treatment [20], other studies did not endorse such an association [21]. Reaching a consensus on this issue requires more research. Therefore, in this study, we aimed to investigate the identity and existence of this association between smoking and drug abuse with treatment failure of TB in Hamadan province, western Iran.

Material and methods

Type of study

This study was a case-control study.

Setting and population

The study was conducted in Hamadan province, western Iran. The study population included all patients with confirmed tuberculosis who were registered by the health system of the province from 2010 to 2018 and who underwent anti-TB treatment. Based on the Iranian national guidelines for the control of TB, sputum smear microscopy (SSM) was used to diagnose TB in patients.

After confirmation of TB in individuals, they underwent directly observed treatment based on the short-course (DOTS) program. However, if positive sputum smear results remained 5 months after the initiation of treatment, the result was labelled treatment failure. Accordingly, in this case-control study, we defined the case group (with treatment failure) as TB patients who, five months after initiation of anti-TB treatment, had positive sputum smear results. On the other hand, we defined the control group as TB patients who, 5 months after initiation of anti-TB treatment, had negative sputum smears. In the case that the patients died before completion of treatment course, or if there was no available data, they were excluded from the study. Accordingly, out of 321 patients registered by the system, 24 had treatment failure (case) and 262 patients were without treatment failure (control) and with available data included in the study. Thirty-five patients were excluded from the study because there was no data available for them.

Variables

According to data registered by the system, variables of this study included age, sex, education level, job, residence, comorbidity, family history of TB, smoking status, number of cigarettes per day, duration of smoking, drug abuse status, and type of drug abuse. For this study, we defined a "smoker" as an individual who smokes at least one cigarette every day.

Statistical analysis

We used bivariate analysis including ANOVA and the chi-square test to assess the difference between case and control groups. Moreover, we used logistic regression to adjust the confounding effect of other variables. An odds ratio with a 95% confidence interval was used as a measure of association. Further, in order to deal with multiple comparison problems in the tests, we used the Bonferroni correction to adjust the p-value. Therefore, a p-value less than 0.004 was statistically significant. The Hosmer and Lemeshow test was used to verify goodness of fit for the regression model.

Ethical considerations

The study has been registered by the Ethics Committee of Hamadan University of Medical Sciences (NO. IR.UMSHA.REC.1397.498). Furthermore, all information collected was considered as confidential.

Results

Out of the 321 registered patients who underwent anti-TB treatment, data for 286 patients

was available. Five months after initiation of anti-TB treatment, sputum results were positive for 24 patients and negative for 262 patients (control group). Out of 35 patients that were without data for analysis, 28 patients (80%) died before completion of the treatment course. Moreover, data for the outcome of seven patients was not retrievable.

Table 1 demonstrates the demographic and risk factor characteristics for the case and control groups. As shown in the table, despite 75% of the case group and 48.5% of the control group being men, the p-value, according to the Bonferroni correction, was less than 0.01. Therefore, sex difference between case and control group was not statistically significant at a level of 0.004. Moreover, we did not find a significant difference between two groups in terms of age, education, job, residence, family history of TB, and co-morbidity ($p > 0.004$).

In terms of smoking, results presented in table 1 showed that the percentage of smokers in case groups is substantially higher than in the control group (58% *vs* 35%). In other words, the odds of patients being smokers was 2.58 times higher in the case group than in the control group. However, this difference was not statistically significant at a level $p > 0.004$. The duration of smoking was significantly associated with treatment failure ($p = 0.001$). Moreover, patients in the case group smoked on average eight cigarettes per day more than patients in the control group ($p < 0.001$). In terms of duration of smoking, the mean duration of smoking in the case group

Table 1. Demographic and risk factor description in case and control groups

	Case (n = 24)	Control (n = 262)	
Mean (SD) age [year]	54 ± 20.9	53.6 ± 20.6	ANOVA [F (1,284) = 0.008, p = 0.93)]
Mean (SD) duration of smoking [year]	17.7 ± 14.3	9.4 ± 13.3	ANOVA [F (1,284) = 8.54, p = 0.004)]
Mean (SD) cigarettes smoked per day [number]	14.7 ± 11.4	6.4 ± 9.4	ANOVA [F (1,276) = 15.86, p = < 0.001)]
Male	18 (75%)	127 (48.5%)	0.01
Education level			
Illiterate	5 (20.7%)	71 (27.1%)	
Primary	4 (16.7%)	55 (21%)	
Guidance school	10 (41.7%)	70 (26.7%)	0.33
High school	1 (4.2%)	38 (14.5%)	
Diploma and more	4 (16.7%)	28 (10.7%)	
Urban	16 (66.7%)	167 (63.7%)	
Job status			
Employee	2 (8.3%)	29 (11.1%)	
Worker	0 (0%)	28 (3.1%)	
Housewife	5 (20.8%)	105 (40 %)	0.17
Freelance	9 (37.5%)	55 (21%)	
Unemployed	3 (12.5%)	6 (2.3%)	
Student	1 (4.2%)	12 (4.5%)	
Other	4 (16.7%)	47 (18%)	
Family history of TB	5 (20.8%)	64 (24.5%)	0.95
Comorbidity	6 (25%)	55 (21%)	0.16
Smoker	14 (58.3%)	92 (35%)	0.02
Drug abuser	11 (45.8%)	57 (21.8%)	0.001
Drug abuse method			
Swallowing	1 (7.3%)	21 (37.6%)	0.32
Injection	8 (57%)	12 (21.4%)	
Inhalation	5 (35.7%)	23 (41%)	

Table 2. Logistic regression analyses of factors associated with treatment failure in TB patients

Variable	Crude odds ratio (95% CI)	p-value	Adjusted odds ratio (95%CI)	p-value
Age	1 (0.98,1.02)	0.93	1 (0.98–1.02)	0.79
Sex	3.2 (1.22,8.2)	0.02	1.55 (0.45–5.31)	0.48
Smoker	2.58 (1.1, 6.1	0.02	1.26 (0.42–3.76)	0.67
Drug abuser	4.2 (1.8, 9.95)	0.001	2.98 (1.02–7.14)	0.047
Constant	—	—	1.210	0.84

was eight years longer than in the control group, which was statistically significant ($p = 0.004$).

In terms of drug abuse status, as demonstrated In table 1, we found that 46% of patients in the case group and 22% in the control group were drug abusers. Therefore, drug abusers were 4 times more likely to have treatment failure ($p < 0.001$). However, when investigating the method of drug abuse between the two groups, the method of abuse did not result in a significant difference ($p = 0.32$).

To adjust for the confounding effect of the variables, we used logistic regression. As shown in Table 2, only drug abuse is significantly associated with treatment failure in TB patients, with a 3 times greater likelihood that failure occurs ($p = 0.047$). The result of the Hosmer and Lemeshow test for goodness of fit for logistic regression models was not significant, which means that the model is a good fit (Chi-square = 3.08, df = 8, $p = 0.93$).

Discussion

In this study, we aimed to explore the association of smoking and drug abuse with treatment failure in TB patients (defined as a positive sputum smear five months after the initiation of treatment). Our study showed that drug abuse was significantly associated with treatment failure. Although the failure rate among smokers and drug abusers was higher than non-smokers and drug abusers, after adjusting for the effects of other factors, only the effect of drug abuse remained as significant (increasing the risk of treatment failure by 3.5 times). This result reveals the major effect of drug abuse on treatment failure. Although we did not observe a significant association between smoking and treatment failure in multivariate analysis, it seems that this association exists. The most important reason for a lack of association between smoking and treatment failure in our study was our small sample size (low power of study). However, there is significant evidence for this association being present in our study. In this study, we investigated the association between the number of cigarettes smoked per day and duration of smoking with treatment failure. We found that a significant association exists between them seeing as the number of cigarettes per day and duration of smoking was substantially higher in patients with treatment failure than patients without treatment failure. In epidemiology, this issue is called "dose–response relationship" [22], which is one of the major criteria for a causal association to be made between an exposure and an outcome of interest. In addition, given that data for smoking and drug abuse was collected before the initiation of treatment, another criterion of causality which is called "temporality" is likely established [22]. This criterion is the most important factor for establishing causality in epidemiology. Another criterion for establishing causality is identifying a consistency of findings [22]. The majority of previous studies confirmed our results. In a cohort study in Peru, it was found that both smoking and drug abuse were significantly associated with treatment failure, and that the effect of drug abuse was stronger than the effect of smoking. The paper recommended identifying smokers and drug abusers before initiating treatment to increase the probability of treatment success of TB [23]. In addition, in a study conducted in Brazil aimed to examine the role of drug abuse as a predictor of treatment failure, it was reported that 33% of drug abusers and 7% of non-drug abusers had treatment failure. Our study had similar results showing that about 34.8% of smokers and 12.5% of non-smokers had treatment failure [24]. However, some studies did not find a significant association between smoking and drug abuse with treatment failure. For example, El-Shabrawy *et al* found that, despite a high rate of treatment failure in smokers compared with non-smokers, no significant association between smoking and treatment failure

existed [21]. Apparently, a small sample size of their study was the main reason for this result. Further, Alo in Fiji did not observe a significant association between smoking status and treatment failure [25]. However, despite these contradictory results, the existence of an association is likely. To properly explain these differing results, we recommend performing a meta-analysis since there is evidence indicating that there is an association between drug abuse and smoking with treatment failure.

With consideration to the association between smoking and drug abuse with treatment failure and the global prevalence of smoking (20%) and drug abuse (2%) in the world [26–28], especially in low and middle-income countries where the prevalence of TB is high, it will be very difficult to control the spread of TB [29]. Many studies show that the prevalence of smoking and drug abuse among TB patients is a critical aspect of disease control. In a study by Burnet, the estimated prevalence of smoking in patients with active and latent infection was 56% and 60%, respectively[30]. Therefore, this high prevalence of smoking in TB patients results in treatment failure and eventually, death. In addition, failure to properly control TB increases the spread of TB in the population. It is also important to note the role of drug abuse and the AIDS epidemic as important factors in the spread of TB [31, 32].

Literature explains the mechanisms of how smoking and drug abuse affect treatment failure. It seems that two likely pathways exist for how smoking and drug abuse influence the treatment outcome. The studies reveal that an interaction of TB with smoking and drug abuse exists at a cellular level and may result in a decreased level of immunity through reduction in activity of macrophages, dendritic cells, and natural killer cells [33]. Moreover, studies demonstrated that smoking and drug abuse are associated with a low adherence to treatment in male TB patients [34].

This study has two messages to policy-makers: Firstly, statistics regarding the high amount of patients with treatment failure in TB is remarkable. As noted before, treatment failure is the biggest threat for the control of TB and, as such, paying special attention to treatment failure is necessary. Secondly, smoking and drug abuse showed a significant effect on treatment failure, and this has been reciprocated by many other studies which also confirm this issue. Therefore, it is recommended to design programs for the cessation of smoking and drug abuse before initiating treatment of TB.

This study has limitations. Firstly, sample size, especially in our case group, is small. Small sample size may reduce the power of study to detect significant differences. This issue is one of the determinants for a non-significant association between smoking and treatment failure. Secondly, we used data registered by the TB system which is known to have problems in accuracy and in incomplete registrations. Thirdly, we could not obtain some important information such as percentage of multidrug resistance and HIV disease status among TB patients. This information may present a more clarified picture of the TB patients we studied. Fourthly, a number of the patients died or were lost to follow up before completion of the treatment course. Therefore, we performed our analysis only on patients who survived, which may have led to selection bias affecting our final result. Based on these limitations, designing a prospective cohort with an accurate registration of information and with interventional studies to assess the effectiveness of smoking and drug abuse cessation programs on treatment failure is recommended.

Conclusion

Our results confirm that drug abuse is associated with treatment failure in TB patients. However, smoking significantly increased the risk of treatment failure as well. Therefore, it suggested that cessation of smoking and drug abuse accompany the initiation of treatment programs for TB patients. Training health workers to be able to detect smokers and drug abusers should also be incorporated into treatment programs to increase the efficacy of TB treatment.

Acknowledgment

The study has been financially supported by Hamadan University of Medical Sciences (No. 9708224887).

Conflict of interest

The authors have no conflict of interest.

References:

1. Gagneux S. Ecology and evolution of mycobacterium tuberculosis. Nat Rev Microbiol. 2018; 16(4): 202–213, doi: 10.1038/nrmicro.2018.8, indexed in Pubmed: 29456241.
2. MacNeil A, Glaziou P, Sismanidis C, et al. Global epidemiology of tuberculosis and progress toward achieving global targets 2017. MMWR Morb Mortal Wkly Rep. 2019; 68(11): 263–266, doi: 10.15585/mmwr.mm6811a3, indexed in Pubmed: 30897077.

3. Dirlikov E, Raviglione M, Scano F. Global tuberculosis control: toward the 2015 targets and beyond. Ann Intern Med. 2015; 163(1): 52–58, doi: 10.7326/M14-2210, indexed in Pubmed: 25915859.
4. World Health Orgnization. Global Tuberculosis Report 2019, 2018.
5. Getahun H, Matteelli A, Abubakar I, et al. Latent mycobacterium tuberculosis infection. N Engl J Med. 2015; 372(22): 2127–2135, doi: 10.1056/NEJMra1405427, indexed in Pubmed: 26017823.
6. Cohen A, Mathiasen VD, Schön T, et al. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2019; 54(3), doi: 10.1183/13993003.00655-2019, indexed in Pubmed: 31221810.
7. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med. 2016; 13(10): e1002152, doi: 10.1371/journal.pmed.1002152, indexed in Pubmed: 27780211.
8. Mahara G, Yang K, Chen S, et al. Socio-Economic predictors and distribution of tuberculosis incidence in Beijing, China: a study using a combination of spatial statistics and GIS technology. Med Sci (Basel). 2018; 6(2), doi: 10.3390/medsci6020026, indexed in Pubmed: 29561814.
9. Imtiaz S, Shield KD, Roerecke M, et al. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J. 2017; 50(1), doi: 10.1183/13993003.00216-2017, indexed in Pubmed: 28705945.
10. Silva DR, Muñoz-Torrico M, Duarte R, et al. Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs. J Bras Pneumol. 2018; 44(2): 145–152, doi: 10.1590/s1806-37562017000000443, indexed in Pubmed: 29791552.
11. Narasimhan P, Wood J, Macintyre CR, et al. Risk factors for tuberculosis. Pulm Med. 2013; 2013: 828939, doi: 10.1155/2013/828939, indexed in Pubmed: 23476764.
12. Gebrezgabiher G, Romha G, Ejeta E, et al. Treatment outcome of tuberculosis patients under directly observed treatment short course and factors affecting outcome in Southern Ethiopia: a five-year retrospective study. PLoS One. 2016; 11(2): e0150560, doi: 10.1371/journal.pone.0150560, indexed in Pubmed: 26918458.
13. World Health Organization. Tuberculosis control: the DOTS strategy (Directly Observed Treatment Short-Course): an annotated bibliography. World Health Organization, 1997.
14. Gandhi NR, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet. 2010; 375(9728): 1830–1843, doi: 10.1016/S0140-6736(10)60410-2, indexed in Pubmed: 20488523.
15. Cherkaoui I, Sabouni R, Ghali I, et al. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. BMC Public Health. 2011; 11(4): 140, doi: 10.1186/1471-2458-11-140, indexed in Pubmed: 21356062.
16. Diallo A, Dahourou DL, Dah TT, et al. Factors associated with tuberculosis treatment failure in the Central East Health region of Burkina Faso. Pan Afr Med J. 2018; 30: 293, doi: 10.11604/pamj.2018.30.293.15074, indexed in Pubmed: 30637077.
17. Diallo A, Dahourou DL, Dah TT, et al. Factors associated with tuberculosis treatment failure in the Central East Health region of Burkina Faso. Pan Afr Med J. 2018; 30: 293, doi: 10.11604/pamj.2018.30.293.15074, indexed in Pubmed: 30637077.
18. Pizzol D, Veronese N, Marotta C, et al. Predictors of therapy failure in newly diagnosed pulmonary tuberculosis cases in Beira, Mozambique. BMC Res Notes. 2018; 11(1): 99, doi: 10.1186/s13104-018-3209-9, indexed in Pubmed: 29402317.
19. Namukwaya E, Nakwagala FN, Mulekya F, et al. Predictors of treatment failure among pulmonary tuberculosis patients in Mulago hospital, Uganda. Afr Health Sci. 2011; 11 Suppl 1: S105–S111, doi: 10.4314/ahs.v11i3.70079, indexed in Pubmed: 22135634.
20. Lackey B, Seas C, Van der Stuyft P, et al. Patient characteristics associated with tuberculosis treatment default: a cohort study in a high-incidence area of Lima, Peru. PLoS One. 2015; 10(6): e0128541, doi: 10.1371/journal.pone.0128541, indexed in Pubmed: 26046766.
21. El-Shabrawy M, El-Shafei D. Evaluation of treatment failure outcome and its predictors among pulmonary tuberculosis patients in Sharkia Governorate, 2013–2014. Egyptian Journal of Chest Diseases and Tuberculosis. 2017; 66(1): 145–152, doi: 10.1016/j.ejcdt.2015.11.002.
22. Greenland S, Lash TL. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Lippincott Williams & Wilkins 2008.
23. Lackey B, Seas C, Van der Stuyft P, et al. Patient characteristics associated with tuberculosis treatment default: a cohort study in a high-incidence area of Lima, Peru. PLoS One. 2015; 10(6): e0128541, doi: 10.1371/journal.pone.0128541, indexed in Pubmed: 26046766.
24. Silva MR, Pereira JC, Costa RR, et al. Drug addiction and alcoholism as predictors for tuberculosis treatment default in Brazil: a prospective cohort study. Epidemiol Infect. 2017; 145(16): 3516–3524, doi: 10.1017/S0950268817002631, indexed in Pubmed: 29173226.
25. Alo A, Gounder S, Graham SM. Clinical characteristics and treatment outcomes of tuberculosis cases hospitalised in the intensive phase in Fiji. Public Health Action. 2014; 4(3): 164–168, doi: 10.5588/pha.14.0022, indexed in Pubmed: 26400804.
26. Bashirian S, Barati M, Mohammadi Y, et al. Factors associated with hookah use among male high school students: the role of demographic characteristics and hookah user and non-user prototypes. J Res Health Sci. 2016; 16(4): 217–223, indexed in Pubmed: 28087855.
27. Organization WH. WHO global report on trends in prevalence of tobacco smoking 2000-2025: World Health Organization; 2018.
28. Peacock A, Leung J, Larney S, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction. 2018; 113(10): 1905–1926, doi: 10.1111/add.14234, indexed in Pubmed: 29749059.
29. World Health Organization. Smoking and tuberculosis: a dangerous combination 2018 [cited 2020]. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/news/news/2018/3/smoking-and-tuberculosis-a-dangerous-combination. [Last accessed: 04.09.2020].
30. Brunet L, Pai M, Davids V, et al. High prevalence of smoking among patients with suspected tuberculosis in South Africa. Eur Respir J. 2011; 38(1): 139–146, doi: 10.1183/09031936.00137710, indexed in Pubmed: 21148230.
31. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009; 48(1): 72–82, doi: 10.1086/594126, indexed in Pubmed: 19046064.
32. Getahun H, Baddeley A, Raviglione M. Managing tuberculosis in people who use and inject illicit drugs. Bull World Health Organ. 2013; 91(2): 154–156, doi: 10.2471/BLT.13.117267, indexed in Pubmed: 23554532.
33. Schneider NK, Novotny TE. Addressing smoking cessation in tuberculosis control. Bull World Health Organ. 2007; 85(10): 820–821, doi: 10.2471/blt.07.034797, indexed in Pubmed: 18038065.
34. Adane AA, Alene KA, Koye DN, et al. Non-adherence to anti-tuberculosis treatment and determinant factors among patients with tuberculosis in northwest Ethiopia. PLoS One. 2013; 8(11): e78791, doi: 10.1371/journal.pone.0078791, indexed in Pubmed: 24244364.

Kamran Khan Sumalani[1], Nousheen Akhter[1], Maqbool Ahmed[2], Dimple Chawla[1], Nadeem Ahmed Rizvi[1]

[1]Department of Pulmonology, Jinnah Postgraduate Medical Center, Karachi, Pakistan
[2]Fatima Jinnah General and Chest Hospital, Quetta, Pakistan

Diagnostic implications of bronchial lavage in patients with pleural tuberculosis

Abstract

Introduction: The presence of *Mycobacterium tuberculosis* in a respiratory specimen is diagnostic in patients with pleural effusion. It is difficult to obtain sputum even after induction in these patients. An alternative method of acquiring respiratory specimens is via bronchial lavage. This study was undertaken to evaluate the diagnostic yield of acid-fast bacilli (AFB) smear, AFB culture, and Xpert assay of bronchial lavage fluid in the workup of pleural tuberculosis patients.

Material and methods: All patients who met the inclusion criteria of the study underwent thoracentesis, pleural biopsy, and bronchial lavage. Specimens of pleural fluid, pleural biopsy, and bronchial lavage fluid were sent for acid fast bacilli smear, culture, and Xpert assay.

Result: Bronchial lavage AFB smear, culture, and Xpert assay was positive in 9.5%, 17.9%, and 26.2% of patients, respectively. It gave an immediate diagnosis in 22 (26.2%) patients.

Conclusion: Bronchial lavage, though not a surrogate to pleural biopsy, offers an additional approach to the early diagnosis of pleural tuberculosis in patients not producing sputum. Besides being diagnostic, this method also has epidemiologic significance in containing the tuberculosis epidemic because detecting Mycobacterium in bronchial lavage confirms that the patient is infectious.

Key words: bronchial lavage, bronchoscopy, pleural tissue, pleural tuberculosis, Xpert assay

Adv Respir Med. 2020; 88: 389–393

Introduction

Globally, tuberculosis (TB) remains one of the most important public health problems. Tuberculous pleural effusion affects approximately 5% of people infected with Mycobacterium tuberculosis (MTB) and is one of the most common forms of extrapulmonary tuberculosis [1]. According to the World Health Organization, Pakistan is ranked fifth among high-burden TB countries worldwide with an estimated 510,000 new TB cases emerging each year.

Diagnosing pleural tuberculosis is difficult due to paucibacillary infection and often requires invasive procedures like pleural biopsy [2]. For a confirmatory diagnosis of tuberculosis, isolation of the bacterium from pleural fluid or pleural tissue is required which is mostly not possible due to the pathogenesis of the disease [3]. It is known that pleural space infections are acquired from initial parenchymal lesions which are usually not obvious on chest radiography [4, 5]. With the use of computed tomography, parenchymal lesions and focal areas of subpleural cavitation can be visualized [6].

The presence of Mycobacterium tuberculosis in a respiratory specimen is diagnostic in patients with pleural effusion. Sputum specimens are often not tested because these patients usually do not produce sputum even after efforts of sputum induction. An alternative to getting respiratory samples in such patients is by testing fluid acquired via bronchial lavage. It is a safe and minimally invasive procedure done under local anesthesia. In addition to having diagnostic value, it can also be used to monitor the progress of patients who test positive and are given antituberculous treatment (ATT). Apart from these diagnostic implications, it may have epidemio-

Address for correspondence: Kamran Khan Sumalani, Department of Pulmonology, Jinnah postgraduate medical center, Karachi, Pakistan; e-mail: drkamrankn@hotmail.com
DOI: 10.5603/ARM.a2020.0149
Received: 16.04.2020
Copyright © 2020 PTChP
ISSN 2451–4934

logic significance as patients in whom MTB is isolated in bronchial lavage are likely contagious and demand thorough contact tracing, especially in endemic countries like Pakistan.

This study was carried out to evaluate the diagnostic yield of acid-fast bacilli (AFB) smear, AFB culture, and Xpert assay in bronchial lavage in the workup of pleural tuberculosis patients.

Material and methods

This was a prospective study completed from September 2016 to December 2018 in Fatima Jinnah General and Chest Hospital and Taj Medical Complex. All patients aged 18 years or older with lymphocytic exudative pleural effusion who were not expectorating and who had failure of sputum induction were included in the study. Patients with known HIV infection, parenchymal abnormalities on chest imaging (radiograph or computed tomography scan), or those who were already on antituberculous drugs for more than 1 week were not included in the study.

The diagnosis of pleural tuberculosis was made if any of the microbiologic tests came out positive or clinically if the patient responded to antituberculous drugs (resolution of fever, weight gain on 2 months of treatment). Patients not meeting the diagnostic standards for tuberculosis were treated as controls.

All patients underwent thoracentesis, pleural biopsy, and bronchial lavage. Pleural fluid was sent for AFB smear, AFB culture, and Xpert assay (Gene Xpert). An ultrasound of the chest was done in all study participants. Abram's pleural biopsy was done in patients with no intrapleural septations on ultrasound. Medical thoracoscopy under local anesthesia was done for those with multiseptated or multi-loculated pleural effusions. Pleural tissue specimens were sent for AFB smear, AFB culture, and histopathology in formalin. Tissue for the Xpert assay was sent in normal saline. Bronchial lavage was done under local anesthesia using flexible bronchoscope. Normal saline was instilled into large airways of both lungs and aspirated back. Bronchial lavage fluid was sent for AFB smear, AFB culture, and Xpert assay. The investigation which confirmed the diagnosis of tuberculosis earliest was also documented as the test giving an 'immediate microbiologic diagnosis'.

Out of a total of 188 patients, 148 patients were included in the final analysis. A study flow diagram is shown in Figure 1.

Written informed consent was obtained for the procedures from study participants. Ethical approval was obtained from the study hospitals ethical review committee. The study was done according to the principles laid down in the Declaration of Helsinki.

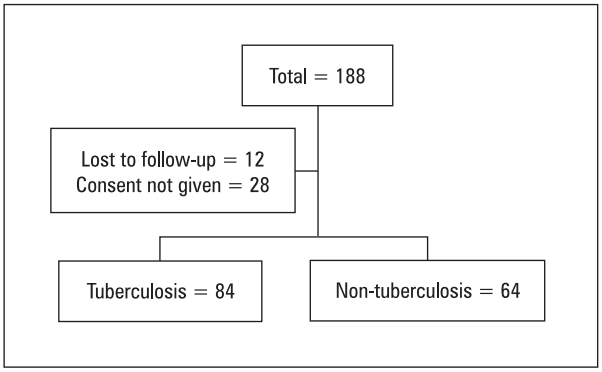

Figure 1. Study flow diagram

SPSS (version 23) was used for statistical analysis. Mean and standard deviation were calculated for age. The independent samples t-test was used to compare the mean between groups where the data was normally distributed. Frequencies and percentages were calculated for categorical variables and compared using the Chi square test and Fisher's exact test (if cells had an expected count of less than 5). A P-value of < 0.05 was identified as being statistically significant. Sensitivity and specificity was calculated for various diagnostic tests.

Result

A comparison of the demographic variables between tuberculosis and non-tuberculosis patient groups is shown in Table 1. The sensitivity of bronchial lavage fluid AFB smear, AFB culture, and Xpert assay was 9.5%, 17.9%, and 26.2%, respectively. The yield of different diagnostic methods is shown in Table 2. The immediate microbiologic diagnosis of tuberculosis based exclusively on bronchial lavage was obtained in (22) 26.2% patients. The yield of different microbiologic tests for immediate diagnosis of pleural tuberculosis is shown in Table 3. The overlap of positive results among various diagnostic methods is shown in Figure 2. No significant complications of bronchoscopy were noted in any of the patients.

Discussion

In Pakistan, as a result of TB being a common infection, a mostly exudative lymphocytic pleural

Table 1. Demographic characteristics of patients

Characteristic	Tuberculosis (n=84)	Non tuberculosis (n=64)	p-value
Age in years ± SD	37.39 ± 16.74	39.48 ± 15.60	0.43
Gender			
Male	54	44	0.56
Female	30	20	
Co morbidities			
Nil	68	49	0.24
Hypertension	4	0	
Diabetes mellitus	9	9	
Chronic liver disease	2	4	
Malignancy	1	2	
Smoking status			
Non-smoker	64	51	0.44
Ex-smoker	2	0	
Current smoker	18	13	

Table 2. Yield of different diagnostic methods in pleural tuberculosis

Investigation	Tuberculosis (n=84)	Non-tuberculosis (n-64)	Sensitivity (%)	Specificity (%)	p-value
Pleural fluid					
AFB smear	1	0	1.2	100	1.00
Xpert assay	9	0	10.7	100	0.005
AFB culture	1	0	1.2	100	1.00
Pleural tissue					
AFB smear	14	0	16.7	100	0.001
Xpert assay	46	0	54.8	100	<0.001
AFB culture	32	0	38.1	100	<0.001
Caseous necrosis on histopathology	56	0	66.7	100	<0.001
Bronchial lavage fluid					
AFB smear	8	0	9.5	100	0.10
Xpert assay	22	0	26.2	100	<0.001
AFB culture	15	0	17.9	100	<0.001

AFB: acid fast bacilli

Table 3. Yield of different diagnostic methods for immediate microbiologic diagnosis of pleural tuberculosis

Diagnostic methods	Immediate diagnosis	Only investigation giving immediate diagnosis
Pleural tissue	45 (53.6%)	38 (45.2%)
Pleural fluid	9 (10.7%)	0
Bronchial lavage fluid	22 (26.2%)	12 (14.3%)

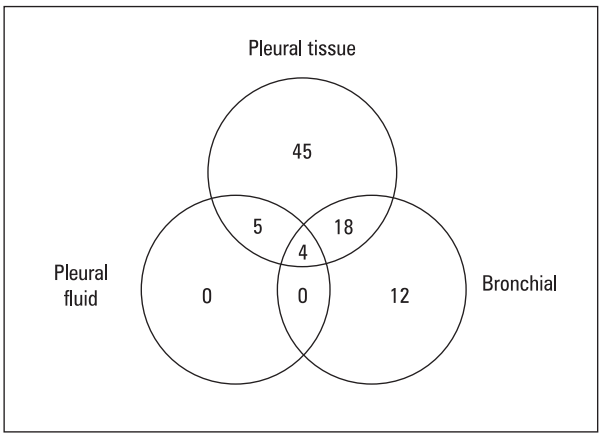

Figure 2. Diagram showing diagnostic overlap among various microbiologic investigations (numbers show the frequency of positive results for tuberculosis)

effusion is treated as TB until proven otherwise. However, without microbiologic confirmation, there remains a problem of delayed diagnosis or misdiagnosis. Due to the low amount of MTB in pleural fluid, tests are often negative for MTB. The current study demonstrates that microbiologic tests done on bronchial lavage fluid in patients with no parenchymal lesions can help in diagnosing tuberculosis.

In our study, the sensitivity of bronchial lavage fluid AFB smear, AFB culture, and Xpert assay was 9.5%, 17.9%, and 26.2%, respectively. Levine and colleagues described that 33% (7/21) of patients with a tuberculous effusion had positive sputum, gastric, or bronchial lavage specimens [7]. There has not been a significant amount of research done on the role of bronchial lavage, but studies have demonstrated that induced sputum has a good diagnostic yield in pleural tuberculosis in patients with and without parenchymal lesions. Conde *et al.* [8] demonstrated that the yield of sputum culture was 6% to 13% higher than that described previously (4–9%) in patients with no parenchymal lesions and similar to those with lesions on chest radiograph [3, 9, 10]. Other similar studies from Los Angeles [11] and India [5, 12] also reported a high yield of sputum induction in pleural tuberculosis.

In our study, AFB was detected in pleural fluid in 1 (1.2%) case on smear, 1 (1.2%) in culture, and 9 (10.7%) on Xpert assay. Antoniskis *et al.* [11] found that 7% of patients had a positive AFB smear on pleural fluid testing. Other studies have shown that AFB culture is positive in < 30% of pleural fluid specimens [9, 13–15].

In the current study, it is shown that pleural tissue AFB smear, culture, and Xpert assay was positive in 16.7%, 38.1% and 54.8% of cases, respectively. The yield of the microbiological tests on pleural fluid and tissue reported by Christopher *et al.* agrees with our results; pleural tissue Xpert was 45%, pleural tissue culture was 39%, pleural fluid culture was 17%, and pleural fluid Xpert was 14% [16].

Bronchial lavage gave an immediate diagnosis in 22 (26.2%) patients and was the only investigation giving an immediate diagnosis in 12 (14.3%) patients. Hence, it gives another approach in the early diagnosis of pleural tuberculosis and it can also help in monitoring patients who test positive during their treatment course.

In contrast to other forms of extrapulmonary tuberculosis, pleural TB can be infectious as demonstrated by the finding of AFB in bronchial lavage. Questions arise whether pleural tuberculosis patients should be isolated until they cease being infectious and whether contact tracing should be done like in pulmonary TB cases. Further studies are needed to evaluate the infectivity of this form of disease as it has significant implications on public health.

Conclusion

Bronchial lavage, though not a surrogate to pleural biopsy, offers an additional approach in the early diagnosis of pleural tuberculosis in patients not producing sputum. Besides being diagnostic, this method also has epidemiologic significance in containing the tuberculosis epidemic as detecting Mycobacterium in bronchial lavage fluid shows the infectivity of pleural tuberculosis.

Conflict of interest

The authors have no conflict of interest to disclose.

References:

1. Arun G, Sethu M, Surendra S, et al. Diagnosis and treatment of tuberculous pleural effusion in 2006. Chest. 2007; 131(3): 880–889.
2. Sahn SA. State of the art. The pleura. Am Rev Respir Dis. 1988; 138(1): 184–234, doi: 10.1164/ajrccm/138.1.184, indexed in Pubmed: 3059866.
3. Berger HW, Mejia E. Tuberculous pleurisy. Chest. 1973; 63(1): 88–92, doi: 10.1378/chest.63.1.88, indexed in Pubmed: 4630686.
4. Seibert A, Haynes J, Middleton R, et al. Tuberculous pleural effusion. Chest. 1991; 99(4): 883–886, doi: 10.1378/chest.99.4.883.
5. Chaudhuri AD, Bhuniya S, Pandit S, et al. Role of sputum examination for acid fast bacilli in tuberculous pleural effusion. Lung India. 2011; 28(1): 21–24, doi: 10.4103/0970-2113.76296, indexed in Pubmed: 21654981.
6. Nakanishi M, Demura Y, Ameshima S, et al. Utility of high-resolution computed tomography for predicting risk of sputum

smear-negative pulmonary tuberculosis. Eur J Radiol. 2010; 73(3): 545–550, doi: 10.1016/j.ejrad.2008.12.009, indexed in Pubmed: 19167853.
7. Levine H, Metzger W, Lacera D, et al. Diagnosis of tuberculous pleurisy by culture of pleural biopsy specimen. Arch Intern Med. 1970; 126(2): 269–271, indexed in Pubmed: 4988357.
8. Conde MB, Loivos AC, Rezende VM, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med. 2003; 167(5): 723–725, doi: 10.1164/rccm.2111019, indexed in Pubmed: 12598215.
9. Epstein DM, Kline LR, Albelda SM, et al. Tuberculous pleural effusions. Chest. 1987; 91(1): 106–109, doi: 10.1378/chest.91.1.106, indexed in Pubmed: 3792061.
10. Bueno C. Cytologic and bacteriologic analysis of fluid and pleural biopsy specimens with Cope's needle. Archives of Internal Medicine. 1990; 150(6): 1190, doi: 10.1001/archinte.1990.00390180034005.
11. Antoniskis D, Amin K, Barnes PF. Pleuritis as a manifestation of reactivation tuberculosis. Am J Med. 1990; 89(4): 447–450, doi: 10.1016/0002-9343(90)90374-m, indexed in Pubmed: 2220878.
12. Ghosal AG, Ghosh S, Guhathakurta R, et al. Sputum AFB positivity in tuberculous pleural effusion with no radiologically apparent parenchymal lung lesion. Ind J Tubrec. 1997; 44: 13–15.
13. Salazar-Lezama M, Quiroz-Rosales H, Bañales-Méndez JL, et al. Diagnostic methods of primary tuberculous pleural effusion in a region with high prevalence of tuberculosis: A study in Mexican population. Rev Invest Clin. 1997; 49: 453–456.
14. Sharma SK, Ryan H, Khaparde S, et al. Extrapulmonary tuberculosis. Indian J Med Res. 2004; 120(4): 316–353, indexed in Pubmed: 15520485.
15. Aggarwal AN, Gupta D, Jindal SK. Diagnosis of tuberculous pleural effusion. Indian J Chest Dis Allied Sci. 1999; 41(2): 89–100, indexed in Pubmed: 10437321.
16. Christopher DJ, Dinakaran S, Gupta R, et al. Thoracoscopic pleural biopsy improves yield of Xpert MTB/RIF for diagnosis of pleural tuberculosis. Respirology. 2018; 23(7): 714–717, doi: 10.1111/resp.13275, indexed in Pubmed: 29486527.

Harish Mahender, Raja Amarnath, Sreenivasan Vadivelu

Department of Respiratory Medicine, Sree Balaji Medical College and Hospital, Bharath University, Chromepet, Chennai, India

A comparative study evaluating C-reactive protein, sputum eosinophils and forced expiratory volume in one second in obese and nonobese asthmatics

Abstract

Introduction: Asthma and obesity are considered inflammatory disorders. Inflammatory markers — sputum eosinophils, C-reactive protein (CRP) and the forced expiratory volume in one second (FEV_1) were analysed to find their association in obese asthmatics and compared with their asthma control test (ACT) to understand these parameters in this phenotype.

Material and methods: After completing the asthma control test (ACT), the CRP, FEV_1 and sputum eosinophils of sixty asthmatics were compared to find the association of them in obese and nonobese asthmatics and contrasted with their ACT. The data were analysed using IBM SPSS V20.0, Mann-Whitney U test (non-parametric test), Pearson's correlation coefficient and Fisher's exact test.

Results: We found significant differences for CRP ($P = 0.001$) and sputum eosinophils ($P = 0.001$) between obese and nonobese asthmatics, both higher in obese asthmatics and with a significant association with body mass index (BMI) ($P < 0.05$). The FEV_1 levels were independent of the BMI levels of asthmatics. There was a significant correlation between the CRP and sputum eosinophils (0.52, $P = 0.001$) for all asthmatics. There was no significant correlation between FEV_1 and sputum eosinophils (nonobese $P = 0.120$, obese $P = 0.388$) and between FEV_1 and CRP (obese $P = 0.423$, nonobese $P = 0.358$) in both obese and nonobese asthmatics. Obesity had an association ($P = 0.001$) with ACT scores (≤ 19).

Conclusions: Sputum eosinophils and CRP were raised in obese asthmatics and had a positive association with BMI. Obese asthmatics had a poorer subjective asthma control than nonobese asthmatics despite FEV_1 being independent of the BMI levels. Measuring the systemic inflammatory markers could help in additional interventions in reducing systemic inflammation and thus possibly facilitating better symptom control.

Key words: C-reactive protein, sputum eosinophils, FEV_1, obese asthmatics, systemic inflammation

Adv Respir Med. 2020; 88: 394–399

Introduction

Asthma is a syndrome characterised by recurrent episodic airway obstruction, airway inflammation and bronchial hyper-responsiveness. It is a syndrome with a variety of phenotypes, where various precipitating factors result in clinical, physiological and pathological manifestations. The main pathogenesis of asthma is the infiltration of inflammatory cells such as eosinophils, basophils, and CD4 + lymphocytes in the airways [1, 2].

Obesity is also considered an inflammatory disorder conveyed by various systemic inflammatory mediators like C-reactive protein (CRP) that leads to an increase in circulating levels of the pro-inflammatory cytokines. CRP is also raised in various systemic inflammations such as diabetes, cardiovascular diseases, collagen vascular diseases, malignancies, and also obesity [3–5]. Various studies have shown that severe asthma is more prevalent in obese patients as compared with patients with normal body mass index (BMI) and that BMI is positively associated with asthma severity [6]. Also, BMI correlates positively with the level of asthma control, with more severe asthmatics having a higher BMI than

Address for correspondence: Harish Mahender, Department of Respiratory Medicine, Sree Balaji Medical College and Hospital, Bharath University, Chromepet, Chennai, India; e-mail: drmharish@gmail.com

DOI: 10.5603/ARM.a2020.0155
Received: 19.04.2020

Copyright © 2020 PTChP

ISSN 2451–4934

those with milder asthma [7, 8]. Thus, obesity seems to be related with asthma severity, but the mechanisms responsible for this relationship are not yet clarified.

There is growing evidence that asthma and obesity are strongly associated with each other and can alter each other's status [9]. Also, the inflammatory cells, sputum eosinophils and interleukin-5 play a major role in airway inflammation in asthmatics, more so in obese asthmatics who are already in a pro-inflammatory state [10]. Evidence of neutrophilic inflammation of the airways in obese asthmatics has also been documented [11], but the association between the non-neutrophilic airway inflammation in obesity, the systemic inflammation and the lung function remains poorly understood, especially in different phenotypes and endotypes of asthma. As the treatment of asthma has evolved from the airway obstruction-based approach to a tailored-endotype and phenotype-based approach, especially in special subsets of asthma like the obese phenotypes, it helps to know the relationship between the inflammatory markers both systemic (CRP) and airway (sputum eosinophils), with the forced expiratory volume in one second (FEV_1) in this regard.

As our understanding of various subtypes of asthma has evolved over years, here we try to evaluate the obese asthmatic subtype and the inflammatory markers associated with both the airway (sputum eosinophils) and systemic marker (CRP), and correlate them with their lung function (FEV_1) and compare the same with nonobese asthmatics. This might help us to understand the systemic inflammatory component of asthma, specifically concerning the obese asthmatic phenotype and the markers associated with it. Correlating these inflammatory markers with the patient's subjective control of symptoms through the asthma control test (ACT) could give us a better understanding of the roles these inflammatory markers play in the symptom control.

The purpose of this cross-sectional study was to evaluate the systemic inflammation using CRP, airway inflammation by measuring sputum eosinophils and the measure of lung function by FEV_1 in obese and nonobese asthmatics, compare and correlate these parameters between the obese and nonobese groups. We also try to ascertain whether there is a significant association between the inflammatory markers (sputum eosinophils, CRP) amongst each other and with FEV_1 and to compare BMI with the asthma control test (ACT) scores.

Materials and methods

Sixty asthmatic patients who presented to the outpatient department of Respiratory Medicine, in Sree Balaji Medical College and Hospital, Chennai. were recruited for the study from 2018 to 2019. We aimed to compare and evaluate CRP, FEV_1 and sputum eosinophils in obese and nonobese asthmatics and to find the association of CRP, FEV_1, and sputum eosinophils among each other and compare BMI with the asthma control test scores (ACT) [12].

Patients with a primary diagnosis of asthma according to the Global Initiative for Asthma (GINA) guidelines, 18 years of age or older were included in this study. Individuals with nonreversible airway obstruction on spirometry (< 12% change in FEV_1) who were unable to do spirometry due to a history of myocardial infarction, congestive heart failure, coronary artery disease, who had a history of smoking, with known comorbidities like diabetes, cardiovascular diseases, collagen vascular diseases and malignancies were excluded from the study.

All the patients who satisfied the inclusion criteria, filled up the asthma control test and were later told to do pulmonary function test — spirometry, serum CRP and sputum sample after deep coughing in a sterile container. Then sputum quality was assessed using both macroscopic and microscopic criteria [13]. Sputum was stained with eosin and haematoxylin and analysed using microscopy to determine the count of eosinophils expressed in percentage, and counts ≥ 3 % was considered to be high [14], BMI ≥ 30 kg/m^2 were considered obese, and CRP > 1 mg/dL was considered high-risk. The ACT is a patient-completed questionnaire for individuals above 12 years of age and consists of five items evaluating the preceding 4 weeks (limitation of activities, shortness of breath, awakenings at night, use of reliever medication and patient's perception of asthma control). Each question has five response options, resulting in scores of 1–5. The sum of all scores yields the total ACT score, a score of less than equal to 19 indicates poorly controlled asthma, and a score greater than equal to 20 indicates good asthma control, the maximum being 25. All the participants had forced expiratory volume 1 second/functional vital capacity (FEV_1/FVC) < 70% with post-bronchodilator reversibility FEV_1 > 12% on spirometry.

Statistical analysis: A total of 60 patients were included in the study. The data were analysed using IBM SPSS V 20.0. Mann-Whitney

U test (non-parametric test) was performed for comparing outcome variables between obese and nonobese groups, Pearson's correlation coefficient was computed to measure the association of the outcome variables amongst each other and Fisher's exact test was used to find the association of BMI with the asthma control test score. P-value < 0.05 was considered to be statistically significant.

Results

There were a total of 60 subjects. Among them, the number of males were 22 (37%) and females were 38 (63%). The mean age was 41.48 (SD = 10.98). All of the participants were classified as obese (BMI ≥ 30) and nonobese (BMI < 30) (Table 1). Among the 60 subjects, 32 were obese and 28 were nonobese (Table 1).

We found statistically significant differences in CRP (P = 0.001) and sputum eosinophils (P = 0.001) between obese and nonobese asthmatics (Table 1). We noted that the median CRP was higher, 2 mg/dL for obese asthmatics compared to 1 mg/dl for nonobese asthmatics (Table 1, Figure 1). Also, the same trend was reflected in median sputum eosinophils, being 6% for obese asthmatics and 2% for nonobese asthmatics (Table 1, Figure 2). However, we did not find any significant difference in FEV_1 between obese and nonobese asthmatics (P = 0.882) (Table 1).

Among the associations between the parameters themselves (Table 2), we observed that there was a significant correlation between the CRP and sputum eosinophils (0.52, P = 0.001) for all asthmatics (Figure 3). We found no significant correlation between FEV_1 and sputum eosinophils (nonobese P = 0.120, obese P = 0.388) and also between FEV_1 and CRP (obese P = 0.423, nonobese P = 0.358) in both obese and nonobese asthmatics. Comparing the BMI with the asthma control test scores (Table 3), we noticed that asthma was not controlled (ACT scores ≤ 19) for 94% of obese asthmatics as compared to only 25% for nonobese asthmatics, and there was a significant association (P = 0.001) between obesity (BMI) and ACT scores.

Table 1. Comparison of outcome variables between obese and nonobese asthmatics. Values presented as median with interquartile range in parenthesis. *Mann-Whitney-u non-parametric test; P value < 0.05 — statistically significant

Outcome	Non-obese (N = 28)	Obese (N = 32)	*P* value*
CRP	1 (0–1)	2 (1–4)	0.001
FEV_1	60 (59–70)	64 (55–71)	0.882
Sputum eosinophils	2 (2–3)	6 (4–7)	0.001

CRP — C-reactive protein; FEV_1 — forced expiratory volume in one second

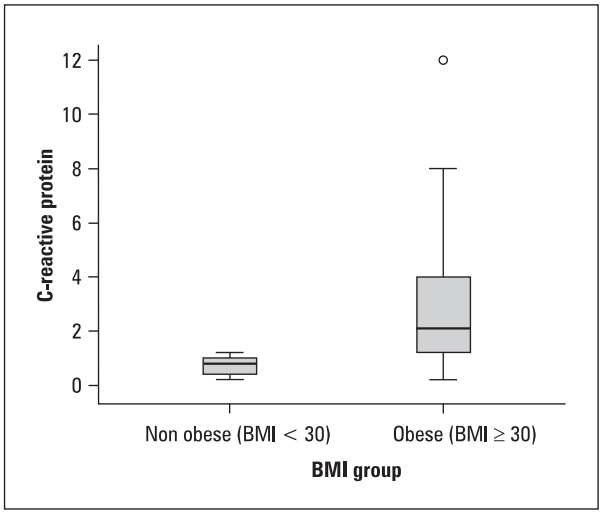

Figure 1. Comparison of C-reactive protein between obese and nonobese asthmatics. BMI — body mass index

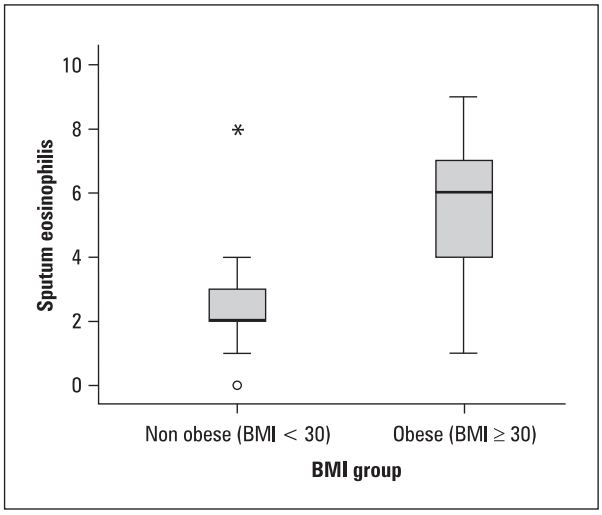

Figure 2. Comparison of sputum eosinophils between obese and nonobese asthmatics

Table 2. Association between outcomes in obese and nonobese asthmatics

		Outcome	FEV_1	Sputum eosinophils
Non-obese (N = 28)	Correlation*	CRP	0.069	0.080
	P value		0.358	0.337
	Correlation*	FEV_1		-0.221
	P value			0.120
Obese (N = 32)	Correlation*	CRP	-0.037	0.301
	P value		0.423	0.053
	Correlation*	FEV_1		-0.054
	P value			0.388
All samples (N = 60)	Correlation*	CRP	-0.012	0.520
	P value		0.464	0.001
	Correlation*	FEV_1		-0.082
	P value			0.268

*Pearson correlation coefficient. P value < 0.05 — statistically significant. CRP — C-reactive protein; FEV1 — forced expiratory volume in one second

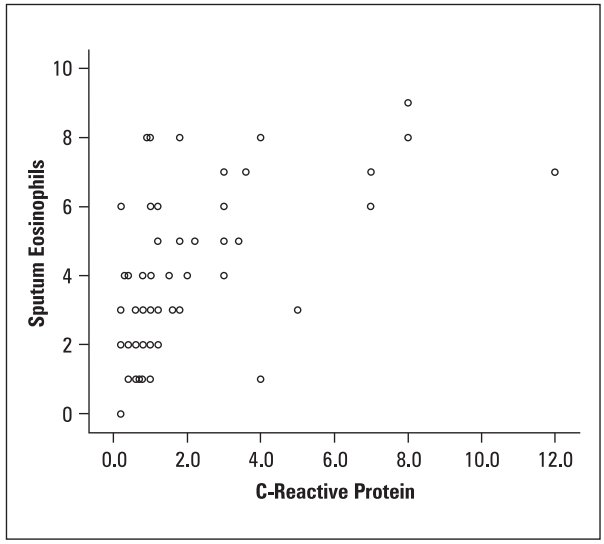

Figure 3. Association between C-reactive protein and sputum eosinophils in all asthmatics

Discussion

This study aimed to compare the CRP, FEV_1 and sputum eosinophils in obese and nonobese asthmatics and to ascertain whether there is an association between the groups. We also sought to find a link between the inflammatory markers — CRP and sputum eosinophils and FEV_1, and also among each other in asthmatics and correlate it with asthma control test scores. To the best of our knowledge, this study is one of the very few studies done to compare the various inflammatory markers in both obese and nonobese asthmatics and probably the first study to try to find an association between the inflammatory markers themselves and with the BMI. We also tried to correlate the inflammatory markers with the self-perception of symptom control through the asthma control test.

With our data, we found that median CRP and sputum eosinophils were higher in obese asthmatics than in nonobese asthmatics. Also, CRP and sputum eosinophils had a positive association with BMI. However, the FEV_1 did not correlate positively with BMI. Our findings were in concordance with the findings of Van Veen *et al.* regarding FEV_1 that has not decreased in obese asthmatics and has not shown a significant difference between obese and nonobese asthmatics [15]. Interestingly, our study was in contrast to the other finding reported in the same study wherein the authors showed that obese asthmatics do not have more airway inflammation as compared with nonobese asthmatics. But in our study, sputum eosinophils and CRP were also found to be higher in obese asthmatics and had a positive correlation with each other for all asthmatics.

Obese asthmatics had a significant association with asthma control test scores, predominant number of obese asthmatics (94%) had uncontrolled ACT (score ≤ 19). Even if the FEV_1 was independent of the BMI levels, our patients who were obese had an increased perception of symptoms reflected through the poor asthma control scores of less than equal to 19. An increase in systemic inflammation in obesity has been well described [16]. It has been suggested that high levels of pro-inflammatory molecules released from adipose tissue into the systemic circulation could

Table 3. Association between body mass index (BMI) and asthma control test (ACT)

	Non-obese (BMI < 30)	Obese (BMI ≥ 30)	P-value*
Asthma not controlled (ACT ≤ 19)	7 (25)	30 (94)	**0.001**
Asthma controlled (ACT > 19)	21 (75)	2 (6)	

Numbers with percentage in parenthesis. *Fisher's exact test; P value < 0.05 — statistically significant

contribute to the airway inflammation, thus increasing the prevalence and poor asthma control in obese asthmatics [17]. In our study, CRP levels were found to be elevated in obese asthmatics and this probably explains that this pro-inflammatory state could lead to increased perception of symptoms. The inflammatory markers (CRP and sputum eosinophils) were independent of the FEV_1 in all asthmatics, and thus perception of breathlessness reflected by the poor asthma control test scores (ACT ≤ 19) in these obese phenotypes of asthmatics could indeed be caused by the systemic inflammation. Many other studies have also demonstrated a positive correlation between elevated CRP levels and asthma control, respiratory impairment and bronchial hyper-reactivity [18–21].

Among the associations between the inflammatory mediators themselves, the CRP and sputum eosinophils showed a positive correlation in all asthmatics. Our study was in agreement with a similar study by Abdelsadek *et al.* who showed a positive correlation with CRP and sputum eosinophils in asthmatics [22]. In this study, however, the BMI wasn't correlated with the inflammatory markers. The mechanism of airway inflammation is complex in obese asthmatics. It can be mediated through various inflammatory mediators like interleukin (IL)-4, IL-5, IL-13, inflammatory cells like eosinophils, mast cells and basophils to name a few apart from the possible overlay of systemic inflammation. Non-eosinophilic inflammation and systemic inflammation could also play an important role in airway inflammation in obese asthmatics.

Obesity has been demonstrated to be a risk factor for asthma and is associated with an increased prevalence of asthma symptoms [23, 24]. But this, whether it is because of systemic inflammation, airway constriction or the change in dynamics of respiration and the restrictive defect or a contributory factor of both, needs to be investigated.

As the asthma treatment guidelines are evolving from a symptom-based approach to a tailored approach, it will be wise to optimise the treatment based on various phenotypes and endotypes, and thus probably reducing an impending exacerbation. Interestingly, many studies have previously shown that treating the airway inflammation led to better asthma control and thus, in turn, reduced hospitalisations and fatal events [25], and if the treatment strategy is aimed at keeping sputum eosinophils low, patients might have fewer asthma exacerbations [26]. Since elevated CRP is often associated with accelerated lung function decline [27], aiming at the treatment based on markers of inflammation both the airway and systemic inflammation is a more scientific and rational approach than treating the physiological effects caused by it, which is particularly relevant, especially in obese asthmatics. These obese asthmatics who have an overlay of systemic inflammation could also be phenotyped as a separate entity. In our study, the CRP and sputum eosinophils were higher in obese asthmatics, which suggests concordance between these biomarkers; and similarly to treating the airway inflammation, whether treating the systemic inflammation in these obese phenotypes leads to better asthma control, needs to be examined. Thus, the measure of systemic inflammatory markers in obese asthmatics with poor disease and symptom control plays an important role, and this should help to ascertain the systemic mediator's role and thus help to devise a treatment plan for these subsets of patients. This should ideally include rigorous weight management plans apart from pharmacological interventions in obese asthmatics which aim at reducing the systemic inflammatory mediators like the CRP levels. This might yield a better asthma control wherein the contributors of breathlessness can also be caused by restrictive lung defect in obesity. Apart from their airway inflammation, measuring the systemic inflammation adds a definitive value in difficult to treat obese asthmatics with poor symptom control. It is hoped that these results will help to understand the systemic inflammation of the obese phenotype of asthma and provide better asthma management. Serial measurements of CRP, sputum eosinophils and FEV_1, additional interventions and follow-ups

could have given us more insights into these parameters in different disease states and during various levels of asthma controls.

Conclusions

Thus, the inflammatory markers sputum eosinophils and CRP were raised in obese asthmatics and had a positive association with BMI. Obese asthmatics had a poorer subjective asthma control than the nonobese asthmatics despite FEV_1 being independent of the BMI levels. Measuring the systemic inflammatory markers in obese asthmatics who do not have adequate subjective symptom control reflected by uncontrolled ACT scores, could add a definitive value and possibly help in additional interventions aimed at reducing systemic inflammation and facilitating better symptom control.

Acknowledgments

We thank the biostatistician Mr. Sriram Ramachandran and all the patients who participated in this study.

Conflict of interest

None declared.

References:

1. Kay AB. The role of eosinophils in the pathogenesis of asthma. Trends Mol Med. 2005; 11(4): 148–152, doi: 10.1016/j.molmed.2005.02.002, indexed in Pubmed: 15823751.
2. Corrigan CJ, Haczku A, Gemou-Engesaeth V, et al. CD4 T-lymphocyte activation in asthma is accompanied by increased serum concentrations of interleukin-5. Effect of glucocorticoid therapy. Am Rev Respir Dis. 1993; 147(3): 540–547, doi: 10.1164/ajrccm/147.3.540, indexed in Pubmed: 8095124.
3. Patel DN, King CA, Bailey SR, et al. Interleukin-17 stimulates C-reactive protein expression in hepatocytes and smooth muscle cells via p38 MAPK and ERK1/2-dependent NF-kappaB and C/EBPbeta activation. J Biol Chem. 2007; 282(37): 27229–27238, doi: 10.1074/jbc.M703250200, indexed in Pubmed: 17652082.
4. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001; 286(3): 327–334, doi: 10.1001/jama.286.3.327, indexed in Pubmed: 11466099.
5. Roberts WL, Moulton L, Law TC, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2. Clin Chem. 2001; 47(3): 418–425, indexed in Pubmed: 11238291.
6. Varraso R, Siroux V, Maccario J, et al. Asthma severity is associated with body mass index and early menarche in women. Am J Respir Crit Care Med. 2005; 171(4): 334–339, doi: 10.1164/rccm.200405-674OC, indexed in Pubmed: 15557134.
7. Saint-Pierre P, Bourdin A, Chanez P, et al. Are overweight asthmatics more difficult to control? Allergy. 2006; 61(1): 79–84, doi: 10.1111/j.1398-9995.2005.00953.x, indexed in Pubmed: 16364160.
8. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J. 2003; 22(3): 470–477, doi: 10.1183/09031936.03.00261903, indexed in Pubmed: 14516137.
9. Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol. 2005; 115(5): 897–909; quiz 910, doi: 10.1016/j.jaci.2004.11.050, indexed in Pubmed: 15867841.
10. Desai D, Newby C, Symon FA, et al. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. Am J Respir Crit Care Med. 2013; 188(6): 657–663, doi: 10.1164/rccm.201208-1470OC, indexed in Pubmed: 23590263.
11. Scott HA, Gibson PG, Garg ML, et al. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011; 38(3): 594–602, doi: 10.1183/09031936.00139810, indexed in Pubmed: 21310876.
12. Thomas M, Kay S, Pike J, et al. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. Prim Care Respir J. 2009; 18(1): 41–49, doi: 10.4104/pcrj.2009.00010, indexed in Pubmed: 19240948.
13. Bartlett J, Breiman R, Mandell L, et al. Community Acquired pneumonia in adults: guidelines for management. Clinical Infectious Diseases. 1998; 26(4): 811–838, doi: 10.1086/513953.
14. Pavord ID, Brightling CE, Woltmann G, et al. Non-eosinophilic corticosteroid unresponsive asthma. Lancet. 1999; 353(9171): 2213–2214, doi: 10.1016/S0140-6736(99)01813-9, indexed in Pubmed: 10392993.
15. van Veen IH, Ten Brinke A, Sterk PJ, et al. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. Allergy. 2008; 63(5): 570–574, doi: 10.1111/j.1398-9995.2007.01597.x, indexed in Pubmed: 18394131.
16. Lessard A, Turcotte H, Cormier Y, et al. Obesity and asthma: a specific phenotype? Chest. 2008; 134(2): 317–323, doi: 10.1378/chest.07-2959, indexed in Pubmed: 18641097.
17. Shore SA, Johnston RA. Obesity and asthma. Pharmacol Ther. 2006; 110(1): 83–102, doi: 10.1016/j.pharmthera.2005.10.002, indexed in Pubmed: 16297979.
18. Szalai AJ. C-reactive protein (CRP) and autoimmune disease: facts and conjectures. Clin Dev Immunol. 2004; 11(3-4): 221–226, doi: 10.1080/17402520400001751, indexed in Pubmed: 15559367.
19. Jousilahti P, Salomaa V, Hakala K, et al. The association of sensitive systemic inflammation markers with bronchial asthma. Annals of Allergy, Asthma & Immunology. 2002; 89(4): 381–385, doi: 10.1016/s1081-1206(10)62039-x.
20. Ford ES. Asthma, body mass index, and C-reactive protein among US adults. J Asthma. 2003; 40(7): 733–739, doi: 10.1081/jas-120023497, indexed in Pubmed: 14626329.
21. Gan WQ, Man SFP, Senthilselvan A, et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004; 59(7): 574–580, doi: 10.1136/thx.2003.019588, indexed in Pubmed: 15223864.
22. Al-Aarag Abdelsadek H, Rawy Abeer M, EL-Behissy Mona M, et al. Study of serum C-reactive protein level and sputum eosinophils in patients with bronchial asthma. E J bronchology. 2015; 9(1): 43–47, doi: 10.4103/1687-8426.153597.
23. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007; 175(7): 661–666, doi: 10.1164/rccm.200611-1717OC, indexed in Pubmed: 17234901.
24. Shore SA. Obesity and asthma: implications for treatment. Curr Opin PulmMed. 2007; 13: 5.
25. Miranda C, Busacker A, Balzar S, et al. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. J Allergy Clin Immunol. 2004; 113(1): 101–108, doi: 10.1016/j.jaci.2003.10.041, indexed in Pubmed: 14713914.
26. Siva R, Green RH, Brightling CE, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002; 360(9347): 1715–1721, doi: 10.1016/S0140-6736(02)11679-5, indexed in Pubmed: 12480423.
27. Rasmussen F, Mikkelsen D, Hancox RJ, et al. High-sensitive C-reactive protein is associated with reduced lung function in young adults. Eur Respir J. 2009; 33(2): 382–388, doi: 10.1183/09031936.00040708, indexed in Pubmed: 19010993.

VIA MEDICA

ORIGINAL PAPER

Shahir Asfahan, Maya Gopalakrishnan, Naveen Dutt, Ram Niwas, Gopal Chawla, Mehul Agarwal, Mahendera Kumar Garg

All India Institute of Medical Sciences, Rajasthan, Jodhpur, India

Using a simple open-source automated machine learning algorithm to forecast COVID-19 spread: A modelling study

Abstract

Introduction: Machine learning algorithms have been used to develop prediction models in various infectious and non-infectious settings including interpretation of images in predicting the outcome of diseases. We demonstrate the application of one such simple automated machine learning algorithm to a dataset obtained about COVID-19 spread in South Korea to better understand the disease dynamics.

Material and methods: Data from 20th January 2020 (when the first case of COVID-19 was detected in South Korea) to 4th March 2020 was accessed from Korea's centre for disease control (KCDC). A future time-series of specified length (taken as 7 days in our study) starting from 5th March 2020 to 11th March 2020 was generated and fed to the model to generate predictions with upper and lower trend bounds of 95% confidence intervals. The model was assessed for its ability to reliably forecast using mean absolute percentage error (MAPE) as the metric.

Results: As on 4th March 2020, 145,541 patients were tested for COVID-19 (in 45 days) in South Korea of which 5166 patients tested positive. The predicted values approximated well with the actual numbers. The difference between predicted and observed values ranged from 4.08% to 12.77% . On average, our predictions differed from actual values by 7.42% (MAPE) over the same period.

Conclusion: Open source and automated machine learning tools like Prophet can be applied and are effective in the context of COVID-19 for forecasting spread in naïve communities. It may help countries to efficiently allocate healthcare resources to contain this pandemic.

Key words: machine learning, COVID-19, coronavirus, pandemic, South Korea

Adv Respir Med. 2020; 88: 400–405

Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in the Wuhan province of China in December 2019, has since spread to many countries, prompting WHO to declare it as a pandemic [1]. As of 11th March 2020, 118 326 cases have been confirmed and 4 292 deaths reported worldwide with the pathogen rapidly spreading to newer areas [2]. Having never encountered this virus before, health care systems are grappling with multiple unknowns about this pandemic and navigating uncharted territories [3]. One of the important parameters to be addressed is the rate and scale of spread in disease naïve communities. Multiple epidemiologic studies are attempting to determine the epidemiology and estimated basic reproduction number (R_0) of the disease to help assess the spread pattern [4]. Predicting the scale of spread will help prepare fragile health care systems, especially in the developing world to get ready and allocate resources accordingly.

Machine learning algorithms have been used to develop prediction models in various infectious and non-infectious settings, including interpretation of images in predicting the outcome of diseases [5]. The ease with which these can be used at a low cost and minimum learning curve is an advantage, especially in epidemic situations. We

Address for correspondence: Gopal Chawla, All India Institute of Medical Sciences, Rajasthan, Jodhpur, India; e-mail: dr.gopalchawla@gmail.com
DOI: 10.5603/ARM.a2020.0156
Received: 24.06.2020
Copyright © 2020 PTChP
ISSN 2451–4934

demonstrate the application of one such simple automated machine learning algorithm to a dataset obtained about COVID-19 spread in South Korea to better understand the disease dynamics. The aim of this study is to demonstrate the ease with which simple algorithms can be used effectively as disease prediction models to help health care systems anticipate new cases and prepare accordingly, especially in resource-limited settings.

Material and methods

Korea's centre for disease control (KCDC) has released in the public domain the database of patients who are being tested for COVID-19 and those who are diagnosed with the same. This dataset is being updated daily and is licensed for research purposes by Creative Commons licence (CC BY-NC-SA 4.0) [6].

"Prophet" is an open-source automated machine learning actuarial modelling system that has been used in insurance and financial services for improving risk management available in the public domain since 2017 [7, 8]. It uses linear and non-linear regression techniques and takes into account seasonality in the final analysis. This approach is a more accurate reflection of patterns of human activities as well as biological variables. Python 3.6 was used as the programming language given its many supporting libraries and ease of use.

Data from 20th January 2020 (when the first case of COVID-19 was detected in South Korea) to 4th March 2020 was accessed from the above-mentioned source. The columns of date and cumulative sum of COVID-19 cases of the corresponding dates were selected and included in the analysis.

A future time series of specified length (taken as 7 days in our study) starting from 5th March 2020 to 11th March 2020 was generated and fed to the model to generate predictions with upper and lower trend bounds of 95% confidence intervals. We used the future time series of 7 days as the disease is rapidly evolving and trends are changing in real time. The model was assessed for its ability to reliably forecast using mean absolute percentage error (MAPE) as the metric.

Results

As of 4th March 2020, 145 541 patients were tested for COVID-19 (in 45 days) in South Korea of which 5 166 persons tested positive (Figure 1).

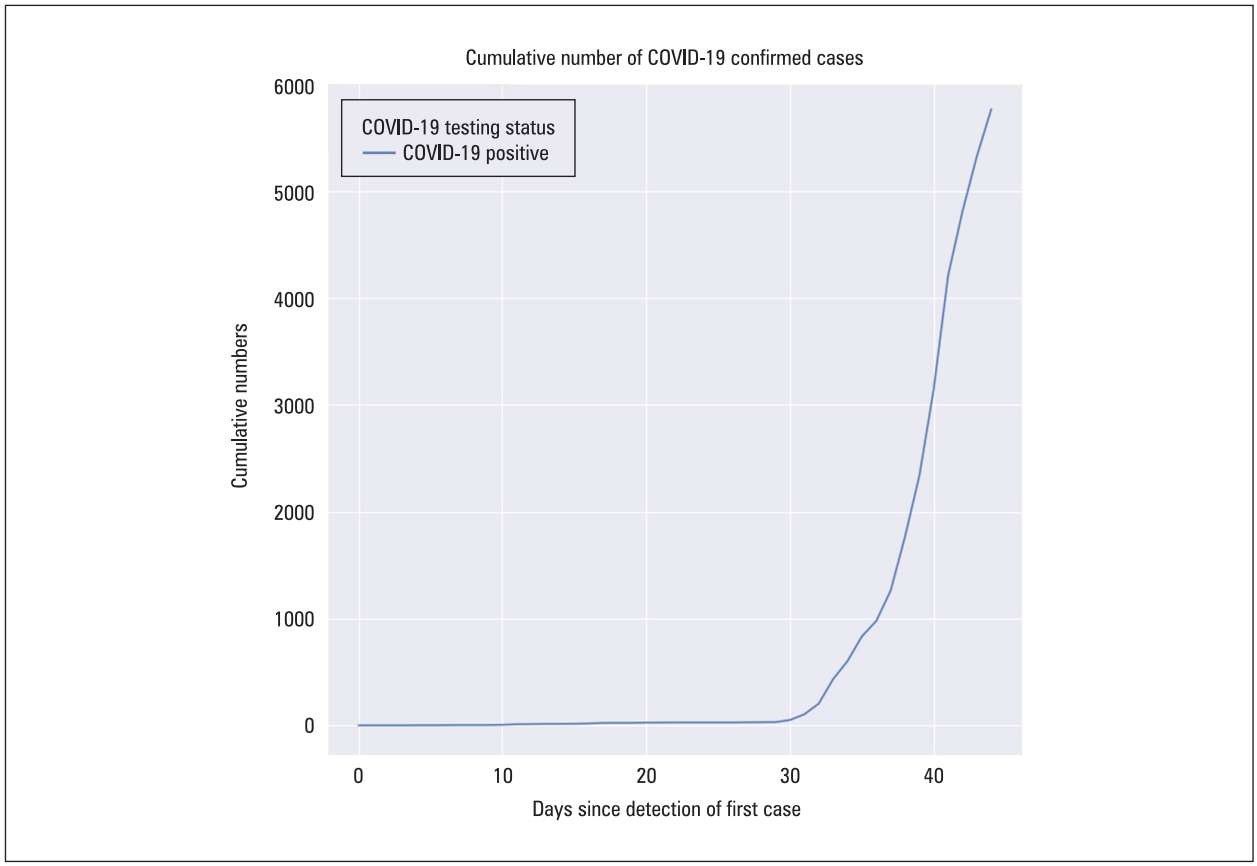

Figure 1. Total number of COVID-19 positive patients in South Korea as of 4th March 2020 plotted over 45 days since the detection of the first case

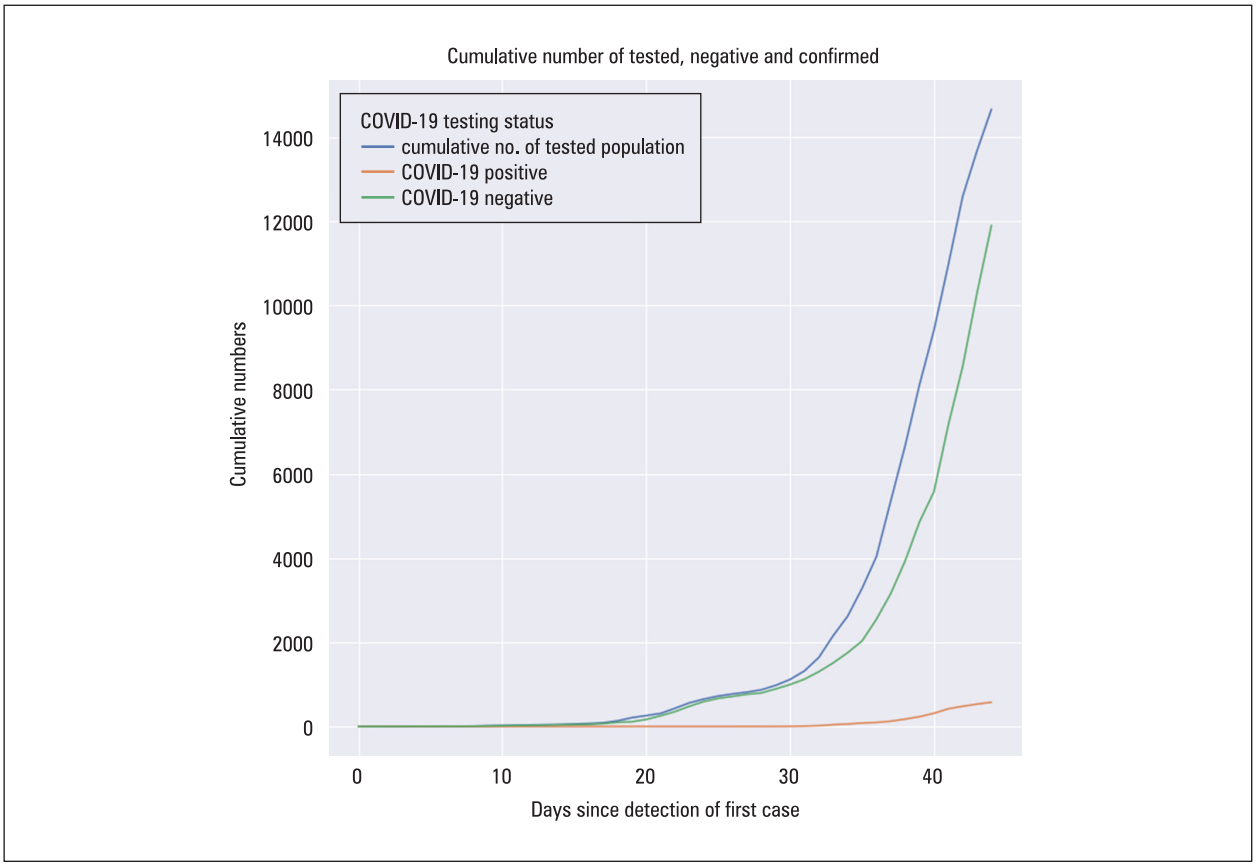

Figure 2. Total number tested as of 4th March 2020 in South Korea were 146 541, of which 5 766 tested positive and the rest were negative

The trend line of the positive and negative cases plotted since the day of detection of the first case are shown in Figure 2. Forecasts estimates were drawn for the next 7 days as shown in Figure 3. The forecasts were made with a confidence interval of 95% represented by the upper and lower range bounds for each prediction as shown in Table 1.

We followed up the actual numbers till 11th March 2020. The predicted values approximated well with the actual numbers. The difference between predicted and observed values ranged from 4.08% to 12.77% (Table 1).

The total increase in the number of actual confirmed cases over the predicted period of 7 days was 1 989, which is an increase of 35.5% over the baseline value on 4th March 2020. On average, our predictions differed from actual values by 7.42% (MAPE) over the same period (Figure 4).

Discussion

COVID-19 is a rapidly evolving pandemic with limited data regarding its spreading potential. Many countries are reporting new cases daily. Several large modelling studies have focussed on nowcasting and forecasting potential domestic and international spread of COVID-19 as well as health care system preparedness for handling disease spread in Africa [9, 10]. A modelling study into COVID-19 evaluating the usefulness and feasibility of isolation has also been recently published [11].

We employed public domain data from South Korea for demonstrating the use of simple open-source automated machine learning algorithm which has been hitherto used for non-medical purposes to help model the current spread of disease in South Korea. Although we are analysing the data of another country, in this digital era where the world has been reduced to a global village, we expect to replicate the performance of a neutral machine learning tool if applied in any other context.

MAPE index of our model for one week was 7.42%, which is indicative of a highly accurate forecasting model [12]. Part of this success was how machine learning model learnt from the training data provided to it and automatically detecting the trend changes and estimating the predictions (Figure 4). The inaccuracy decreased to a minimum over the middle of predictions and

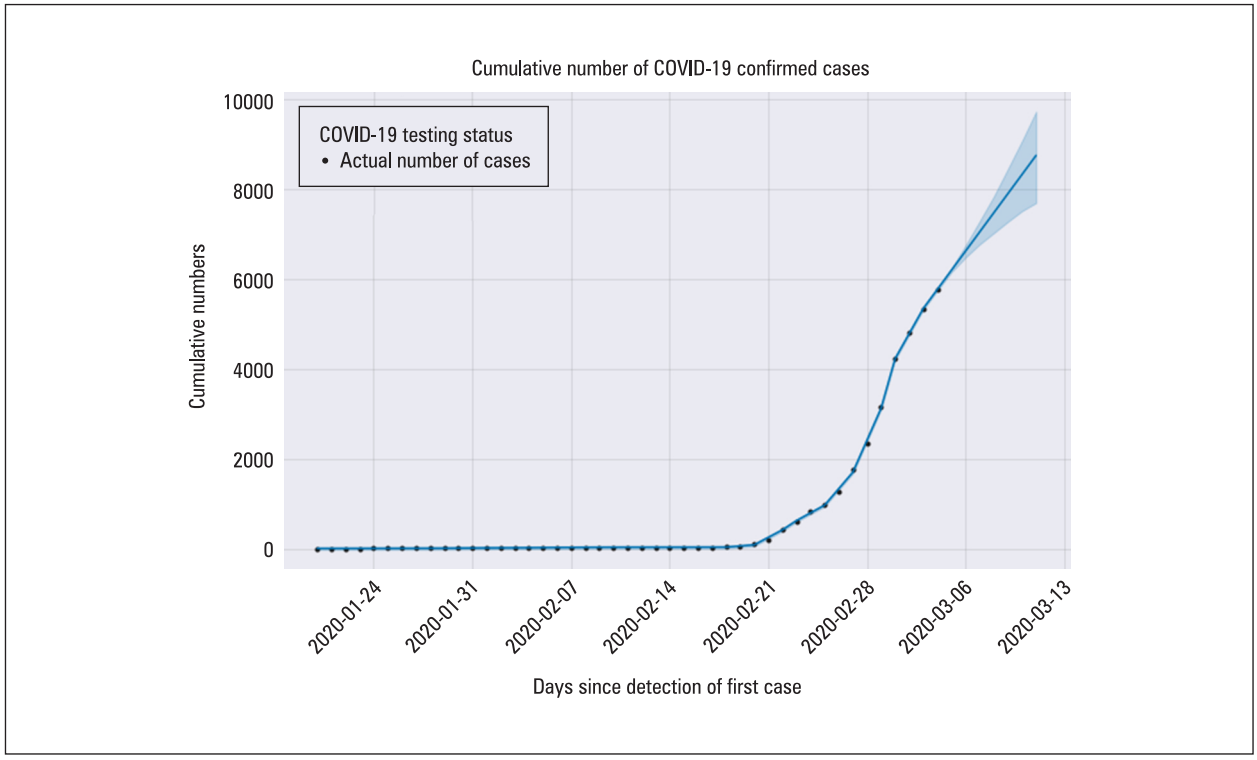

Figure 3. Black dots represent actual values till 4th March 2020 and the blue line indicates the predictions for the next 7 days with the shaded blue designating 95% confidence intervals

Table 1. Actual numbers versus the predicted numbers till 11th March 2020 (as of the day of writing this manuscript, with upper and lower 95% confidence intervals) with the difference and percentage change of predicted values

Date	Actual numbers	Predicted numbers	Predicted lower limit	Predicted upper limit	Difference between actual and predicted numbers	Percent difference between actual and predicted numbers
05.03.2020	5766	6192.34	6144.153	6236.549	-426.3397742	-7.39
06.03.2020	6284	6617.772	6486.003	6744.628	-333.7715647	-5.31
07.03.2020	6767	7043.203	6788.055	7273.402	-276.2033551	-4.08
08.03.2020	7134	7467.634	7064.978	7839.158	-334.6351456	-4.69
09.03.2020	7382	7894.067	7333.481	8455.096	-512.066936	-6.94
10.03.2020	7513	8319.499	7555.599	9061.543	-806.4987264	-10.73
11.03.2020	7755	8744.931	7749.495	9722.656	-989.9305169	-12.77

then continued to increase towards the end of the predictive period. Machine learning algorithms are data hungry and need larger data for more accurate predictions over a longer period. In a fast moving and novel pandemic we do not have this luxury, hence restricting ourselves to a limited period as of the date of this analysis, with larger data in the future, longer range predictions would be possible [13].

We have learnt from China and Italy on how intensive care units can get easily overwhelmed with patients suffering from COVID-19 [14, 15]. This outbreak seems to test the capacity of health care systems like never before, even in developed countries. Hence the application of machine learning to anticipate and arrange health care resources a week in advance might make a big difference in managing the pandemic.

The advantage of this approach of forecasting is that it takes local factors into account rather than global aspects. This machine learning tool is able to factor in changes and figure out any pattern in the rise or fall of cases, including seasonality and can be used during the initial slow

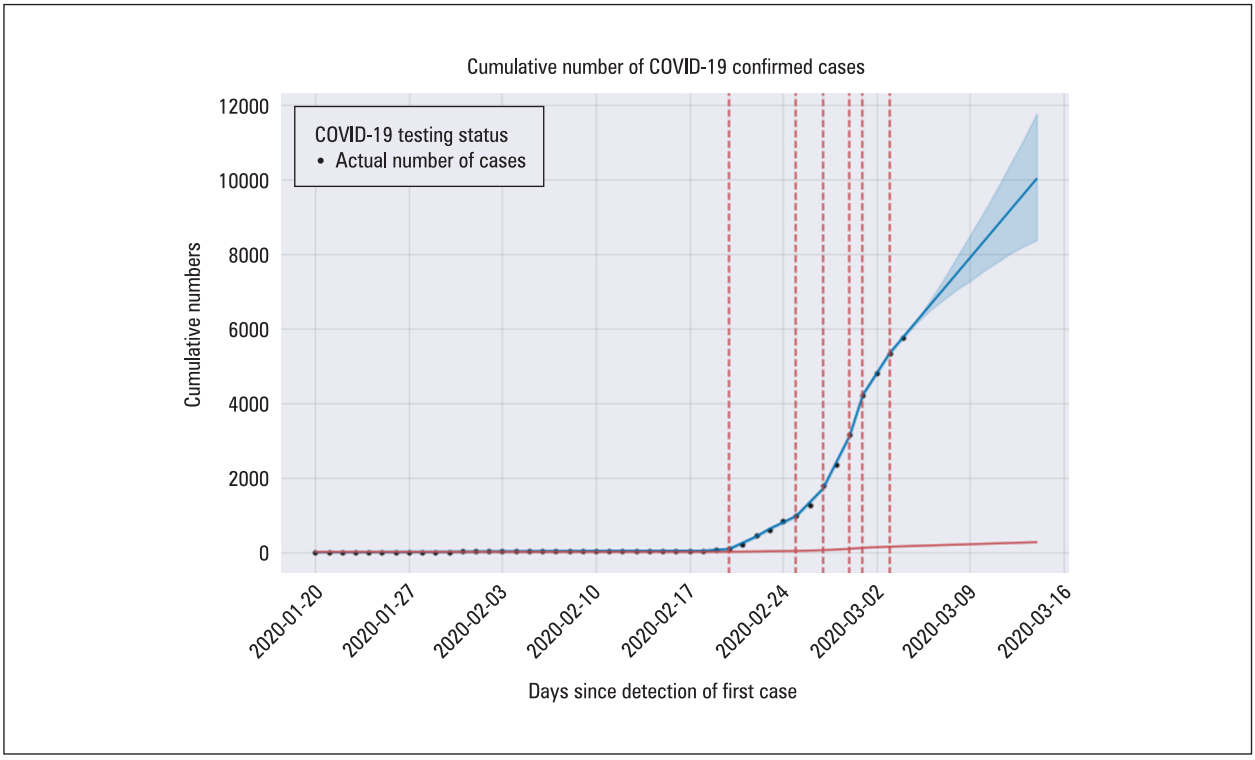

Figure 4. Dotted red lines indicate the automatic trend changes detected by our machine learning model

rise, followed by steep rise, eventual fall in cases or even any seasonal recurring trends [7]. The approach and threshold of one country's testing strategy might differ from another, so one-size-fits-all attitude may not work best. Using the data from a particular region and forecasting based on that may accurately reflect the pattern that is likely to arise in that particular region. Although we agree that in an ideal world, epidemiology should be consistent between countries but on the practical plane, the difference between health care systems between countries might be too stark to make reasonable parallels. As the case fatality ratios become clearer, models like these might be useful to calculate in advance the number of intensive care beds/ECMO units that might be required and also to assess whether public health strategies are effective.

Our study has several limitations involving the assumptions used in the preparation of this model. We employed a linear model, as in the short term, we don't anticipate saturation in the total number of the vulnerable population. This limits the applicability in the long term. Also, calculations of replication potential and spread potential were not performed as the aim of the study was to demonstrate the ease of use and applicability of the machine learning algorithm rather than a large-scale forecasting project. Also, since the intent of the study was to evaluate the performance of new technologies into disease modelling, we did not go into the aspect of the effect of national responses to the pandemic if any in the preceding period of forecast, although that is certainly a possibility and may need an appropriate selection of response measures and the predictive period where the difference between predictive and actual numbers may demonstrate the effect of measures like social distancing and 'lockdown' on the rate and extent of the spread of the pandemic.

Conclusions

Open source and automated machine learning tools like Prophet can be applied and are effective in the context of COVID-19 for forecasting spread in naïve communities. It may help countries to efficiently allocate health care resources to contain this pandemic.

Conflict of interest

None declared.

References:

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020; 395(10229): 1054–1062, doi: 10.1016/s0140-6736(20)30566-3.
2. World Healt Organization. Coronavirus disease (COVID-19) pandemic. Available online: www.who.int/emergencies/diseases/novel-coronavirus-2019. [Last accessed at: 05.10.2020].
3. Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of COVID-19 — studies needed. N Engl J Med. 2020; 382(13): 1194–1196, doi: 10.1056/NEJMp2002125, indexed in Pubmed: 32074416.
4. Fauci AS, Lane HC, Redfield RR. COVID-19 — navigating the uncharted. N Engl J Med. 2020; 382(13): 1268–1269, doi: 10.1056/NEJMe2002387, indexed in Pubmed: 32109011.
5. Skrede OJ, Raedt SDe, Kleppe A, et al. Deep learning for prediction of colorectal cancer outcome: a discovery and validation study. The Lancet. 2020; 395(10221): 350–360, doi: 10.1016/s0140-6736(19)32998-8.
6. KCDC. Available online: http://www.cdc.go.kr. [Last accessed at: 09.05.2020].
7. Taylor SJ, Letham B. Prophet: forecasting at scale. Facebook Research. Available online: https://research.fb.com/blog/2017/02/prophet-forecasting-at-scale/. [Last accessed at: 05.10.2020].
8. Fang WX, Lan PC, Lin WR, et al. Combine Facebook prophet and LSTM with BPNN forecasting financial markets: the Morgan Taiwan Index. 2019 International Symposium on Intelligent Signal Processing and Communication Systems (ISPACS). 2019, doi: 10.1109/ispacs48206.2019.8986377.
9. Gilbert M, Pullano G, Pinotti F, et al. Preparedness and vulnerability of African countries against importations of COVID-19: a modelling study. The Lancet. 2020; 395(10227): 871–877, doi: 10.1016/s0140-6736(20)30411-6.
10. Wu J, Leung K, Leung G. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. The Lancet. 2020; 395(10225): 689–697, doi: 10.1016/s0140-6736(20)30260-9.
11. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. The Lancet Global Health. 2020; 8(4): e488–e496, doi: 10.1016/s2214-109x(20)30074-7.
12. Meade N. Industrial and business forecasting methods. J Forecast. 1983; 2(2): 194–196, doi: 10.1002/for.3980020210.
13. van der Ploeg T, Austin PC, Steyerberg EW. Modern modelling techniques are data hungry: a simulation study for predicting dichotomous endpoints. BMC Med Res Methodol. 2014; 14: 137, doi: 10.1186/1471-2288-14-137, indexed in Pubmed: 25532820.
14. Kuo L. Wuhan nurses' plea for international medics to help fight coronavirus. The Guardian. 26.02.2020. Available online: www.theguardian.com/world/2020/feb/26/wuhan-nurses-plea-international-medics-help-fight-coronavirus. [Last accessed: 05.10.2020].
15. Orecchio-Egresitz H. Faced with tough choices, Italy is prioritizing young COVID-19 patients over the elderly. That likely "won't fly" in the US. Buisness Insider. 11.03.2020. Available online: www.businessinsider.in/science/news/faced-with-tough-choices-italy-is-prioritizing-young-covid-19-patients-over-the-elderly-that-likely-wont-fly-in-the-us-/articleshow/74567872.cms. [Last accessed at: 05.10.2020].

Patryk A Sobczak[1], Justyna M Sobczak[1], Sebastian Majewski[1], Joanna Miłkowska-Dymanowska[1], Zofia Kurmanowska[2], Karolina Szewczyk[2], Ewa Tyczkowska-Sieroń[3], Adam J Białas[2], Adam Antczak[4], Paweł Górski[1], Wojciech J Piotrowski[1]

[1]Department of Pneumology and Allergy, 1st Chair of Internal Medicine, Medical University of Lodz, Lodz, Poland
[2]Department of Pathobiology, 1st Chair of Internal Medicine, Medical University of Lodz, Lodz, Poland
[3]Department of Biology and Parasitology, 1st Chair of Biology and Medical Microbiology, Medical University of Lodz, Lodz, Poland
[4]Department of General and Oncological Pneumonology, 1st Chair of Internal Diseases, Medical University of Lodz, Lodz, Poland

The role of bronchoscopy in diagnosis of chronic cough in adults: a retrospective single-center study

Abstract

Introduction: Cough is one of the most frequent symptoms reported to pulmonologists. The role of bronchoscopy in the diagnostic work-up of chronic cough is not clearly defined. The aim of this study was to evaluate the utility of fiberoptic bronchoscopy (FOB) and additional testing of samples collected during FOB in the differential diagnosis of chronic cough in adults.

Material and methods: This was a single-center retrospective study. Out of 7115 conventional white light FOB examinations, we finally selected 198 with cough as the only indication.

Results: In 40.9% of bronchoscopic examinations, no visible cause of cough was found. Visual signs of chronic bronchitis (CB) were detected in 57.6% of reports. Only in 3 cases (1.5%) bronchoscopy revealed a potential cause of chronic cough other than CB. *Mycobacterium tuberculosis* or other mycobacteria were spotted in none of the samples. In 91.1% of bronchoalveolar lavage (BAL) cytologic examinations, at least one cell count abnormality was detected, but only in case of increased percentage of eosinophils, it might be considered clinically relevant. In 53% of bacteriological culture results, at least one potentially pathogenic bacterium was isolated.

Conclusions: The present study results strengthen the evidence that FOB combined with additional testing of airway specimens obtained during FOB is not a powerful tool in the differential diagnosis of chronic cough, and FOB as a diagnostic tool may be overused. The appropriate timing and decision regarding referral for FOB and additional testing of achieved material requires careful clinical consideration.

Key words: fiberoptic bronchoscopy, cough, differential diagnosis, bacterial cultures, bronchoalvelar lavage

Adv Respir Med. 2020; 88: 406–411

Introduction

Cough is a protective reflex of the respiratory system that clears the airways from mucus, fluids, particles or other material [1]. An occasional, sporadic cough is normal and healthy. A cough that persists for several weeks or one that brings the blood, bloody or discolored sputum or an excessive amount of airway mucus may indicate a condition that requires medical attention. Cough itself belongs to the most frequent respiratory symptoms for which patients seek help from primary care physicians and/or pulmonologists [2]. Taking into account the symptom duration, it is subdivided into three categories, namely: acute — defined as lasting less than 3 weeks, subacute — 3–8 weeks duration, and chronic cough which persists longer than 8 weeks [3].

Differential diagnosis of chronic cough in the first line should include common causes like upper airway cough syndrome (UACS), asthma, eosinophilic bronchitis, gastroesophageal reflux

Address for correspondence: Patryk A Sobczak, Department of Pneumology and Allergy, 1st Chair of Internal Medicine, Medical University of Lodz, Lodz, Poland; e-mail: patryk.a.sobczak@gmail.com
DOI: 10.5603/ARM.a2020.0140
Received: 20.05.2020
Copyright © 2020 PTChP
ISSN 2451–4934

disease (GERD), chronic obstructive pulmonary disease, pulmonary fibrosis, or bronchiectasis. Additionally, drugs (e.g. ACEI, angiotensin-converting enzyme), exposure to cigarette smoke and environmental pollution should be taken into account [1]. Animal studies indicate that cough stress to the airway wall generates a self-perpetuating cough-reflex cycle [4]. It is of note that the causes of cough may overlap. It has been shown in a prospective cohort study of patients with chronic cough that this symptom was due to one condition in 73%, to two conditions in 23%, and to three conditions in 3% of the subjects [5].

According to the most up-to-date ERS guidelines on the diagnosis and treatment of chronic cough [7], the initial evaluation of a patient should include a detailed medical history (most importantly ACEI use, smoking history and irritants exposure), physical examination, chest radiography, lung function tests, and conditionally FeNo and blood eosinophilia. Recommended initial management includes: stopping risk factors, empirical treatment with oral or inhaled steroids or proton pomp inhibitors (PPI) in symptomatic GERD [7]. In a patient with normal chest X-ray and unsuccessful initial management, additional evaluation is suggested, with bronchoscopy at the very end of the list, after esophageal manometry, induced sputum, sputum acid-fast bacilli (AFB), laryngoscopy, methacholine challenge and chest CT [6]. Still, fiberoptic bronchoscopy (FOB) may be a reasonable tool for the anatomical and dynamic assessment of the airways and offers a sampling of distal airways for cytologic and microbiologic studies.

There is a substantial body of evidence suggesting that FOB has a limited role in the diagnosis of patients when chronic cough is the only indication and when no findings in imaging studies are detected [8–10]. However, in selected instances, e.g., the necessity of sampling, presence of risk factors of malignancy, refractory cough, in immunocompromised patients or when "uncommon causes" are considered, the clinical benefit of FOB is noted [8, 10–13].

The present study aimed to evaluate the utility of FOB and additional testing of samples collected using FOB in the differential diagnosis of chronic cough. We hypothesize that the visualization of the airways itself is not sufficient to determine the underlying cause of chronic cough, but reasonably selected additional tests of airway samples collected during FOB may increase its diagnostic value.

Material and methods

The study is a retrospective, single-center, observational cohort study of patients referred with a diagnosis of chronic cough to the Bronchoscopy Unit of the Department of Pneumology and Allergy and the Department of General and Oncological Pulmonology of Medical University of Lodz FOB examinations were performed between November 2006 and April 2017 by experienced pulmonologists. During this period, 7115 conventional white light FOB examinations were carried out. The results of examinations were routinely collected in a digital database. Due to the retrospective nature of the study, no ethics committee approval was needed.

Study inclusion criteria were the following: diagnosis of chronic (> 8 weeks) unexplained cough as the only indication for FOB and no radiological findings (chest radiography and/or chest computed tomography); aged above 18. Patients with any lung-related disease diagnosed before FOB referral (e.g. neoplasm, asthma, COPD, sarcoidosis) or presenting with other accompanying symptoms (e.g. hemoptysis) were excluded from the study.

All patients' cases which met study eligibility criteria were analyzed. Medical documentation, the outcome of FOB examinations and results of additional testing of samples collected during FOB: tests to exclude tuberculosis infection AFB smears and cultures], non-specific microbiological cultures of bronchial washings and cytologic examinations of bronchoalveolar lavage fluid (BALf) were analyzed.

Drug resistance definitions used in our study are based on the previously published definitions by Magiorakos [14]. Based on the previously used methodology of building worksheets for categorizing bacteria to a particular group of resistance, we created worksheets for bacteria found in our study.

Results

After careful review of the study inclusion and exclusion criteria, we have finally enrolled 198 patients in the study, 121 females (61%) and 77 males (39%), with the median age of 51.5 years (37.75–61). Figure 1 shows the flow chart of patient selection for the study.

Chronic bronchitis signs were visualized in 114 (57.6%) patients. The endoscopic diagnosis of chronic bronchitis was based on the visual assessment when the following features were present: dilated mucus glands' ducts, atrophic mucosa, mucus aggregation, hyperemia, mucosal fragility.

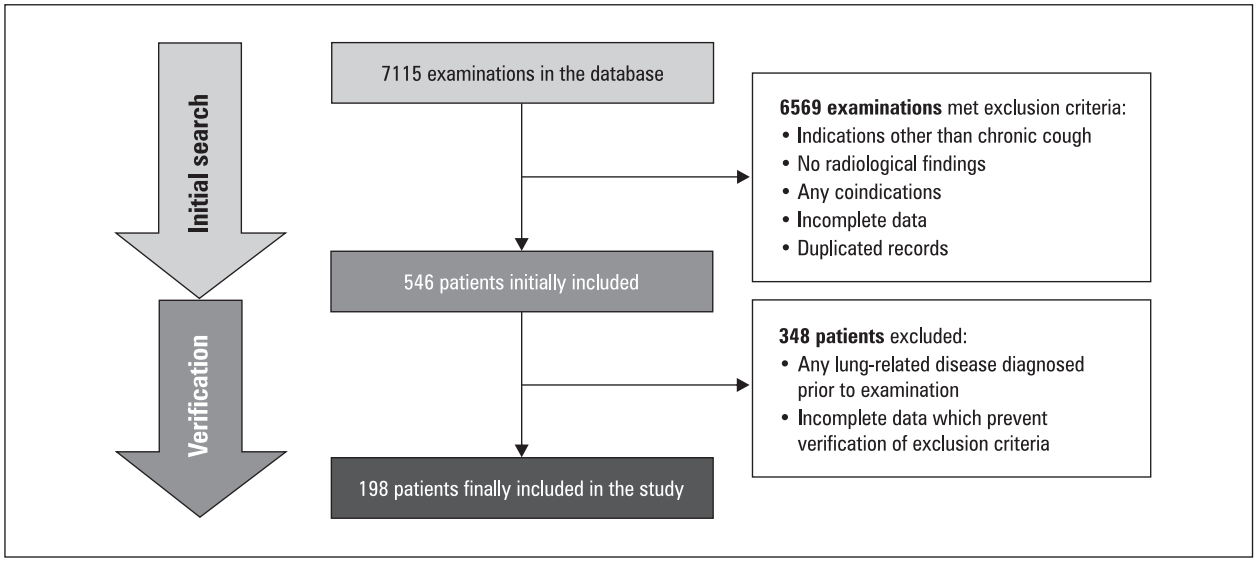

Figure 1. The flow chart showing patient selection to the study

In 81 (40.9%) examinations, no visible lesions of the airways were noted. In three (1.5%) patients, FOB revealed the probable cause of chronic cough: suspicion of a tumor (pathology not determined, sent to another center and lost to follow-up), bronchial polyp, and tracheomalacia (Figure 2).

None of the studied patients had a positive result of tuberculosis testing (AFB smear and/or culture). In 45 (22.7%) patients, bronchoalveolar lavage (BAL) was performed. In 41 cases (91.1%), BALf cytologic examination showed at least one cell count abnormality, in 12 cases (26.7%), at least three abnormalities, see Table 1. In 5 (11.1%) examinations eosinophils count of ≥ 3% was detected.

In 111 (56%) FOB examinations, non-specific bacteriological cultures were performed. One potentially pathogenic bacterium was detected in 51 (46%) samples, and 2 potentially pathogenic bacteria were detected in 8 (7%) samples. There were 2 alert pathogens within cultured bacteria. Remaining 52 (46.8%) cultures were sterile.

Multidrug resistance (MDR) was detected in case of 40 bacterial strains (59.7%), and in 1 case (1.5%), extensive drug resistance (XDR) was identified. In 21 (36%) patients with positive cultures, FOB revealed no visible airway changes. Isolated bacterial strains are shown in Table 2.

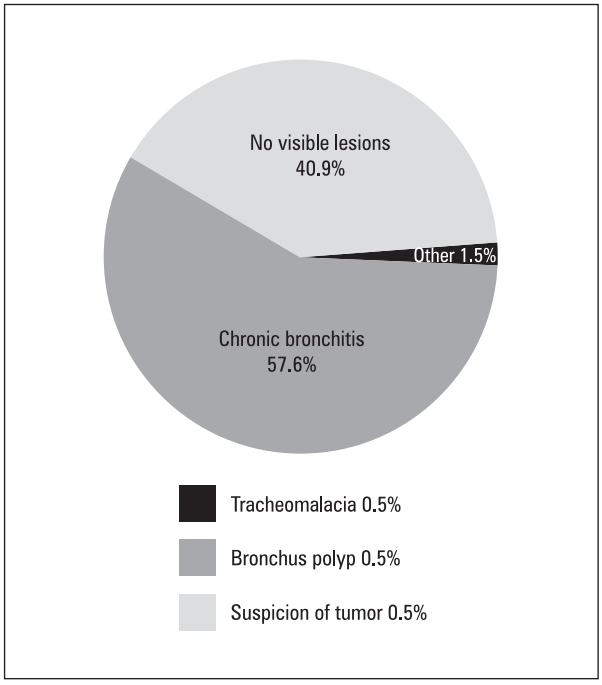

Figure 2. Fiberoptic bronchoscopy outcome

Discussion

This retrospective, observational, cohort study aimed to evaluate the utility of FOB in the differential diagnosis of chronic cough. Our study results showed that only 1.5% of FOB examinations revealed directly probable cause of chronic cough. 57% of the subjects had endoscopic signs of chronic bronchitis. However, we need to keep in mind that this is a subjective operator's assessment and chronic bronchitis is a clinical definition. Therefore, we suggest that such an endoscopic conclusion might be overused, especially when the operator is looking for potential cause of chronic cough and does not identify any other pathology. It is worth mentioning that according to Markovitz *et al.*, respiratory tract inflammation may be induced by the act of cough-

Table 1. BALf cell count analysis

	Normal value	Number of abnormal BALf cell count results [n, (%)]	Median value (IQR)
All cells	$< 10^6$	31 (68.9%)	1.4×10^6 ($9.8 \times 10^6 – 22.43 \times 10^6$)
Neutrophils	< 3%	5 (11.1%)	4.3% (3.8–4.65%)
Lymphocytes	< 15%	32 (71.1%)	24% (19–29%)
Eosinophils	< 0.5%	15 (33.3%)	2% (1–3%)
Monocytes	< 0.5%	2 (4.4%)	1% (1%)
Basophils	< 0.5%	2 (4.4%)	1.8% (1.2–2.4%)

BALf — bronchoalveolar lavage fluid

Table 2. Bacterial species and number of positive culture results from bronchial washings

Bacterial species	Number of positive results
Moraxella catarrhalis	29
Staphylococcus aureus	12
Streptococcus pneumoniae	9
Serratia mercescens ESBL-	4
Streptococcus agalactiae	3
Acinetobacter baumanii	1
Corynobacterium striatum	1
Escherichia coli	1
Klebsiella oxytoca	1
Klebsiella pneumoniae ESBL+	1
Streptococcus anginosus	1
Streptococcus C	1
Streptococccus constellatus	1
Streptococcus parasanguinis	1
Streptococcus vestibularis	1

ing itself [10]. Additionally, 41% of the studied subjects had no visible airway changes in FOB. Taken together, our results suggest that FOB has a limited role in the diagnosis of chronic cough as the only indication, which is concordant with previously published observations.

The substantial body of evidence suggests that FOB may be overused in the diagnosis of respiratory conditions. Sen *et al.* have suspected that unnecessary FOB is most likely overused in the evaluation of respiratory symptoms (e.g. cough, hemoptysis) [15]. Moreover, Gasparini and Barnes have deduced that FOB provides a little diagnostic information in the context of patients with no radiological findings [8, 9]. It is of note that Irwin *et al.* concluded that FOB has the least relative usefulness of the components (e.g. medical history, physical examination, pulmonary function testing, upper gastrointestinal studies, esophageal pH monitoring, sinus or chest X-rays) of the diagnostic protocol of chronic cough [5].

However, many authors, including those mentioned above, have agreed that FOB is a very useful tool in a properly selected subgroup of patients. According to Irwin *et al.,* in case of suspicion of malignancy (e.g. smoking or hemoptysis history), even if chest radiography is normal, FOB is indicated [11]. Moreover, when sampling is needed (e.g. BALf, transbronchial biopsy, microbiologic culture or cytology) FOB is a desired technique [2, 5, 8, 15].

Markovitz and Irwin have proposed a simple recipe to maximize the yield of FOB and not to overuse that examination. They have advised performing early FOB only when the radiological image is abnormal or when a patient is immunocompromised, even if radiological findings are absent. Otherwise, delaying FOB until the most common causes are excluded, and other diagnostic procedures are exhausted, is recommended [10].

Collecting samples from the respiratory tract to carry out additional testing to expand the diagnostic yield of FOB is a common practice. There is a knowledge gap in the literature how such sampling and additional testing impact on the efficacy of FOB in the differential diagnosis of chronic cough. Moreover, clear indications when additional testing should be applied are lacking. In this retrospective analysis, in 45 (22.7%) cases of all 198 FOB examinations, BAL was performed. Five results (2.5% of all 198 patients and 11% of patients subjected to BAL) of BALf cell counts showed an increased number of eosinophils ≥ 3%. This quantity, but in sputum, is a criterion used for the diagnosis of nonasthmatic eosinophilic bronchitis (NAEB) — one of the probable causes of chronic cough. Nevertheless, cytologic examination of BALf can equally be used for diagnosis of NAEB [16]. Although in our study, BALf analysis results were abnormal in almost

all patients, the observed abnormalities are not characteristic of any specific diagnosis. The most commonly observed abnormalities were an increased total number of BALf cells and an elevated percentage of BALf lymphocytes — the finding that is suggestive of many interstitial lung diseases [17]. However, according to some authors, an increased percentage of lymphocytes is a non-specific finding, probably related to the cough itself [18]. Both an increased number of cells and an elevated percentage of lymphocytes may be related to low-grade bronchial inflammation induced by mechanical insult triggered by unrestrained bursts of cough.

In the case of 111 of all 198 FOB examinations (56%), bronchial washings for cultures were collected, 59 (53.1%) of them were positive, which potentially could uncover the cause of undetermined chronic cough. Due to a retrospective character of the study, it was impossible to follow the patients with positive culture results. Specifically, we do not have any knowledge whether the culture-based antibiotic treatment was introduced, and if so, whether was it effective.

Our study results support the use of additional testing to increase the diagnostic efficacy of FOB. The diagnostic yield of FOB increased from 1.5% (direct visualization of the tracheobronchial tree) to 33.8% by combining BALf cytologic examinations and bronchial washings cultures. Similar conclusions were presented by Heching *et al.*, who increased the diagnostic yield of FOB from 26% to 68% after the addition of microbiologic cultures and histopathologic analysis of specimens [19].

On the other hand, in one study on the utility of FOB in the differential diagnosis of chronic cough, 27 out of 48 FOB procedures included bronchial washings for cultures, and only 3 of them were positive. Furthermore, these three patients were treated with the appropriate course of antimicrobials, which has not improved their cough. According to the authors, this indicates that cultured bacteria have signified contamination, colonization, or were not responsible for cough [9].

In the case of our analysis, all 59 positive cultures identified a total of 67 bacteria. Among them, 40 (59.7%) presented MDR, and 1 (1.5%) was XDR. We are unable to determine which and how many of these bacteria were causes of chronic cough in the studied cohort, nevertheless, so widespread drug resistance might pose a problem in bacterial eradication if such a clinical decision is undertaken. The simple explanation for so frequent detection of MDR bacterial strains would possibly be the common use of antibiotics in everyday clinical ambulatory practice in patients with cough, however, we do not have any data to proof that in our cohort of patients this was true.

Another additional test that is routinely performed in patients with chronic cough undergoing FOB is AFB smears and BALf or bronchial washings cultures for *Mycobacterium tuberculosis* (MTB). Our results demonstrating none of positive results for MTB detection clearly show that in subjects with normal chest X-ray, and when the only symptom was chronic cough, these tests were simply useless.

Interestingly, in 21 (36%) of patients with positive cultures, FOB revealed no visible airway changes. This result may lead to many different hypothetical conclusions. Barnes *et al.* suggest that these bacteria can be a contamination, colonization, or do not explain cough [9]. On the other hand, if found pathogens are the cause of cough, it is a significant argument for collecting samples for microbiological cultures during every single FOB in such a clinical indication.

Taken together, we and others suggest the appropriate balance between the risk and benefits of using FOB in the diagnostic process of chronic cough. Moreover, when a decision of performing FOB is undertaken, additional testing, such as microbiological cultures or BALf analysis should be considered on the case by case basis. The recently published study by Heching *et al.* showed a marked increase of the diagnostic yield by adding microbiological cultures and pathology analysis to the visual assessment [20]. The current update of "ERS guidelines on the diagnosis and treatment of chronic cough in adults and children" discuss a non-invasive alternative in the diagnosis management. The use of fractional exhaled nitric oxide (FeNO) in breath or blood eosinophilia have been proposed to assess airway eosinophilia, but the evidence is still very low [6].

Limitations

There are several limitations of our study which need to be considered. First of all, as a retrospective, single-institution study, it is saddled with all limitations associated with this type of data collection, including lack of data or other potential confounding factors. Furthermore, cultures were not performed in all studied subjects referred for FOB. Moreover, we do not know if positive cultures had any impact on how patients were treated, what was the outcome of treatment, and finally, if cultured microbes were the intrinsic

and sole cause of chronic cough. Furthermore, agents included in worksheets for categorizing bacteria found in our study differ from agents used by Magiorakos [14].

Conclusions

The present study results strengthen the evidence that FOB combined with additional testing of airway specimens obtained during FOB is not a powerful tool in the differential diagnosis of chronic cough and may be overused. The appropriate timing and decision regarding referral for FOB requires careful clinical consideration.

Acknowledgements

The authors want to express their gratefulness to all the employees of the Bronchoscopy Unit of the Department of Pneumology and Allergy and the Department of General and Oncological Pulmonology of Medical University of Lodz for their great contribution to this study. In particular we thank: Jerzy Marczak, Jadwiga Kroczyńska-Bednarek, Kamil Szyszow, Marek Zięba, Sylwia Kryczkowska-Krawczyk and Anna Lewandowska. Authors want also to thank Mr. Józef Sobczak for his contribution to this study.

Author contributions

Conception PS, JMD, AJB, WJP, design PS, JMD, WJP; drafting of the manuscript PS, JS, SM and WJP; acquisition of data PS, JS, ZK, KS analysis and interpretation of data PS, JS, SM, JMD, AJB, WJP, drafting the manuscript for important intellectual content all authors; all authors critically revised the manuscript and gave approval of the version to be published.

Funding

The costs of this study were defrayed from regular finances of the Department of Pneumology and Allergy of the Medical University of Lodz.

Conflict of interest

Authors declare no conflicts of interests related to this research.

References:

1. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet. 2008; 371(9621): 1364–1374, doi: 10.1016/S0140-6736(08)60595-4, indexed in Pubmed: 18424325.
2. Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. Chest. 1998; 114(2 Suppl Managing): 133S–181S, doi: 10.1378/chest.114.2_supplement.133s, indexed in Pubmed: 9725800.
3. Irwin R, Madison J. The diagnosis and treatment of cough. N Engl J Med. 2000; 343(23): 1715–1721, doi: 10.1056/nejm200012073432308, indexed in Pubmed: 11106722.
4. Hara J, Fujimura M, Ueda A, et al. Effect of pressure stress applied to the airway on cough-reflex sensitivity in Guinea pigs. Am J Respir Crit Care Med. 2008; 177(6): 585–592, doi: 10.1164/rccm.200703-457OC, indexed in Pubmed: 18187695.
5. Smyrnios NA, Irwin RS, Curley FJ, et al. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis. 1990; 141(3): 640–647, doi: 10.1164/ajrccm/141.3.640, indexed in Pubmed: 2178528.
6. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020; 55(1), doi: 10.1183/13993003.01136-2019, indexed in Pubmed: 31515408.
7. Benich JJ, Carek PJ. Evaluation of the patient with chronic cough. Am Fam Physician. 2011; 84(8): 887–892, indexed in Pubmed: 22010767.
8. Gasparini S. Indications for diagnostic bronchoscopy in adults. Monaldi Arch Chest Dis. 2011; 75(1): 24–31, doi: 10.4081/monaldi.2011.236, indexed in Pubmed: 21626989.
9. Barnes TW, Afessa B, Swanson KL, et al. The clinical utility of flexible bronchoscopy in the evaluation of chronic cough. Chest. 2004; 126(1): 268–272, doi: 10.1378/chest.126.1.268, indexed in Pubmed: 15249470.
10. Markowitz D, Irwin R. Is bronchoscopy overused in the evaluation of chronic cough? Journal of Bronchology. 1997; 4(4): 332–336, doi: 10.1097/00128594-199710000-00016.
11. Irwin R, Baumann M, Bolser D, et al. Diagnosis and management of cough executive summary. Chest. 2006; 129(1), doi: 10.1378/chest.129.1_suppl.1s.
12. Sen RP, Walsh TE. Fiberoptic bronchoscopy for refractory cough. Chest. 1991; 99(1): 33–35, doi: 10.1378/chest.99.1.33, indexed in Pubmed: 1984981.
13. Prakash UBS. Uncommon causes of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006; 129(1 Suppl): 206S–219S, doi: 10.1378/chest.129.1_suppl.206S, indexed in Pubmed: 16428713.
14. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012; 18(3): 268–281, doi: 10.1111/j.1469-0691.2011.03570.x, indexed in Pubmed: 21793988.
15. Sen R, Walsh T. Bronchoscopy enough or too much? Chest. 1989; 96(4): 710–712, doi: 10.1378/chest.96.4.710.
16. Lai K, Chen R, Peng W, et al. Non-asthmatic eosinophilic bronchitis and its relationship with asthma. Pulm Pharmacol Ther. 2017; 47: 66–71, doi: 10.1016/j.pupt.2017.07.002, indexed in Pubmed: 28687463.
17. Meyer KC, Raghu G, Baughman RP, et al. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med. 2012; 185(9): 1004–1014, doi: 10.1164/rccm.201202-0320ST, indexed in Pubmed: 22550210.
18. Mund E, Christensson B, Grönneberg R, et al. Noneosinophilic CD4 lymphocytic airway inflammation in menopausal women with chronic dry cough. Chest. 2005; 127(5): 1714–1721, doi: 10.1378/chest.127.5.1714, indexed in Pubmed: 15888851.
19. Heching M, Pertzov B, Rosengarten D, et al. Using bronchial biosies and cultures to imrove the diagnostic yield of bronchoscoy for chronic unexlained cough. B38 Issues in understing and managing cough. American Thoracic Society; 2018: A3195–A3195. doi:10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A3195. : A3195–A3195.
20. Heching M, Rosengarten D, Shitenberg D, et al. Bronchoscopy for chronic unexplained cough: use of biopsies and cultures increase diagnostic yield. J Bronchology Interv Pulmonol. 2020; 27(1): 30–35, doi: 10.1097/LBR.0000000000000629, indexed in Pubmed: 31651543.

Ahmed Taha[1], Tayseer Zaytoun[1], Hany Eid[1], Ayman Baess[2], Ehab Elreweny[1]

[1]Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, Egypt
[2]Department of Chest Diseases, Faculty of Medicine, Alexandria University, Egypt

Echocardiographic assessment of the right ventricle and its correlation with patient outcome in acute respiratory distress syndrome

Abstract

Introduction: Acute respiratory distress syndrome (ARDS) is a life-threatening chest disease associated with a poor outcome and increased mortality. It may lead to pulmonary hypertension and, eventually, right ventricular failure. These changes can be investigated by transthoracic echocardiography (TTE) which is considered a non-invasive and cost-effective modality. We studied the role of right ventricular function in the prediction of the severity and mortality in ARDS.

Material and methods: In this observational study, 94 patients suffering from ARDS were subjected to TTE to evaluate the parameters of right ventricular function by measuring tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area change (RV-FAC), myocardial performance index (Tei index), and systolic pulmonary artery pressure (SPAP) to assess their relation to the severity and mortality in ARDS.

Results: TAPSE, SPAP, Tei index, and RV-FAC showed significant differences between survivors and non-survivors after 30 days (all $p < 0.001$). An increased length of *intensive care unit* stay was significantly correlated with TAPSE, Tei index, and RV-FAC ($p = 0.002$, 0.007, and 0.013, respectively). Meanwhile, the length of mechanical ventilation days was significantly correlated with the Tei index only ($p < 0.001$). Multivariate regression analysis found that TAPSE and the Tei index were independent factors affecting mortality ($p = 0.004$, and 0.006, respectively). RV-FAC, with a cut-off point $\leq 57\%$, had the highest sensitivity, while TAPSE, with a cut-off point ≤ 17 mm, had the highest specificity to predict mortality.

Conclusions: Transthoracic echocardiographic parameters of the right ventricle could be used to predict severity and mortality in patients with ARDS with high sensitivity and specificity.

Key words: acute respiratory distress syndrome, transthoracic echocardiography, tricuspid annular plane systolic excursion, systolic pulmonary artery pressure, fractional area change

Adv Respir Med. 2020; 88: 412–419

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by hypoxemia, non-cardiac alveolar edema, and diminished lung compliance [1]. It varies in both incidence and outcome in the different healthcare facilities, but the incidence of ARDS was estimated to be between 1.5–79 cases per 100000 [2]. Death rates in ARDS are still significant despite management plans implemented by different health organizations; it was estimated to be between 35–45% according to an international observational study carried out in 50 countries [3].

Although ARDS has circulatory complications such as hypotension, decreased cardiac output, myocardial infarction, and arrhythmias, it mainly affects the right heart [4]. The pathological effect of ARDS on pulmonary vasculature was described more than 30 years ago by the term pulmonary vascular disease (PVD). This term delineates the functional and structural sequences affecting the pulmonary vasculature and the right ventricle (RV) in ARDS [5]. Patients

Address for correspondence: Ahmed Taha, Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, Egypt; e-mail: alexalexawy@gmail.com
DOI: 10.5603/ARM.a2020.0153
Received: 04.03.2020
Copyright © 2020 PTChP
ISSN 2451–4934

with PVD may progress to the severe form called acute cor pulmonale, which is classified as right ventricular dysfunction with a high mortality rate 60–70% [6].

Hypoxemia in ARDS is due to diffuse alveolar damage and pulmonary capillary endothelial damage leading to increased permeability of the alveolocapillary membrane and influx of exudate into the alveoli leading to diminished lung compliance [7]. Pulmonary hypertension in ARDS is developed by increased exudate in the alveoli, endothelial dysfunction with superimposed thrombosis in pulmonary capillaries, pulmonary vasoconstriction induced by hypoxemia to redistribute blood flow to ventilated alveoli and limit ventilation perfusion mismatch, and a high PEEP leading to alveolar distension and an increase in the resistance of pulmonary vasculature [8–10]. All these changes lead to right ventricular failure [11].

Pulmonary vascular diseases and right-sided heart failure could be assessed by invasive and noninvasive maneuvers. Most of the research about the function of the RV used invasive techniques such as pulmonary artery catheterization and transesophageal echocardiography (TEE) [12, 13]. However, due to the limited use and availability of these maneuvers in the management of ARDS across most intensive care units (ICUs), a more available screening modality to evaluate the function of the RV in ARDS is needed [14]. Transthoracic echocardiography (TTE) is a noninvasive and cost-effective method that can assess and monitor the right ventricular function [13].

Evaluation of the RV by TTE in ARDS could be done using indices such as systolic pulmonary artery pressure (SPAP), right ventricular fractional area change (RV-FAC), tricuspid annular plane systolic excursion (TAPSE), and myocardial performance index (MPI, Tei index) [15].

Our study aimed to identify the role of right ventricular function using TTE in predicting the mortality in ARDS.

Materials and methods

Patients

We studied 94 adult patients with ARDS criteria according to the Berlin definition. They were admitted between January 2018 and March 2019 to the Critical Care Medicine Department in Alexandria Main University Hospital. All patients were on invasive mechanical ventilation. We excluded patients who were less than 18 years old, had significant mitral or aortic stenosis and/or insufficiency, congestive heart failure, any lung disease that may affect the right ventricular function and pressure such as interstitial lung diseases and COPD, a poor echocardiographic window, and patients with tricuspid regurgitation. All patients meeting the inclusion and exclusion criteria were enrolled in our study. Informed consent was taken from the next of kin before conducting the study. The study was approved by the ethics committee of our institution.

Data collection

Patients included in the study were classified as survivors and non-survivors according to 30 day mortality. Demographic data, arterial blood gases (ABG) just before the echocardiographic exam, PaO_2/FiO_2 ratio, Acute Physiology and Chronic Health Evaluation II score (APACHE II), ventilatory data just before the echocardiographic exam (PEEP, plateau pressure, driving pressure), days of mechanical ventilation (MV), and length of intensive care unit (ICU) stay were analyzed between both groups. Furthermore, TTE was done within 48 hours of ARDS diagnosis to assess the right ventricular function parameters which included TAPSE, SPAP, Tei index, and RV-FAC.

Transthoracic echocardiographic data

The following right ventricular function parameters were recorded and measured using the American society of echocardiography 2010 guidelines for right heart assessment in adults [15]:

1. Tricuspid annular plane systolic excursion (TAPSE) was obtained by placing the cursor of M-mode at the lateral border of the tricuspid annulus and calculating the annulus motion longitudinally at peak systole.
2. Right ventricular fractional area change (RV-FAC) was obtained by making a trace along the endocardium of the RV in both relaxation and contraction phases starting at the annulus, passing through apex, and ending back at the annulus in a four chamber view. FAC is calculated as (end diastolic area – end systolic area) × 100/(end diastolic area).
3. Systolic pulmonary artery pressure (SPAP) can be estimated only in the presence of tricuspid regurgitation. The doppler signal of tricuspid regurgitation was estimated by placing the continuous wave doppler line in line with the tricuspid regurgitation jet. SPAP is calculated using the Bernoulli equation [4 $(V)^2$ + right atrial pressure] where V is the velocity of the tricuspid regurgitation jet (in meters per second), and the right atrial

pressure is obtained from central venous pressure (CVP).

4. Myocardial performance index (MPI; Tei index): Tei index is the sum of the isovolumic contraction and the isovolumic relaxation time divided by ejection time, or [(IVRT + IVCT)/ET]. For calculation of the Tei index, a pulsed tissue doppler cursor was placed along lateral margin of the tricuspid valve annulus.

Statistical analysis

Mean differences of age, pH, PaO_2/FiO_2 ratio, $PaCO_2$, serum bicarbonate (HCO_3), plateau pressures, PEEP, driving pressures, APACHE II score, TAPSE, RV-FAC, Tei index, and SPAP between survivors and non-survivors were analyzed using the Student t-test. Days of mechanical ventilation and length of ICU stay were analyzed using the Mann Whitney test. The Chi-square test was used to compare between sex, comorbidities, and ARDS classification (mild-moderate-severe) in both groups. The correlation between (TAPSE, RV-FAC, Tei index, SPAP) and (PaO_2/FiO_2 ratio, MV days, length of ICU stay) was evaluated using Pearson coefficients. The multivariate logistic regression model was used to assess the effect of covariates on mortality. Agreement (sensitivity, specificity) for PaO_2/FiO_2 ratio, APACHE II score, and echocardiographic right ventricular parameters were calculated to predict mortality. The results were analyzed using the IBM SPSS software package (version 20.0). Sample size calculation was done by the Community Medicine Department in our institution using Epi 7 software for sample size calculation. It was based on a 30% reported mortality rate among ICU-admitted ARDS patients [16] in the Alexandria Main University Hospital which has an average admission of 120 patients every 6 months (based on ICUs statistics). The minimum sample size required to achieve 80% study power and 95% confidence limits was 87 patients.

Results

Patients were classified into 2 groups, survivors (34 patients, 36.2%) and non-survivors (60 patients, 63.8%) according to 30 day mortality. With regards to demographic data, there was a significant difference between both groups regarding age; survivors were younger than non-survivors ($p = 0.045$). The same, however, was not true with regards to sex and the cause of ARDS ($p = 0.092$, 0.261 respectively). The arterial blood gases significantly differed between both groups with survivors having a higher pH ($p < 0.001$), a lower $PaCO_2$ ($p < 0.001$), and a lower HCO_3 ($p = 0.013$) as compared to non-survivors. The PaO_2/FiO_2 ratio was significantly lower in the non-survivor group compared with the survivor group ($p = 0.006$). There was a significant difference between the two groups in terms of ARDS classification ($p = 0.025$) and APACHE II score as it was lower in survivors than non-survivors ($p < 0.001$) (Table 1).

Regarding the ventilatory parameters in both groups, there were a significant difference with regards to PEEP and plateau and driving pressures ($p < 0.001$). Survivors had lower days of mechanical ventilation compared to non-survivors (3.0 *vs* 7.5 days, respectively; $p = 0.001$). Also, survivors had a lower length of ICU stay in comparison to non-survivors (5.0 *vs* 8.0 days, respectively; $p = 0.001$) (Table 1).

Regarding the right ventricular function parameters survivors had a higher RV-FAC compared to non-survivors (57.91 ± 12.89 *vs* 41.88 ± 11.70%, respectively; $p < 0.001$). TAPSE was significantly higher in survivors in comparison to non-survivors (20.91 ± 3.79 *vs* 14.12 ± 3.22 mm, respectively; $p < 0.001$). Survivors had a lower SPAP than non-survivors (46.76 ± 6.73 *vs* 54.65 ± 7.25 mm Hg, respectively; $p < 0.001$). Also, survivors had a lower Tei index compared to non-survivors (45.15 ± 4.48 *vs* 51.67 ± 5.02, respectively; $p < 0.001$) (Table 1).

The right ventricular function parameters were analyzed according to their correlation with the severity of ARDS in terms of PaO_2/FiO_2 ratio, days of mechanical ventilation, and length of ICU stay. PaO_2/FiO_2 ratio and length of ICU stay were significantly correlated with RV-FAC, Tei index, and TAPSE, while the length of mechanical ventilation days was significantly correlated with the Tei index only (Table 2).

The association of the echocardiographic parameters of the right ventricle with mortality was further assessed with a logistic regression model using age, PaO_2/FiO_2 ratio, PEEP, RV-FAC, SPAP, Tei index, and TAPSE. Univariate analysis revealed that age, PaO_2/FiO_2 ratio, PEEP, RV-FAC, SPAP, Tei index, and TAPSE were associated with increased hospital mortality in ARDS. Multivariate regression was analyzed to determine which parameters were independently related to mortality and revealed that TAPSE ($p = 0.004$), Tei index ($p = 0.006$), and PEEP ($p = 0.036$) were independently associated with mortality (Table 3).

The ROC curve was used to test the right ventricular function parameters, PaO_2/FiO_2 ratio, and APACHE II score to predict mortality as shown

Table 1. Comparison between survivors and non-survivors of ARDS regarding baseline characteristics and right ventricular function parameters

Characteristics	Survivors (n = 34)	Non-survivors (n = 60)	P value
Age[years] (mean ± SD)	50.88 ± 14.99	57.2 ± 13.28	**0.045**
Sex [n%]			0.092
Male	22(64.7)	28(46.7)	
Female	12(35.3)	32(53.3)	
Cause of ARDS [n%]			0.261
Pulmonary causes			
Pneumonia	18 (52.9)	32 (53.3)	
Lung contusions	10 (29.4)	13 (21.7)	
Drowning	6 (17.6)	9 (15)	
Extra pulmonary causes			
Pancreatitis	0 (0)	3 (5)	
Intra-abdominal sepsis	0 (0)	2(3.3)	
Postoperative	0 (0)	1 (1.6)	
Diabetes mellitus [n%]	5 (14.7)	10 (16.6)	0.803
Hypertension [n%]	2 (5.8)	3 (5)	^{FE}p=1.00
Chronic kidney disease [n%]	3 (8.8)	6 (10)	^{FE}p=1.00
Liver failure [n%]	1(2.9)	2(3.3)	^{FE}p=1.00
Shock [n%]	4 (11.8)	9 (15)	^{FE}p=1.00
APACHE II (mean ± SD)	14.76 ± 4.60	42.57 ± 12.22	**< 0.001**
PaO_2/FiO_2 ratio (mean ± SD)	150.0 ± 42.69	123.1 ± 46.19	**0.006**
ARDS classification [n%]			**0.025**
Mild	5 (14.7)	7 (11.7)	
Moderate	26 (76.5)	33 (55.0)	
Severe	3 (8.8)	20 (33.3)	
pH (mean ± SD)	7.43 ± 0.04	7.30 ± 0.05	**< 0.001**
$PaCO_2$ [mm Hg] (mean ± SD)	32.62 ± 3.03	47.52 ± 6.29	**< 0.001**
HCO_3 [mEq/L] (mean ± SD)	22.79 ± 2.28	23.83 ± 1.66	**0.013**
Plateau pressure [cmH_2O] (mean ± SD)	27.06 ± 5.67	34.03 ± 4.03	**< 0.001**
PEEP [cmH_2O] (mean ± SD)	12.18 ± 2.70	14.43 ± 2.34	**< 0.001**
Driving pressure [cmH_2O] (mean ± SD)	14.68 ± 4.92	19.52 ± 4.40	**< 0.001**
Days of MV min.–max. (median)	1.0 – 9.0 (3)	1.0 – 10.0 (7.5)	**0.001**
Length of ICU stay min.–max. (median)	3.0 – 11.0 (5)	3.0 – 10.0 (8)	**0.001**
RV-FAC [%] (mean ± SD)	57.91 ± 12.89	41.88 ± 11.70	**< 0.001**
SPAP [mm Hg] (mean ± SD)	46.76 ± 6.73	54.65 ± 7.25	**< 0.001**
Tei index (MPI) (mean ± SD)	45.15 ± 4.48	51.67 ± 5.02	**< 0.001**
TAPSE [mm] (mean ± SD)	20.91 ± 3.79	14.12 ± 3.22	**< 0.001**

P: p value for comparing between the two studied groups, statistically significant at $p \leq 0.05$ (Boldface type).
APACHE II — Acute Physiology Age Chronic Health Evaluation II; ARDS — acute respiratory distress syndrome; HCO_3 — serum bicarbonate; MV — mechanical ventilation; $PaCO_2$ — partial pressure of carbon dioxide; PEEP — positive end expiratory pressure; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; Tei index (MPI) — myocardial performance index

in Figure 1. It became clear that the APACHE II score with a cutoff point < 24 had the highest sensitivity and specificity to predict mortality in ARDS (AUC 0.984; 95% CI 0.959–1.009) with p < 0.001. Regarding right ventricular function parameters, we found that RV-FAC with a cutoff point ≤ 57% had the highest sensitivity to predict mortality (AUC 0.825; 95% CI 0.732–0.918) with p < 0.001, followed by Tei index with a cutoff point > 47 (AUC 0.844; 95% CI 0.765–0.922) with

Table 2. Correlation between right ventricular function parameters with PaO_2/FiO_2 ratio, mechanical ventilation days, and length of ICU stay

Parameters of right ventricular function	PaO_2/FiO_2 ratio		Mechanical ventilation days		Length of ICU stay	
	r	p	r	p	r	p
RV-FAC	0.292	**0.004**	-0.083	0.427	-0.255	**0.013**
SPAP	-0.146	0.160	0.048	0.643	0.117	0.260
Tei index (MPI)	-0.256	**0.013**	0.424	**< 0.001**	0.274	**0.007**
TAPSE	0.232	**0.025**	-0.182	0.079	-0.309	**0.002**

R: Pearson coefficient, statistically significant at $p \leq 0.05$ (Boldface type).
ICU — intensive care unit; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; Tei index (MPI) — myocardial performance index

Table 3. Univariate and multivariate analysis of the parameters affecting mortality

	Univariate		Multivariate	
	P	OR (95%CI)	p	OR (95%CI)
PaO_2/FiO_2 ratio	**0.009**	0.987 (0.978–0.997)	0.966	1.001 (0.974–1.028)
PEEP	**< 0.001**	1.436 (1.180–1.748)	**0.036**	2.030 (1.047–3.935)
RV-FAC	**< 0.001**	0.901 (0.862–0.942)	0.138	0.892 (0.767–1.037)
SPAP	**< 0.001**	1.180 (1.090–1.276)	0.054	1.424 (0.994–2.039)
Tei index (MPI)	**< 0.001**	1.31 (1.167–1.477)	**0.006**	1.796 (1.187–2.718)
TAPSE	**< 0.001**	0.631 (0.532–0.750)	**0.004**	0.396 (0.211–0.741)
Age	**0.041**	1.032 (1.001–1.065)	0.110	1.081 (0.983–1.189)

#: all variables with $p < 0.05$ was included in the multivariate, statistically significant at $p \leq 0.05$ (Boldface type).
CI — confidence interval; OR — odd's ratio; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; Tei index (MPI) — myocardial performance index

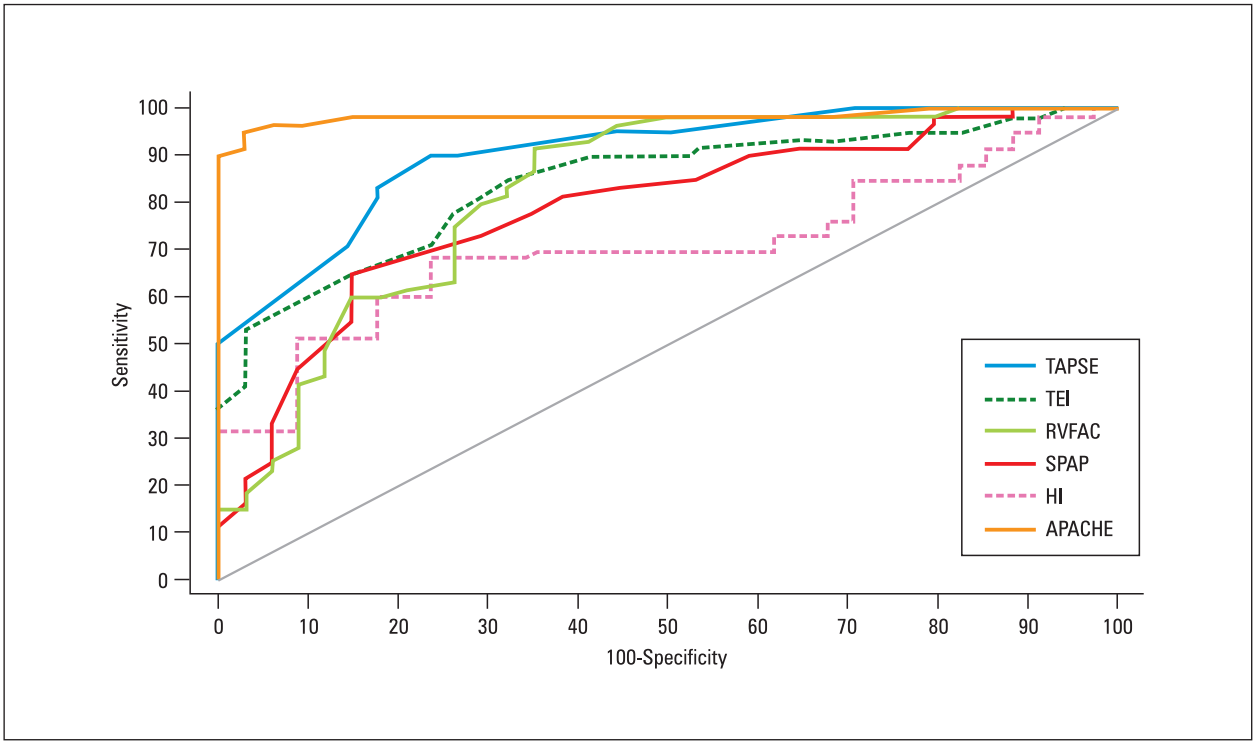

Figure 1. ROC curve for right ventricular function parameters, APACHE II score, and PaO_2/FiO_2 ratio (HI) to predict mortality in ARDS

Table 4. Agreement (sensitivity, specificity) for right ventricular function parameters, APACHE II score, and PaO2/FiO2 ratio to predict mortality in ARDS

	AUC	P	95% CI	Cut off	Sensitivity	Specificity	PPV	NPV
APACHE II	0.984	**< 0.001**	0.959–1.009	>24	95.00	97.06	98.3	91.7
TAPSE	0.904	**< 0.001**	0.844–0.964	≤ 17	83.33	82.35	89.3	73.7
Tei index	0.844	**< 0.001**	0.765–0.922	> 47	85.0	67.65	82.3	71.9
RV-FAC	0.825	**< 0.001**	0.732–0.918	≤ 57	91.67	64.71	82.1	81.5
SPAP	0.789	**< 0.001**	0.695–0.884	> 50	73.33	70.59	81.5	60.0
PaO_2/FiO_2 ratio	0.708	**0.001**	0.605–0.812	≤ 124	68.33	76.47	83.7	57.8

Statistically significant at p ≤ 0.05 (Boldface type).
APACHE II — Acute Physiology Age Chronic Health Evaluation II; ARDS — acute respiratory distress syndrome; AUC — area under a curve; CI — confidence Intervals; MPI — myocardial performance index; p value — probability value; RV-FAC — right ventricle fractional area change; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion;

$p < 0.001$. TAPSE, with a cutoff point ≤ 17 mm, was the most specific right ventricular function parameter to predict mortality (AUC 0.904; 95% CI 0.844–0.964) with $p < 0.001$, followed by SPAP with a cutoff point >50 mm Hg (AUC 0.789; 95% CI 0.695–0.884) with $p < 0.001$ (Table 4).

Discussion

Regarding demographic data of the patients, we found a significant difference between both groups with regards to age which was similar to the study by Balzer *et al*. who studied predictors of survival in ARDS [17].

In our study, ABG parameters differed significantly between both groups. In the study by Shah *et al.*, they found a significant difference only with regards to pH, which they explained as being a result of their small sample size which limited the ability of their study to reveal the differences among other parameters [18]. Similarly to our study, Osman *et al.*, who studied the prognosis of right ventricular failure in ARDS in a larger sample size than Shah *et al.*, found significant differences between both groups regarding pH and $PaCO_2$ [19].

We found significant differences between survivors and non-survivors with regards to PaO_2/FiO_2 ratio and APACHE II score. These results were also found in the studies completed by Shah *et al.* and Osman *et al.* [18–19]. Our results were similar to the LUNG SAFE study, which was performed in 459 ICUs in 50 countries, with regards to age, sex, etiology of ARDS, pH, and PaO_2/FiO_2 ratio [20].

In our study, we found significant differences between both studied groups regarding plateau, driving pressures, and PEEP. Claude Guerin *et al.*, who studied the driving pressure effect on mortality in ARDS patients, also found that plateau and driving pressures were significantly different between survivors and non-survivors [21]. Also, Amato *et al.* found that driving pressure was most strongly associated with survival [22]. However, that was not found in the study conducted by Shah *et al.* as they did not find any significant difference with regards to ventilatory parameters between the studied groups. Again, they explained this result as a drawback of their small sample size [18].

Regarding the indices of right ventricular function, our study showed that survivors and non-survivors differed significantly with regards to TAPSE, Tei index, RV-FAC, and SPAP. In 2 studies by Shah *et al.* and Wadia *et al.*, they found a significant difference between survivors and non-survivors with regards to TAPSE only. This may be due to the sample size of their studies and due to the fact that they did not assess the parameters in all patients due to a poor echocardiographic window which was part of the exclusion criteria in our study [18, 23]. In another study by Adi Aran *et al.* who evaluated the prognostic value of echocardiography in pediatric ARDS, they found a higher mortality rate in patients with right ventricular dysfunction defined by RV-FAC less than 45% [24].

Our study showed that the PaO_2/FiO_2 ratio significantly correlated with RV-FAC, Tei index, and TAPSE. This was a similar finding in the Adi Aran *et al.* study which found a significant correlation between PaO_2/FiO_2 ratio and TAPSE and Tei index, respectively [24]. Also, the significant correlation between PaO_2/Fi_{O2} ratio and RV-FAC was found in a meta-analysis by Justin Lee *et al.* who concluded that acute hypoxemia mostly

affects systolic function of the right ventricle, which is accurately estimated with RV-FAC [25]. Meanwhile, there was no significant correlation between PaO_2/FiO_2 ratio and SPAP, and this could be explained by the pathophysiology of hypoxemia-associated pulmonary hypertension which is caused by vascular remodeling rather than hypoxemia-induced arterial narrowing. This results in SPAP being elevated only after a significant period of time [26].

We found a significant correlation between the length of ICU stay with TAPSE and RV-FAC. Gajanana *et al.* studied the association between TAPSE and mortality in the ICU and found a correlation between a prolonged ICU stay and low TAPSE [27]. Also, Vallabhajosyula *et al.* found that a RV-FAC less than 35% was associated with a prolonged ICU stay in comparison with normal right ventricular function in septic patients [28]. Also, we found a significant correlation between the Tei index and the duration of mechanical ventilation. Similarly, El Ashmawy *et al.*, who studied the role of the Tei index in the prediction of weaning failure in COPD patients, found higher Tei index values in patients with failed weaning [29].

Multivariate regression analysis found that TAPSE, Tei index, and PEEP were significant independent factors of mortality. Shah *et al.* found that TAPSE was the only independent factor associated with mortality and this could be explained by their small sample size [19]. We tested agreement for the right ventricular function parameters to predict mortality and found that TAPSE < 17 mm had the highest specificity (82.35%), and that RV-FAC had the highest sensitivity (91.67%). In a study by Tamborini *et al.* involving 750 patients with various heart diseases, a TAPSE value of < 17 mm was highly specific for right ventricular dysfunction but had very low sensitivity [30]. Also, Shah *et al.* found that non-survivors had a TAPSE value of < 17 mm (upper limit of 95% confidence interval: 16.77 mm) [19].

Limitation of the study

Larger sample size studies are needed to increase the power of the study and limit the margin of error. Multicenter studies are needed to improve the external validity and support wide changes in practice.

Conclusions

Transthoracic echocardiographic parameters of the right ventricle could be used to predict mortality in patients with ARDS with high sensitivity and specificity.

Conflict of interest

The authors have declared no conflict of interest.

References:

1. Fanelli V, Vlachou A, Ghannadian S, et al. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thorac Dis. 2013; 5(3): 326–334, doi: 10.3978/j.issn.2072-1439.2013.04.05, indexed in Pubmed: 23825769.
2. Villar J, Martínez D, Mosteiro F, et al. An early PEEP/FIO2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2007; 176(8): 795–804, doi: 10.1164/rccm.200610-1534OC, indexed in Pubmed: 17585106.
3. Abe T, Madotto F, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016; 315(8): 788–800, doi: 10.1001/jama.2016.0291, indexed in Pubmed: 26903337.
4. Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. Am J Respir Crit Care Med. 2017; 195(3): 331–338, doi: 10.1164/rccm.201603-0645OC, indexed in Pubmed: 27513822.
5. Voelkel NF. Mechanisms of hypoxic pulmonary vasoconstriction. Am Rev Respir Dis. 1986; 133(6): 1186–1195, doi: 10.1164/arrd.1986.133.6.1186, indexed in Pubmed: 3334415.
6. Repessé X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. Chest. 2015; 147(1): 259–265, doi: 10.1378/chest.14-0877, indexed in Pubmed: 25560864.
7. Davey-Quinn A, Gedney JA, Whiteley SM, et al. Extravascular lung water and acute respiratory distress syndrome--oxygenation and outcome. Anaesth Intensive Care. 1999; 27(4): 357–362, doi: 10.1177/0310057X9902700404, indexed in Pubmed: 10470388.
8. Squara P, Dhainaut JF, Artigas A, et al. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. Intensive Care Med. 1998; 24(10): 1018–1028, doi: 10.1007/s001340050710, indexed in Pubmed: 9840234.
9. Zapol WM, Snider MT, Zapol WM, et al. Vascular obstruction causes pulmonary hypertension in severe acute respiratory failure. Chest. 1977; 71(2 suppl): 306–307, doi: 10.1378/chest.71.2_supplement.306, indexed in Pubmed: 836381.
10. Price LC, McAuley DF, Marino PS, et al. Pathophysiology of pulmonary hypertension in acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2012; 302(9): L803–L815, doi: 10.1152/ajplung.00355.2011, indexed in Pubmed: 22246001.
11. Matthay MA, Kallet RH, Kallet RH, et al. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. Respir Care. 2004; 49(9): 1008–1014, indexed in Pubmed: 15329171.
12. Stevens K, McCabe C, Jones C, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005; 366(9484): 472–477, doi: 10.1016/S0140-6736(05)67061-4, indexed in Pubmed: 16084255.
13. Cepkova M, Kapur V, Ren X, et al. Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. Chest. 2007; 132(3): 836–842, doi: 10.1378/chest.07-0409, indexed in Pubmed: 17573490.
14. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. Intensive Care Med. 2013; 39(10): 1725–1733, doi: 10.1007/s00134-013-2941-9, indexed in Pubmed: 23673401.

15. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685–713; quiz 786, doi: 10.1016/j.echo.2010.05.010, indexed in Pubmed: 20620859.
16. M. Zabmon, J-L. Vincer. Mortality rate for patients with acute lung injury/ARDS have decreased over time. Chest . 2008; 133(5): 1120–1127.
17. Balzer F, Menk M, Ziegler J, et al. Predictors of survival in critically ill patients with acute respiratory distress syndrome (ARDS): an observational study. BMC Anesthesiol. 2016; 16(1): 108, doi: 10.1186/s12871-016-0272-4, indexed in Pubmed: 27821065.
18. Shah TG, Wadia SK, Kovach J, et al. Echocardiographic parameters of right ventricular function predict mortality in acute respiratory distress syndrome: a pilot study. Pulm Circ. 2016; 6(2): 155–160, doi: 10.1086/685549, indexed in Pubmed: 27252840.
19. Osman D, Monnet X, Castelain V, et al. Incidence and prognostic value of right ventricular failure in acute respiratory distress syndrome. Intensive Care Med. 2009; 35(1): 69–76, doi: 10.1007/s00134-008-1307-1, indexed in Pubmed: 18839137.
20. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med. 2016; 42(12): 1865–1876, doi: 10.1007/s00134-016-4571-5, indexed in Pubmed: 27757516.
21. Guérin C, Papazian L, Reignier J, et al. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care. 2016; 20(1): 384, doi: 10.1186/s13054-016-1556-2, indexed in Pubmed: 27894328.
22. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015; 372(8): 747–755, doi: 10.1056/NEJMsa1410639, indexed in Pubmed: 25693014.
23. Wadia SK, Shah TG, Hedstrom G, et al. Early detection of right ventricular dysfunction using transthoracic echocardiography in ARDS: a more objective approach. Echocardiography. 2016; 33(12): 1874–1879, doi: 10.1111/echo.13350, indexed in Pubmed: 27558525.
24. Aran Ad, Joseph M, Lorenzo C, et al. Shivanand. The clinical role and prognostic value of echocardiography in pediatric ARDS: a retrospective study. Critical Care Medicine. 2018; 46(1): 100.
25. Lee JZ, Low SW, Pasha AK, et al. Comparison of tricuspid annular plane systolic excursion with fractional area change for the evaluation of right ventricular systolic function: a meta-analysis. Open Heart. 2018; 5(1): e000667, doi: 10.1136/openhrt-2017-000667, indexed in Pubmed: 29387425.
26. Enson Y, Giuntini C, Lewis C, et al. The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest. 1964; 43: 1146–1162, doi: 10.1172/JCI104999, indexed in Pubmed: 14171792.
27. Gajanana D, Seetha Rammohan H, Alli O, et al. Tricuspid annular plane systolic excursion and its association with mortality in critically ill patients. Echocardiography. 2015; 32(8): 1222–1227, doi: 10.1111/echo.12926, indexed in Pubmed: 25728401.
28. Vallabhajosyula S, Kumar M, Pandompatam G, et al. Prognostic impact of isolated right ventricular dysfunction in sepsis and septic shock: an 8-year historical cohort study. Ann Intensive Care. 2017; 7(1): 94, doi: 10.1186/s13613-017-0319-9, indexed in Pubmed: 28884343.
29. El-Ashmawy H, Helmy T, El-Awady S, et al. Tei Index versus Pro BNP as Predictors of Weaning Failure in Mechanically Ventilated Chronic Obstructive Pulmonary Disease Patients. Open Journal of Respiratory Diseases. 2015; 05(03): 63–69, doi: 10.4236/ojrd.2015.53007.
30. Tamborini G, Pepi M, Galli CA, et al. Feasibility and accuracy of a routine echocardiographic assessment of right ventricular function. Int J Cardiol. 2007; 115(1): 86–89, doi: 10.1016/j.ijcard.2006.01.017, indexed in Pubmed: 16750277.

Afroditi K Boutou[1], Katerina Manika[2, 3], Marija Hajimitrova[2], Georgia Pitsiou[4], Pinelopi Giannakopoulou[5], Evdokia Sourla[3, 4], Ioannis Kioumis[3, 4]

[1]Department of Respiratory Medicine, G Papanikolaou Hospital, Thessaloniki, Greece
[2]Department of Respiratory Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[3]Adult Cystic Fibrosis Unit, Aristotle University of Thessaloniki, Thessaloniki, Greece
[4]Department of Respiratory Failure, Aristotle University of Thessaloniki, Thessaloniki, Greece
[5]Department of Cardiology, G Papanikolaou Hospital, Thessaloniki, Greece

Longitudinal changes in exercise capacity among adult cystic fibrosis patients

Abstract

Introduction: Longitudinal data regarding changes in exercise capacity among adult cystic fibrosis (CF) patients are currently scarce. The aim of this brief report was to assess changes in exercise capacity among adult CF patients with stable and mild-to-moderate disease eight years after their initial evaluation.

Material and methods: Maximum cardiopulmonary exercise testing (CPET) was utilized. Other assessments included Doppler echocardiography, the 6-minute walking test, spirometry, and lung volume evaluation.

Results: Eleven (6 male, 5 female) patients completed both evaluations (initial and after eight years). During follow-up, indices of ventilatory impairment (such as ventilatory reserve; p=0.019, and ventilatory equivalent for carbon dioxide; p = 0.047) deteriorated significantly following a decline in respiratory function measurements. Peak oxygen uptake (VO_2), both as an absolute (26.6 ± 8.46 *vs* 23.89 ± 6.16 mL/kg/min; p = 0.098) and as a % of predicted value (71.21 ± 16.54 *vs* 70.60 ± 15.45; p = 0.872), did not deteriorate. This is also true for oxygen pulse (p = 0.743), left heart ejection fraction (p = 0.574), and pulmonary artery systolic pressure (p = 0.441). However, the anaerobic threshold, both as an absolute (p = 0.009) and as a % of predicted value (p = 0.047), was significantly lower during follow-up.

Conclusion: In adult CF patients with stable, mild-to-moderate disease, a peak VO_2 may be preserved for several years. However, even in these patients, deconditioning is present.

Adv Respir Med. 2020; 88: 420–423

Key words: cardiopulmonary exercise testing, peak oxygen uptake, anaerobic threshold, longitudinal study, adult cystic fibrosis patients

Introduction

Exercise impairment in patients with cystic fibrosis (CF) is well established and has been attributed to a variety of pulmonary and non-pulmonary factors [1]. Although several tests have been previously adopted to assess exercise capacity in this patient population, cardiopulmonary exercise testing (CPET) offers an integrative assessment of the pulmonary, cardiovascular, and skeletal muscle system responses during exercise [2]. Moreover, peak oxygen uptake (VO_2), which is assessed during maximum CPET, is related to quality of life and is a strong predictor of hospitalization and mortality in adult CF patients [3–6].

As CF is a progressive disease, exercise capacity may deteriorate in time following pulmonary and extra-pulmonary manifestations. However, data on longitudinal changes of peak VO_2 and other CPET variables in adult CF patients are currently scarce. In the few available studies, changes in CPET variables were followed up for 12–18 months [7, 8], a period probably not long enough for disease deterioration to manifest. Moreover, all available studies were conducted in children or adolescents [7, 8]. However, several

Address for correspondence: Afroditi K Boutou, Department of Pulmonary Medicine, G Papanikolaou Hospital, Thessaloniki, Greece; e-mail: afboutou@yahoo.com
DOI: 10.5603/ARM.a2020.0145
Received: 25.02.2020
Copyright © 2020 PTChP
ISSN 2451–4934

different, non-specific factors may complicate the pathophysiology of exercise limitation of the adolescent versus adult CF patient population (e.g. age of first CF presentation, effects of aging on cardiovascular function, different CPET approach, cautious caregiver that limits exercise participation, etc.) [3, 9]. Therefore, findings cannot be generalized. Under this scope, we conducted a pilot longitudinal study to assess the changes in peak VO_2, anaerobic threshold (AT), and other CPET variables eight years after initial evaluation in a population of adult CF patients with mild-to-moderate disease.

Materials and methods

Between September 2010 and June 2011, 17 adult CF patients prospectively underwent maximum CPET and Doppler echocardiogram; the details are published elsewhere [1]. From this initial population, all surviving adult CF patients who had not undergone lung transplantation, were not lost to follow-up, and gave informed consent for participation were re-assessed between October 2018 and September 2019. All participating patients were regularly attending the adult CF unit of a major chest hospital in Greece, were life-long non-smokers, and were in a stable condition. In case of an exacerbation during the baseline assessment, the patient was properly treated and re-entered the protocol after at least 3 months of disease stabilization. Patients who received long-term oxygen treatment or presented with any contraindications for CPET were excluded. Ethical approval for the study protocol was received from the G Papanikolaou Hospital Scientific Committee.

The study protocol consisted of two visits conducted within a frame of one week. During the first visit, all patients underwent spirometry, lung volume measurement, and a 6-minute walking distance (6MWD) test. During the second visit, all patients underwent a transthoracic echocardiographic study (Philips medical system, Andover, MA, USA). Pulmonary artery systolic pressure (PASP), ejection fraction, and left and right heart dimensions were obtained by previously recommended techniques (10,11). Following this, all patients conducted a maximum CPET on a cycle ergometer. The exercise protocol required 2 minutes of unloaded pedaling with a ramp increase of work rate by 10-15 watts/minute until exhaustion followed by 3 minutes of recovery. The Borg dyspnea scale and the Borg Rate of Perceived exertion (RPE) were also recorded. Statistical analysis was conducted utilizing the SPSS, version 20 for Windows XP. The Shapiro-Wilk test was applied to assess whether the distribution of data was normal or not. The paired samples t-test or the Wilcoxon rank test were utilized for group comparisons based on the normality of distribution of values with a level of $p < 0.05$ considered significant.

Results

Eleven patients (6 male, 5 female) who suffered from mild-to-moderate disease completed both assessments (initial, and after eight years). Seven patients had a Medical Research Council (MRC) dyspnea scale rating of 0–1, 3 patients had a rating of 2, and only one patient had a rating of 3. Moreover, the number of annual CF exacerbations which required hospitalization and intravenous antibiotic treatment was also limited in most of the cases. Specifically, 9 patients had 0-1 such exacerbations annually and only two had ≥ 3. Compared to the initial assessment, respiratory function, evaluated by forced expiratory volume in 1 second (FEV_1), and total lung capacity (TLC) deteriorated. However, forced vital capacity (FVC) was similar during follow up (Table 1). The body mass index (BMI) of patients did not change longitudinally, while left heart function (as assessed by ejection fraction, $p = 0.574$) and systolic pulmonary artery pressure ($p = 0.441$) was also similar during follow-up.

Changes in the exercise capacity of these patients are also presented in Table 1. The follow-up 6MWD was significantly lower when compared with the initial one (605 ± 58.5 *vs* 513 ± 73.45; $p = 0.001$) and patients presented with more severe desaturation during the test. Maximum exercise capacity, as assessed by absolute peak VO_2 (26.6 ± 8.46 *vs* 23.89 ± 6.16; $p = 0.098$), % of predicted peak VO_2 (71.21 ± 16.54 *vs* 70.60 ± 15.45; $p = 0.872$), and % of predicted peak work rate (WR) (65.2 ± 13.63 *vs* 63.7 ± 15.09; $p = 0.559$) was below normal, but similar between the two evaluations. On the contrary, AT (both as an absolute and as a % of predicted values) was significantly lower during the second evaluation ($p = 0.009$ and $p = 0.048$, correspondingly). As for the rest of CPET parameters, the ventilatory equivalent for carbon dioxide at AT (VE/VCO_2@ AT) was higher ($p = 0.047$) and the ventilatory reserve by the end of the exercise was lower ($p = 0.019$) during follow-up, although it should be noted that peak minute ventilation (VE) did not differ between the two time periods. The oxygen pulse (peak VO_2/peak heart rate), Borg dyspnea,

Table 1. Longitudinal changes of anthropometrics, lung function, echocardiographic parameters and exercise capacity variables among adult CF patients

Parameters	Initial evaluation	Follow-up evaluation	p
Age [years]	27.2 (4.15)	34.63 (3.98)	<0.001
Body mass index [kg/m^2]	22.2 (2.65)	23.1 (3.65)	0.231
Forced expiratory volume in 1 second (FEV_1) % predicted	2.62 (1.17) 66.72 (21.7)	1.99 (0.81) 56.41 (19.14)	0.012 0.028
Forced vital capacity (FVC) % predicted	3.33 (1.1) 76.96 (18.17)	3.15 (1.06) 76.53 (21.1)	0.294 0.914
FEV_1/FVC	77.42 (18.87)	62.33 (13)	0.005
Total lung capacity [%predicted]	81.69 (14.71)	69.83 (14.25)	0.005
Ejection fraction [%]	66.6 (4.3)	66.4 (3.9)	0.574
Pulmonary artery systolic pressure [mm Hg]	24.18 (6.57)	24.72 (5.87)	0.441
6 minute walking distance [m]	605 (58.5)	513 (73.45)	0.001
SpO_2 rest* [%]	95 (4)*	95 (5)*	0.726**
SpO_2 nadir* (during 6 minute walking test) [%]	94 (15)*	92 (15)*	0.005**
Peak oxygen uptake mL/kg/min % predicted	 26.6 (8.46) 71.21 (16.54)	 23.89 (6.16) 70.60 (15.45)	 0.098 0.872
Anaerobic threshold mL/kg/min % predicted	 17.95 (5.09) 47.63 (10.58)	 14.12 (4.47) 41 (12.51)	 0.009 0.048
Peak work rate watts % predicted	 117.6 (40.2) 65.2 (13.63)	 101.1 (36) 63.7 (15.09)	 0.013 0.559
Borg dyspnea* (at peak VO_2)	3 (6)*	5 (8)*	0.347**
Borg RPE* (at peakVO_2)	4 (6)*	5 (5)*	0.354**
Peak VO_2/peak heart rate [% predicted]	83.94 (15.61)	82.13 (13.86)	0.743
VE/VCO_2@AT	31.2 (3.73)	33.6 (3.78)	0.047
Peak minute ventilation [lit]	60.89 (23.61)	63.19 (23.1)	0.483
Ventilatory reserve (MVV-peak VE) [lit]	40 (30.98)	16.7 (17.8)	0.019

All data are presented as mean (SD), unless otherwise indicated. *Median (range). **Wilcoxon rank test was utilised for group comparisons.
MVV — maximum voluntary ventilation; RPE — rate of perceived excursion; SpO_2 — pulse oxymeter oxygen saturation; VE/VCO_2@AT — ventilatory equivalent for carbon dioxide at anaerobic threshold; VE — minute ventilation; VO_2 — oxygen uptake

and Borg RPE scores were also similar during the two evaluations.

Discussion

Pulmonary, cardiac, metabolic, or peripheral muscle disorders may all negatively impact peak VO_2 [2]. Previous literature indicated that a peak VO_2 may be largely preserved in children and adolescents with mild CF [8, 9, 12]. In our study, VE/VCO_2 increased (indicating an increase in dead space ventilation) as was expected, and breathing reserve decreased during follow up. These abnormalities are frequently present among patients with CF even when peak VO_2 is preserved [7, 9] because they follow the pattern of typical respiratory function decline. Respiratory limitation is an important pathophysiological factor of dyspnea and exercise limitation in chronic respiratory diseases [13]. Nevertheless, correlations between exercise outcome parameters and FEV_1 and/or FVC are often weak or absent in CF patients [3, 8], which suggests that respiratory restriction might not always be the major cause of exercise limitation. Moreover, cardiac index is a strong predictor of exercise outcome during CPET in CF patients [14]. The fact that oxygen pulse (an index of cardiac output) along with echocardiographic indices of left heart function and pulmonary circulation did not deteriorate in our study may partially explain why peak VO_2 did not further decrease after eight years.

Contrary to peak VO_2, both the 6MWD and AT declined with time. The 6MWD test is considered a submaximal exercise test [15] so its decline cannot accurately reflect the maximal exercise capacity of the patients, but it associates well with most activities of daily living [15]. Moreover, the reduced AT, without signs of cardiovascular involvement, probably reflects the physical inactivity and deconditioning that has been frequently observed among CF patients [16, 17]. Exertional dyspnea, or the fear of it, combined with malnutrition, muscle cachexia, and disease exacerbations are only some of the causes [18].

Conclusion

In conclusion, in a population of CF patients with mild-to-moderate disease, the maximum exercise capacity did not decline further over 8 years. This is contrary to AT and 6MWD, which did decline. To our knowledge, no other study has yet provided data of such a long-term follow-up regarding CPET variables in this patient population. This study's findings are somewhat limited by the small number of participants and by the fact that only patients with mild-to-moderate disease, which remained relatively stable over the years, were analyzed. However, our study does make the point that, even in CF patients with long-term preserved peak VO_2, physical deconditioning may be present. As CF patients with higher aerobic fitness present with better quality of life and higher survival [17], one could hypothesize that comprehensive exercise programs with continuous training in the long-term might be an important adjunct to regular treatment, even for CF patients with milder disease.

Conflict of interest

None to declare for any of the authors.

References:

1. Manika K, Pitsiou GG, Boutou AK, et al. The impact of pulmonary arterial pressure on exercise capacity in mild-to-moderate cystic fibrosis: a case control study. Pulm Med. 2012; 2012: 252345, doi: 10.1155/2012/252345, indexed in Pubmed: 22900167.
2. Albouaini K, Egred M, Alahmar A, et al. Cardiopulmonary exercise testing and its application. Postgrad Med J. 2007; 83(985): 675–682, doi: 10.1136/hrt.2007.121558, indexed in Pubmed: 17989266.
3. Smith L, Reilly CC, MacBean V, et al. Physiological markers of exercise capacity and lung disease severity in cystic fibrosis. Respirology. 2017; 22(4): 714–720, doi: 10.1111/resp.12954, indexed in Pubmed: 27882640.
4. Nixon PA, Orenstein DM, Kelsey SF, et al. The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med. 1992; 327(25): 1785–1788, doi: 10.1056/NEJM199212173272504, indexed in Pubmed: 1435933.
5. de Jong W, Kaptein AA, van der Schans CP, et al. Quality of life in patients with cystic fibrosis. Pediatr Pulmonol. 1997; 23(2): 95–100, doi: 10.1002/(sici)1099-0496(199702)23:2<95::aid-ppul4>3.0.co;2-n, indexed in Pubmed: 9065946.
6. Pérez M, Groeneveld IF, Santana-Sosa E, et al. Aerobic fitness is associated with lower risk of hospitalization in children with cystic fibrosis. Pediatr Pulmonol. 2014; 49(7): 641–649, doi: 10.1002/ppul.22878, indexed in Pubmed: 24019231.
7. Hatziagorou E, Kampouras A, Avramidou V, et al. Exercise responses are related to structural lung damage in CF pulmonary disease. Pediatr Pulmonol. 2016; 51(9): 914–920, doi: 10.1002/ppul.23474, indexed in Pubmed: 27171573.
8. Weir E, Burns PD, Devenny A, et al. Cardiopulmonary exercise testing in children with cystic fibrosis: one centre's experience. Arch Dis Child. 2017; 102(5): 440–444, doi: 10.1136/archdischild-2016-310651, indexed in Pubmed: 27919886.
9. Bar-Yoseph R, Ilivitzki A, Cooper DM, et al. Exercise capacity in patients with cystic fibrosis vs. non-cystic fibrosis bronchiectasis. PLoS One. 2019; 14(6): e0217491, doi: 10.1371/journal.pone.0217491, indexed in Pubmed: 31194748.
10. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016; 37(1): 67–119.
11. Schiller NB. Two-dimensional echocardiographic determination of left ventricular volume, systolic function, and mass. Summary and discussion of the 1989 recommendations of the American Society of Echocardiography. Circulation. 1991; 84(3 Suppl): I280–I287, indexed in Pubmed: 1884497.
12. Van Iterson EH, Wheatley CM, Baker SE, et al. The coupling of peripheral blood pressure and ventilatory responses during exercise in young adults with cystic fibrosis. PLoS One. 2016; 11(12): e0168490, doi: 10.1371/journal.pone.0168490, indexed in Pubmed: 27997623.
13. Ferrazza AM, Martolini D, Valli G, et al. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. Respiration. 2009; 77(1): 3–17, doi: 10.1159/000186694, indexed in Pubmed: 19145106.
14. Van Iterson EH, Wheatley CM, Baker SE, et al. The relationship between cardiac hemodynamics and exercise tolerance in cystic fibrosis. Heart Lung. 2016; 45(3): 283–290, doi: 10.1016/j.hrtlng.2016.03.001, indexed in Pubmed: 27045901.
15. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166(1): 111–117, doi: 10.1164/ajrccm.166.1.at1102, indexed in Pubmed: 12091180.
16. Urquhart DS, Vendrusculo FM. Clinical interpretation of cardiopulmonary exercise testing in cystic fibrosis and implications for exercise counselling. Paediatr Respir Rev. 2017; 24: 72–78, doi: 10.1016/j.prrv.2015.09.009, indexed in Pubmed: 26515919.
17. Williams CA, Benden C, Stevens D, et al. Exercise training in children and adolescents with cystic fibrosis: theory into practice. Int J Pediatr . 2010; Published online 2010 Sep 19., doi: 10.1155/2010/670640, indexed in Pubmed: 670640.
18. Gea J, Casadevall C, Pascual S, et al. Respiratory diseases and muscle dysfunction. Expert Rev Respir Med. 2012; 6(1): 75–90, doi: 10.1586/ers.11.81, indexed in Pubmed: 22283581.

VIA MEDICA

REVIEW

Zbigniew Putowski, Marcelina Czok, Piotr S Liberski, Łukasz J Krzych

Chair and Department of Anaesthesiology and Intensive Care, Medical University of Silesia in Katowice, Poland

Basics of mechanical ventilation for non-anaesthetists. Part 1: Theoretical aspects

Abstract

The expanding number of chronic respiratory diseases and the new COVID-19 outbreak create an increasing demand for mechanical ventilation (MV). As MV is no longer limited to intensive care units (ICU) and operating rooms (OR), more clinicians should acquaint themselves with the principles of mechanical ventilation. To fully acknowledge contemporary concepts of MV, it is crucial to understand the elemental physiology and respiratory machine nuances. This paper addresses the latter issues and provides insight into ventilation modes and essential monitoring of MV.

Key words: mechanical ventilation, acute respiratory distress syndrome, mechanical ventilators, respiratory physiology, mechanical ventilation modes

Adv Respir Med. 2020; 88: 424–432

Introduction

The epidemic of childhood paralysis (poliomyelitis) in 1952 in Denmark was a breakthrough in the development of modern mechanical ventilation. Then, for the first time on a large scale, positive pressure ventilation was applied. Self-inflating bags (so-called Ambu) were used, thanks to which, the given respiratory volume was pressed into the lungs, significantly reducing the mortality of patients with severe acute respiratory failure. Although the procedure was poorly standardised and fraught with the risk of complications, the event itself revolutionised the approach to mechanical ventilation. Polish data demonstrate that more than 70% of patients hospitalised in intensive care units (ICU) require treatment with a ventilator [1]. All patients in operating theatres, undergoing general anaesthesia, also require mechanical ventilation with a ventilator built into the anaesthesia apparatus. In addition to applications within the ICU and operating theatre, there is an increasing incidence of diseases requiring periodic respiratotherapy at home, i.e., chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome.

Furthermore, due to the current COVID-19 pandemic, the number of people requiring mechanical ventilation is growing. The latest data regarding SARS-CoV-2 indicate that mechanical ventilation must be implemented in 56% of patients admitted to ICU [2], and a rapidly growing population of patients requiring ventilation may exceed the number of available intensive care facilities. Accordingly, basic knowledge about the ventilators and the rules for their operation should be propagated (Table 1).

Physiology and physics of breathing

The human respiratory system is designed to increase the dimensions of the chest and create negative pressure, which allows suction of the air through the mouth and nose (according to Boyle-Mariotte's law [4], with the increase in gas volume, its pressure decreases). Gas, therefore, travels through the bronchial tree and reaches the alveoli, levelling the pressure gradient between the lungs and the atmosphere. The sucked air takes part in gas exchange and then the chest returns to its primary state resulting in exhalation due to reversal of pressure — collapsing chest

Address for correspondence: Łukasz J Krzych, Chair and Department of Anaesthesiology and Intensive Care, Medical University of Silesia in Katowice, Poland; e-mail: l.krzych@wp.pl
DOI: 10.5603/ARM.a2020.0143
Received: 27.04.2020
Copyright © 2020 PTChP
ISSN 2451–4934

Table 1. Basic, non-surgical indications for mechanical ventilation [3]

Protection from the respiratory tract obstruction in patients with reduced level of consciousness (Glasgow coma scale ≤ 8 pkt)
Hypercapnic ($PaCO_2$ > 60 mm Hg) respiratory failure due to hypoventilation (respiratory muscles/respiratory tract / thoracic wall disorders)
Hypoxemic respiratory failure — SaO_2 < 90% during passive oxygen therapy, or PaO_2 < 60 mm Hg
Circulatory failure in which mechanical ventilation can reduce the oxygen cost of breathing

creates a positive pressure (in relation to atmospheric pressure) that throws the volume of air out the lungs into the atmosphere.

To breathe, the lungs must overcome a certain work of breathing (WOB), which is expressed as WOB [J] = V × p, where "V" is a volume of inhaled air, while "p" is the pressure produced (in case of physiological breath — vacuum) required to overcome resistance and perform inhalation.

The suction of air has to overcome two types of resistance. The first, representing 70% of the breathwork, is an elastic resistance (potential energy accumulated in elastic lung tissue), the second resistance, which represents about 30%, is the so-called non-elastic resistance (air resistance and viscosity resistance of gases). Calculations indicate that in one minute, at rest, breathing work of about 3 J is performed. In incapacitated people, due to increased respiratory propulsion, energy expenditure can increase to about 15 J/min [5]. Then the energy expenditure is already the maximum and the only way to improve the patient's condition is to use mechanical ventilation, which can reduce and even endure the need for any work by the patient.

The lungs, as well as the chest, have their compliance, which is expressed with the following formula: C [mL/cmH_2O] = V/p, where "C" is compliance, "V" is the volume of air and "P" is intra-alveolar pressure. Compliance shows the ability of the lungs to increase volume without a significant rise in alveolar pressure. The higher the "C", the greater the lung's ability to maintain low pressure [6]. Compliance is important since an increase in pulmonary pressure can lead to "barotrauma" (pressure lung damage). All ventilators have respiratory pressure sensors and, in case there is an unwanted increase, overpressure valves open, releasing excessive gas.

The sucked gas, flowing through the respiratory tract, encounters resistance from the walls of the trachea, larynx and bronchi. This resistance is expressed by the following formula:

R [cmH_2O/L/s] = 8 hl/Δpr^4, where "h" means the viscosity of the gas, "l" — pipe length, "r" — radius of the tube and "Δp" is a pressure gradient at the beginning and end of the tube (respiratory system). Resistance means the pressure gradient in the respiratory system that must be applied to trigger a specific airflow. The essential element of this formula is the radius of the respiratory tract — the smaller it is, the greater the resistance. In case of diseases that reduce the diameter of the respiratory tract (i.e., too narrow intubation tube, a tube filled with mucus), the ventilator must use higher pressures to provide the patient with adequate respiratory volume within the correct time. It should also be remembered that the mere use of an intubation tube (which has a lower diameter than physiological trachea) and the inspiratory arm of the ventilator (prolongation of the physiological respiratory tract) increases resistance in the ventilation system [6].

One of the most important parameters for ventilation is the pressure measured in the respiratory system at the end of the expiration. This is a crucial parameter for the effectiveness of mechanical ventilation. Often, as a result of a disease, an increase in the elastic forces of the lungs occurs and the alveoli collapse, worsening the efficacy of gas exchange. An example of such a disorder is acute respiratory distress syndrome (ARDS) or hyaline membrane disease in newborns, both associated with a deficiency of surfactant. Surfactant reduces the surface tension of the alveoli [6, 7], which is expressed by Laplace's law: σ [dyn/cm] = p × r / 2, where "σ" is surface tension, "p" is the pressure that pushes the walls of the alveoli, "r" — the radius of the alveoli. As a result of surfactant deficiency, surface tension increases, thus alveoli collapse. Artificial increase in the positive end-expiratory pressure (PEEP) applied by the ventilator allows to oppose the force collapsing the alveoli and thus maintaining the patency of the airways.

During mechanical ventilation, the anatomical dead space must be taken into consideration. Physiologically, conductive parts of the respiratory system (larynx, trachea and bronchi) do not participate in gas exchange. Hence a certain volume of sucked air remains unused. If a person inhales 500 mL of air, approximately 150 mL remains in the dead space [6]. A ventilator's pipe system enlarges this space, which is especially important during exhalation — if there is a significant expansion of a dead space, there may

be a situation in which a part of exhaled air will remain in artificial airways and the next breath will cause the remaining volume to be sucked again (to understand this fact, it may be worth imagining breathing underwater with excessively long tube). It is particularly important and poses a critical danger in ventilation of newborns, where the respiratory volumes are minimal. It should be remembered that anatomical respiratory tract and respiratory system of the ventilator, constituting a dead space, have compliance as well. This means that during ventilation with positive pressures, the respiratory tract expands, and therefore, the dead space increases. If we assume that the compliance of the dead space is 2 mL/1 cmH_2O, then with a positive pressure of 25 cmH_2O, the dead space will increase by as much as 50 mL [8].

Monitoring ventilation is not an easy task. One of its elements is the evaluation of the pressure-time curve (Figure 1A). Its analysis allows to understand how pressure behaves in the patient's respiratory system. The following figure illustrates a situation in which the ventilator is intended to push the given volume into the patient's respiratory system.

Point (1) illustrates the start of the inspiratory phase by the ventilator. A positive pressure is produced, which from point (1) to (2) takes on the curve a near-vertical form (rapidly increasing pressure), overcoming the resistance of the system. This is also due to the fact that the compliance of the ventilation tube (orotracheal, nasotracheal, tracheotomy) and the pipe system is very low. Then, the pressure increases with slightly less dynamics, which is due to the patient's respiratory tract compliance. It should be remembered that in people with increased respiratory resistance, e.g. in an asthma attack, increasing pressure will show higher values. At point (3), the peak pressure of the inhaled air is achieved (PIP, peak inspiratory pressure). Then the ventilator interrupts inhalation (but does not start expiration yet). The previously produced pressure suddenly drops (4), which is directly due to the compliance of the patient's lungs. Then this pressure slightly decreases to a value known as plateau pressure. If the patient's lungs had lower compliance than healthy ones, plateau pressure would show higher values. After that, the ventilator starts expiratory phase, leading to a drop in pressure to a point (6), where it is equated with the final exhaust pressure, which usually takes a positive value (PEEP), provided by a ventilator [9].

Construction of the ventilation system

In addition to the ventilator and electricity, the ventilation system includes a source of compressed gases, an inhaled arm, the patient's respiratory system and an expiratory arm (Figure 2).

Gas source for ventilator

Today's hospitals are equipped with central compressed gas source systems. They are the driving force behind artificial ventilation pneumatics. The ventilator is connected to two such tanks, one with oxygen (Figure 2 A1) and the other with air (Figure 2 A2). The pressure in the tanks is about 5 bar (5098 cmH_2O) [10]. This is very high pressure for the respiratory system, so the ventilator is also responsible for reducing pressure to tolerated values. Gases should be dry, free of water vapor. The connection to the gas tank, nevertheless, contains water traps to prevent water from entering the ventilatory system.

Ventilator

There are several types of ventilators. However, due to the capacity restrictions of the manuscript, the most commonly used type of respirator (pneumatic-electric) will be described [10]. Due to the additional structure variability of the device depending on the manufacturer, for easier understanding of the article, the Puritan-Bennet 840 ventilator® (used in our centre) was described as an example. Regardless of the ventilator model, the physical aspects of ventilation remain the same. As mentioned earlier, the gases from the tank must be subjected to pressure reduction. For this purpose, the ventilator has pressure regulators (Figure 2B) that precisely lower the pressure of gases to the optimal values for the functioning of the machine. Then the gases flow through the so-called flowmeters (Figure 2C). These are the devices operating on the principle of a pneumotachograph and use Hagen-Poiseuille law: $V\ [l/s] = \Delta p r^4 / 8\ hl$, where "V" means flow, "Δp" — pressure gradient at the beginning and end of the tube (system), "r" is the radius of the tube, "h" — the viscosity of the flowing liquid (gas) and "l" is the length of the tube.

The gas flows through the resistance pipes and creates the pressure gradient, which is measured by the pressure sensor. According to the formula above, a higher pressure gradient indicates a higher flow. Information from the pressure sensor, obtained by analysing the pressure force on the sensor membrane, is transmitted to the ventilator processor. Then, the gas goes to the so-called pro-

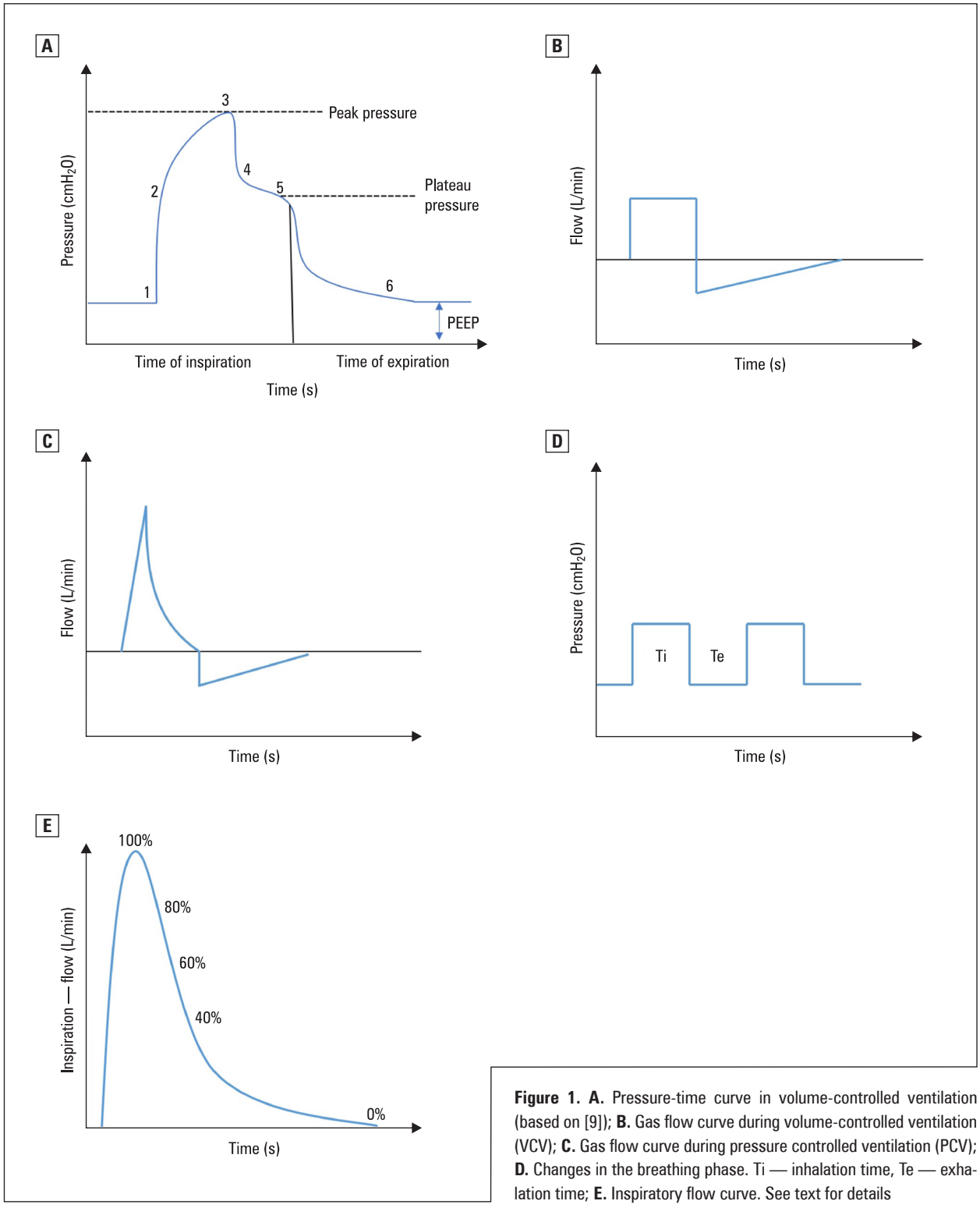

Figure 1. A. Pressure-time curve in volume-controlled ventilation (based on [9]); **B.** Gas flow curve during volume-controlled ventilation (VCV); **C.** Gas flow curve during pressure controlled ventilation (PCV); **D.** Changes in the breathing phase. Ti — inhalation time, Te — exhalation time; **E.** Inspiratory flow curve. See text for details

portional solenoid valve (Figure 2D), controlled by a ventilator processor. It can modify the volume flowing through the ventilator in a very accurate way. This structure is thus responsible for creating an adequate volume of gas to be found in the patient's respiratory system. The ventilator also has a safety overpressure valve (Figure 2E). In the event of an unwanted increase in the gas pressure in the ventilator system (usually a limit pressure of 100–120 cmH_2O), the valve (spring or electrically controlled) is unlocked and the gas from the ventilator is released. It is worth mentioning that this structure also provides the patient with access to atmospheric air, in case of a sudden loss of air in

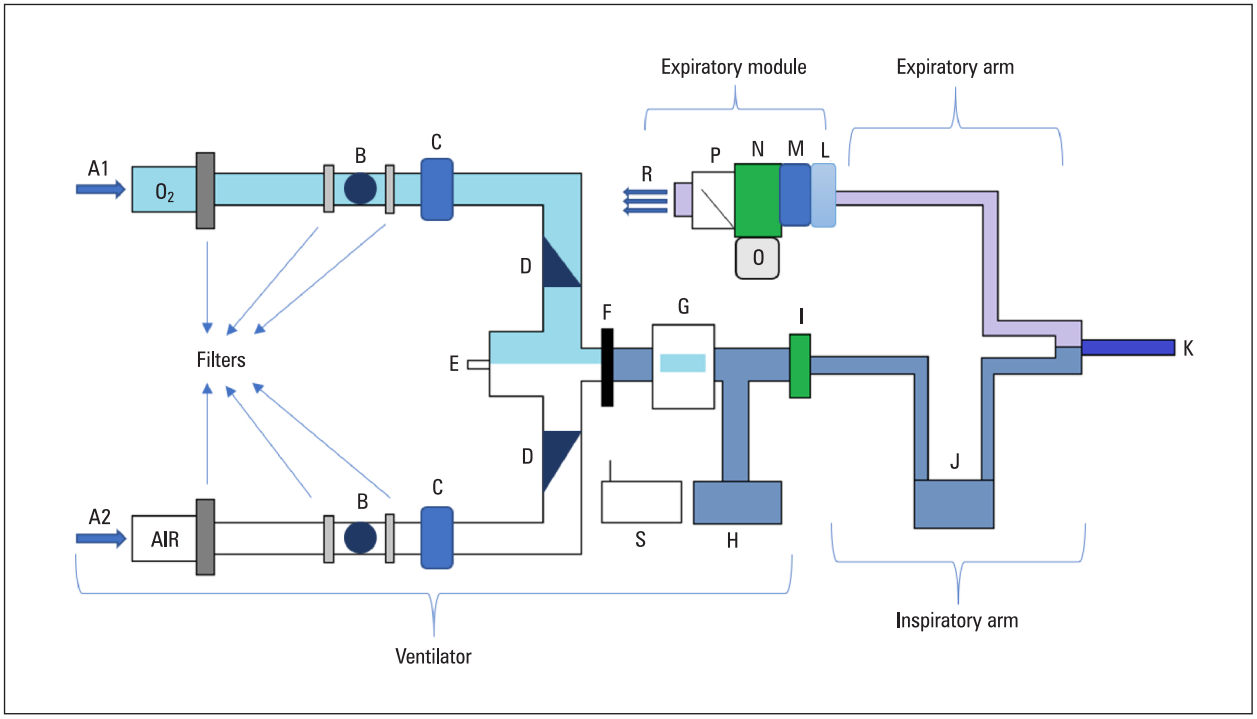

Figure 2. Ventilation system (based on [11])

the system (the patient can then take air from the environment with his own breath). Then, the oxygen and air merge in the system. Then the ventilator must measure the oxygen concentration in the inhaled mixture, which is done with a galvanic cell (Figure 2G). As a result of the chemical reaction (O_2 + KOH), a voltage correlated with oxygen concentration is formed. Depending on the patient's demand, the oxygen concentration in the mixture can range from 21% to 100%. A one-way valve (Figure 2F) is responsible for the direct supply of gases to the inspiratory arm. During inspiration, it opens, releasing a pre-prepared mixture. The pressure of such a compound is measured again by the pressure sensor (Figure 2H). The next, an essential and integral part of the ventilator is the atmospheric pressure sensor (Figure 2R), as all pressures recorded by the ventilator refer to the atmospheric pressure value. Therefore, if the recorded pressure in the respiratory system was 10 mm Hg, it was in fact 770 mm Hg (10 + 760 mm Hg). If for some reason, atmospheric pressure had fallen and the ventilator did not make a correction, then the applied pressures in the patient's respiratory system would be significantly higher, as it would still refer to the original atmospheric pressure. The problem of frequent and large changes in atmospheric pressures occurs, for example, in case of air transport of an intubated and mechanically ventilated patient [10–11].

Inspiratory arm

The inspiratory arm brings the air to the patient's respiratory system. There must be a filter (Figure 2I) between the ventilator and the arm. Although the gases delivered to the patient are free of microbes, if the aforementioned overpressure valve is used, there may be airflow in the opposite direction — from the patient to the ventilator, creating a threat of microbial contamination. Gases from hospital gas tanks are dry and have a lower temperature than body temperature. One of the functions of the human respiratory tract (especially the nose), is moisturising and warming the inhaled air. In ventilated patients, due to the use of intubation tubes or tracheostomy tubes, this element of the respiratory tract is omitted and unchanged air enters the lungs. The inhaled arm must, therefore, take over the function of warming and hydration. Air passes through the water chamber and heater (Figure 2J) (or heat and moisture exchanger, HME), where it gets saturated with water vapour. The air reaching the lungs should be moistened at a rate of 33 to 41 mg/L with a temperature of 34–41°C. Relative humidity should be 100%.

The warmed and moistened gas travels along with the system through the inhaled arm. Therefore, if it is not actively heated, the gas temperature will decrease in it, which means that the absolute humidity of the air will drop and steam

will begin to condense on the walls of the pipe. This carries the risk of increased resistance in the system. This is prevented by water traps, thanks to which the water flows into the reservoir, according to the force of gravity. Instead of water traps, active heating of the inhaled arm can be used. As a result, the moisture gas temperature will not drop, so the absolute humidity will remain identical to that created in the humidifier (a similar solution must be introduced in the expiratory arm). After passing through the inspiratory arm, the air flows into the intubation tube (Figure 2K) and then into the patient's lungs [8, 10–12].

Expiratory arm

After inhalation and gas exchange, exhalation time comes. The inspiratory valve closes, the expiratory valve opens and the breathing mixture flows through the expiratory arm. The air then enters the expiratory module, where it passes through the flowmeter (Figure 2L), the pressure sensor (Figure 2M), the filter (Figure 2N), the water trap (Figure 2O) and the expiratory valve (Figure 2P). The expiratory valve not only opens and closes to allow exhalation, but is also able to produce PEEP: thanks to the possibility of controlled, partial opening or closing, it increases expiratory resistance in the patient's respiratory system, creating the positive pressure at the end of the expiration (PEEP), and thus increasing the volume and pressure of gas in the alveoli. The gas mixture then leaves the ventilation system, getting into ambient air (Figure 2R) [8, 10, 11].

Basic variables and ventilation modes

Ventilation mode is the result of the variables described below, which together provide the most effective breathing for the patient. Unfortunately, to this day, there are no fully unified and standardised rules for naming the modes and as a rule, every company producing ventilators introduces its own nomenclature, which can be confusing for the novice user.

Control

"Control" refers to the way gas is delivered to the patient's lungs. There are two basic types of controls. The first is the volume-controlled ventilation (VCV) (Figure 1B) — a ventilator presses a fixed volume of air, regardless of the resulting pressure in the respiratory system (irrespective of compliance and resistance). The rigidly accepted respiratory volume carries a higher risk of lung damage (if the pressures in the patient's lungs were too high). The second way of control is pressure-controlled ventilation (PCV). Here, inverse to the volume-controlled, the ventilator determines the appropriate pressure to be applied in the respiratory tract during breath (Figure 1C). The volume of the pressed air will, therefore, reach the value based on the set pressure. This method allows for better cooperation between the actively breathing patient and the ventilator (the machine does not affect the respiratory volume directly). This means that the patient can partially control the inspiratory volume with his own efforts. Pressure control also compensates gas leakage in the ventilation system. If the intubation tube cuff is leaking, there is a risk of gas escaping from the lungs. In PCV, the ventilator will pursue adequate pressure in the respiratory system. In volume control, such leak carries the risk of an unnoticed decrease in ventilation [12]. The question which of the aforementioned types of control brings a better result of treatment, for now, remains unanswered. The results of a randomised study published by Chacko *et al.* in 2015 suggest that there is no significant difference in reducing patient mortality between described ventilation methods [14].

Breathing sequence

The breathing sequence is used to determine how the frequency of breathing is carried out. There are three basic types of breathing sequence: CMV (continuous mandatory ventilation), in which the doctor rigidly sets the strict number of breaths to be provided by the ventilator. This sequence does not give the patient the opportunity to initiate his own inspiration; IMV (intermittent mandatory ventilation), in which the doctor determines the frequency of breaths, however, the patient can initiate his own breath between mandatory breaths, which is recognised by the ventilator and assisted; and CSV (continuous spontaneous ventilation), in which every breath is initiated by the patient, while the ventilator acts only as a breath-support [15].

Control type

The type of control determines the target of the ventilation. If the VCV is carried out, then the goal may be a ventilation volume equal to 6 mL/kg of ideal body weight (IBW). This target is known as the set point. The ventilator will adjust the appropriate pressures in the system so that the volume set by the doctor is applied. There is also the auto set-point in which the ventilator decides what target to achieve at the

moment — e.g., in the volume-assured pressure support mode, ventilation starts with pressure control, and then completes the patient's inspiration by volume control to maintain a specific volumetric target of ventilation. In the Servo type, the ventilator recognises the patient's respiratory work and, depending on it, adjusts the degree of pressure or volume support to it. An example of such solution is the PAV mode (proportional assist ventilation) [16].

There are two additional types of controls that relate not only to a single inspiration, as the ones described above (PCV, VCV), but to the analysis of the previous breaths and then, subsequently, modify the parameters to the changing respiratory conditions. Thus, there is an adaptive type that analyses the resulting respiratory volume in the interval between breaths and then modifies the pressures so that at the next breath, it is as close as possible to the original assumption. The type of optimisation assumes the automatic adaptation of set-points to optimise respiratory work of the patient (WOB). Such solutions are used in adaptive support ventilation (ASV) mode [15].

Inhalation trigger

Pushing the air into the patient's lungs can be initiated in different ways (so-called trigger). The first, the easiest one is time triggering. This means that the ventilator initiates the breath itself in a certain time interval. If we set the breathing rate for 15 times per minute, that means the inspiration will be triggered by a ventilator every 4 seconds, with a given inspiration-to-expiration ratio. It is used in CMV mode. The second type is the pressure trigger — the patient, wanting to inhale the air, provokes a drop in pressure in the ventilation system. The ventilator, thanks to the presence of pressure sensors, recognises this phenomenon as an impulse to initiate a breath. While setting the pressure threshold to trigger inhalation, it should be remembered that it is not too low because of a risk of spontaneous, unintentional inducing the ventilator. The next, third way of triggering, is the flow trigger. It is the most popular type in spontaneous breathing modes. The ventilator recognises the moment to start the breath by the patient's attempt to inhale, but the sensors in this method are flowmeters, which identify the airflow [13].

Change of the respiratory phase (Figure 1D)

There are three most common methods for changing the phase of breathing. Time change means that a clinician can directly set the time needed for inspiration — for e.g., 3 seconds. After this time, the ventilator will automatically switch to an expiration mode. It is also possible to set the time ratio of inhalation to exhalation (I:E). If I:E is e.g., change 1:2, it means that for 20 breaths/min, breathing cycle would last 3 seconds (60/20) and the time spent on inhalation would be 1 second and 2 seconds for exhalation (thus, 1:2 ratio). Usually, I:E ratio of 1:2 is set [18]. However, it should be remembered that in patients with hyperinflation of the lungs (e.g. in patients with emphysema), the expiration period must be extended to remove the residual air more effectively [19]. On the other hand, with the increase in the number of breaths, usually above 20/minute, the duration of the expiration should be reduced to allow effective inspiration — usually I:E 1:1.5 or 1:1. Another type of phase change is flow change, which is usually used in pressure control. The ventilator changes the inspiration phase to expiration when the inhalation flow drops to a certain percentage value (Figure 1E) — usually 25% of maximal flow. The third way of changing the breathing cycle is the pressure phase, commonly used in volume control. When the maximum permitted pressure in the respiratory system is reached, the inhalation phase changes to expiration. This protects the patient's lungs from barotrauma [13].

The synthesis of these issues is presented in Table 2.

One of the most common modes used is the SIMV + PS — mandatory ventilation using volume control in a patient who does not initiate the breath himself. However, if the patient initiates his own breaths, the mode switches to the so-called Pressure Support (PS), in which breathing is carried out with pressure support. In this way, the patient is protected from central apnoea, but is also able to interfere in his breathing cycle, so the risk of dis-synchrony of the patient-ventilator is reduced [20]. A simple algorithm showing the selection of ventilation mode is shown in Figure 3.

Conclusions

At the root of mechanical ventilation are physical issues, without which it is impossible to understand the specifics of the work of the ventilator. Familiarisation with these considerations is the gateway to understanding the concurrent concepts of ventilation. Respiratotherapy includes the integration of many components, the most important of which is the patient. It is necessary to be aware of the limitations and dangers

Table 2. Examples of popular mechanical ventilation modes [14, self-modified]

Mode	Control	Mandatory breaths				Spontaneous breaths		
		Breathing sequence	Control type	Triggering	Phase change	Control type	Triggering	Phase change
VCV	Volume	CMV	Set-point	Time	Time	—	—	—
SIMV	Volume	IMV	Set-point	Time/flow	Time	Set-point	Pressure	Pressure
PS	Pressure	CSV	—	—	—	Set-point	Pressure	Pressure
CPAP	Pressure	CSV	—	—	—	Set-point	Pressure	Pressure
PAV	Pressure	CSV	—	—	—	Optimazation	Flow	Flow

CMV — continuous mandatory ventilation; CPAP — continuous positive airway pressure; CSV — continuous spontaneous ventilation; IMV — intermittent mechanical ventilation; PS — pressure support; PAV — proportional assisted ventilation; SIMV — synchronized intermittent mandatory ventilation; VCV — volume controlled ventilation;

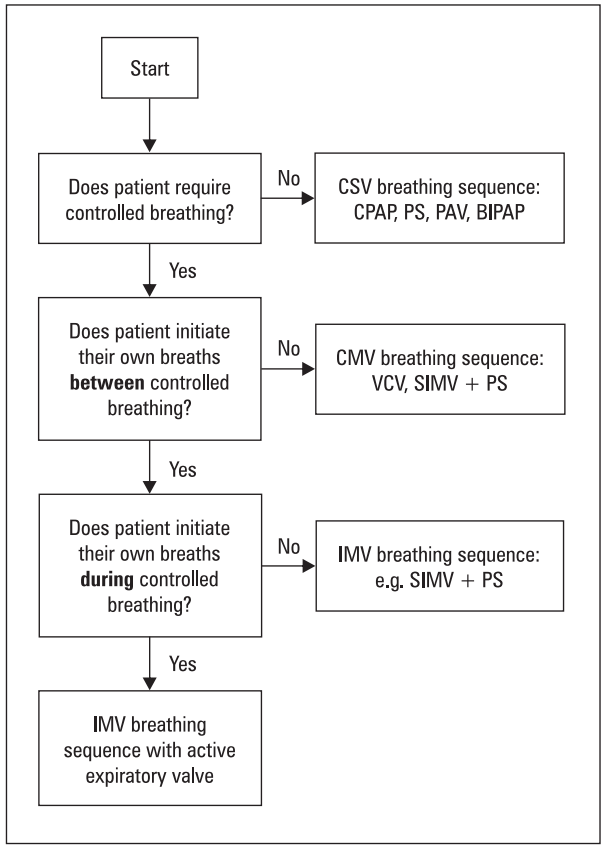

Figure 3. Algorithm of basic selection of ventilation mode [14, self-modification]. BIPAP — biphasic positive airway pressure; CMV — controlled mechanical ventilation; CPAP — continuous positive airway pressure; IMV — intermittent mechanical ventilation; PAV — proportional assist ventilation; PS — pressure support; SIMV + PS — synchronized intermittent mechanical ventilation + pressure support; VCV — volume controlled ventilation

arising from the use of positive pressures, which, despite being at odds with the physiological way of breathing, are now the most common method of sustaining human breathing.

Conflict of interest

None declared.

References:

1. Kübler A, Maciejewski D, Adamik B, et al. Mechanical ventilation in ICUs in Poland: a multi-center point-prevalence study. Med Sci Monit. 2013; 19: 424–429, doi: 10.12659/MSM.883930, indexed in Pubmed: 23727991.
2. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020; 8(5): 475–481, doi: 10.1016/s2213-2600(20)30079-5.
3. Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. Mayo Clin Proc. 2017; 92(9): 1382–1400, doi: 10.1016/j.mayocp.2017.05.004, indexed in Pubmed: 28870355.
4. Pilawski A, Puchalik M. Strukturalne właściwości materii, Podstawy biofizyki: podręcznik dla studentów medycyny. Pilawski A (ed.). PZWL, Warszawa 1985: 69–95.
5. Pilawski A. Biofizyka układu oddechowego, Podstawy biofizyki: podręcznik dla studentów medycyny. Pilawski A (ed.). PZWL, Warszawa 1985: 311–323.
6. Gutkowski P, Konturek S. Fizjologia oddychania, fizjologia człowieka. Podręcznik dla studentów medycyny. Konturek S (ed.). Elsevier Urban & Partner, Wrocław 2013: 235–303.
7. Halliday HL. The fascinating story of surfactant. J Paediatr Child Health. 2017; 53(4): 327–332, doi: 10.1111/jpc.13500, indexed in Pubmed: 28271629.
8. Yuan Lei. Budowa systemu wentylacyjnego, Respiratory. Przewodnik Kliniczny. Łazowski T (ed.). Makmed, Lublin: 2018, 65–97.
9. Rittner F. Curves and loops in mechanical vVentilation. Drager Technology for Life Dragerwerk AG and Co KGaA, Lubeck, 2015: 4–60.
10. Traczyk J. Budowa respiratora, wentylacja mechaniczna — teoria i praktyka. Maciejewski D, Wojnar-Gruszka K (ed.). α-medica press, Bielsko-Biała 2016: 61–117.
11. Service Manual Puritan Bennet 840 Ventilator System. Available online: www.medtronic.com/content/dam/covidien/library/us/en/product/acute-care-ventilation/PB840_Technical_Reference_Manual_EN_10067720D00.pdf. [Last acccessed at: 10.02.2020].
12. Yuan Lei. Nawilżanie, nebulizacja i filtrowanie gazów. Respiratory. Przewodnik Kliniczny. Łazowski T (ed.). Makmed, Lublin 2018: 101–133.
13. Yuan Lei. Podstawowe zmienne i typy oddechu. Respiratory. Przewodnik Kliniczny. Łazowski T (ed.). Makmed, Lublin 2018: 137–161.

14. Chacko B, Peter J, Tharyan P, et al. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Cochrane Database of Systematic Reviews. 2015, doi: 10.1002/14651858.cd008807.pub2.
15. Chatburn RL. Classification of ventilator modes: update and proposal for implementation. Respir Care. 2007; 52: 301–323.
16. Younes M. Proportional assist ventilation, a new approach to ventilatory support: theory. American Review of Respiratory Disease. 1992; 145(1): 114–120, doi: 10.1164/ajrccm/145.1.114.
17. Yuan Lei. Podstawowe zmienne i typy oddechu. Respiratory. Przewodnik Kliniczny. Łazowski T (ed.). Makmed, Lublin 2018: 137–161.
18. Park JHa, Lee JS, Lee JH, et al. Effect of the prolonged inspiratory to expiratory ratio on oxygenation and respiratory mechanics during surgical procedures. Medicine (Baltimore). 2016; 95(13): e3269, doi: 10.1097/MD.0000000000003269, indexed in Pubmed: 27043700.
19. Reddy RM, Guntupalli KK. Review of ventilatory techniques to optimize mechanical ventilation in acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2007; 2: 441–452.
20. Maciejewski D. Podstawowe tryby wentylacji mechanicznej. Wentylacja mechaniczna — teoria i praktyka. Maciejewski D, Wojnar-Gruszka K (ed.). α-medica press, Bielsko-Biała 2016, 154–193.

Askin Gulsen

Department of Pneumology, University of Lübeck, Lübeck, Germany

Bronchoscopic lung volume reduction using coil therapy: complications and management

Abstract

Nonsurgical approaches involving bronchoscopic lung volume reduction (BLVR) have been developed in the last decade. One of these, the BLVR coil procedure, is a treatment option for patients with homogeneous and heterogeneous end-stage emphysema and a forced expiratory volume in 1 second (FEV_1) of 15–45%. This treatment decreases hyperinflation and improves lung function, the quality of life, and exercise capacity. It is very important to prepare patients for treatment, premedications, anesthesia applications, intubation, post-procedure follow-up and treatments. Further, it has been observed that various complications can develop during and after the procedure. Generally, the observed and reported complications are chronic obstructive pulmonary disease (COPD) exacerbation, chest pain, mild bleeding, pneumonia, pneumothorax, and respiratory failure. Rarely, aspergillus cavitation (coil-related aspergilloma), bronchopleural fistula and penetration into the pleural space, bronchiectasis, coil-associated inflammatory response and opacities, and hiccups are observed. Common complications are usually mild or moderate, while the rare ones can be life-threatening (except hiccup), so early diagnosis and treatment are necessary. However, patients treated with BLVR have lower mortality rates than untreated patients with similar morbidity. Based on the findings of this review, we can estimate that premedication one day before and just before the procedure may reduce potential complications. Some medical centers apply and recommend 30-day macrolide treatment after the procedure. New generation supraglottic devices may be preferred to avoid complications due to endotracheal intubation. Moreover, further research is needed to identify risk factors, prevent potential complications, and a common consensus is required for routine preventive treatment.

Key words: bronchoscopic, lung volume reduction, coil, complication, management

Adv Respir Med. 2020; 88: 433–442

Introduction

Emphysema is a chronic lung disease that causes pulmonary parenchymal damage, hyperinflation, loss of elastic recoil, and progressive dyspnea [1]. In the last stage of emphysema, there is a marked decrease in exercise capacity and the quality of life, and a consequent restriction of daily activities. During this period, long-acting bronchodilators (β2-agonist and anti-muscarinic) and drugs (phosphodiesterase-4 inhibitors, methylxanthines, and mucolytic agents) are administered to reduce the severity of symptoms and frequency of exacerbations [2]. In addition, smoking cessation, education and self-management, nutritional support, and pulmonary physiotherapy are recommended from the early stages of the disease [2]. However, when respiratory failure develops after a few years, long-term oxygen therapy at home becomes necessary, and in cases of hypercapnia, non-invasive mechanical ventilation is added [3]. While medical treatment of emphysema does not impact long-term outcomes in clinical practice, invasive treatment can be administered to very few patients.

Lung transplantation is an option for patients with forced expiratory volume in 1 sec (FEV_1) < 15–20%, but it is often not feasible due to a lack of organ availability and the need for specially experienced hospital personnel and equipment [4]. Studies conducted over the last 10 years have reported that the removal of nonfunctional lung parenchyma by lung volume reduction surgery may increase pulmonary function and improve

Address for correspondence: Askin Gülsen, Department of Pneumology, University of Lübeck, Germany; e-mail: askingulsen@hotmail.com
DOI: 10.5603/ARM.a2020.0152
Received: 19.05.2020
Copyright © 2020 PTChP
ISSN 2451–4934

the quality of life in patients [5, 6]. The 2014 National Emphysema Therapy Examination Trial emphasized the importance of patient selection for this treatment owing to the high incidence of postoperative complications (pulmonary and non-pulmonary) and early mortality [6].

Therefore, nonsurgical approaches involving bronchoscopic lung volume reduction (BLVR) have been developed in the last decade. One of these, the BLVR coil procedure, is a treatment option for patients with homogeneous and heterogeneous end-stage emphysema and an FEV_1 of 15–45% [7, 8]. This treatment decreases hyperinflation and improves lung function, the quality of life, and exercise capacity. In a review covering the studies conducted in 2012–2018, BLVR coil therapy showed an increase in FEV_1 values (mean + 130 mL, 12.1%), a decrease in residual volume (RV) (mean -420 mL, 16.5%) and a rise in 6-minute walking test (mean + 47 m) [7]. However, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 guidelines limit BLVR interventions to patients with advanced emphysema refractory to optimized medical treatment [2]. Further, it has been observed that various complications can develop during and after the procedure [9].

To this end, the main objective of this review is to determine the incidence of complications associated with BLVR coil treatment, both during the procedure and the follow-up period; to analyze the possible risk factors; and to discuss potential treatment options.

Material and methods

Four international databases (Google Scholar, Web of Science, SCOPUS and PubMed) have been crawled using specified keywords to obtain appropriate articles: endoscopic or bronchoscopic, lung volume reduction, coil, complication, and case reports. The "Related articles" section in Google Scholar and PubMed was used to obtain related and similar papers. Original articles, case reports, and case series were included.

Features of the BLVR coil procedure

Preparation of patients for the procedure

Patient preparation is very important prior to BLVR coil treatment (Table 1). Before the procedure, patients must have quit smoking, received pulmonary physiotherapy for at least 6 months, and be under optimal medical treatment. Pre-procedure arterial oxygen partial pressure and carbon dioxide partial pressure must be > 50 mm Hg and < 55 mm Hg, respectively [9, 10]. It is essential to evaluate right ventricular function using transthoracic echocardiography prior to the BLVR procedure. Systolic pulmonary artery pressure > 50 mm Hg is considered a contraindication for BLVR coil therapy. The use of anticoagulants should also be considered as the BLVR coil procedure is contraindicated for patients on continuous treatment with anticoagulants, although there is no clear contraindication for those taking acetylsalicylic acid.

Table 1. Preparation of patients

1.	Determination of target lobe by HRCT and perfusion scintigraphy
2.	Ensuring optimum inhaler treatment
3.	Pulmonary physiotherapy (at least 6 months)
4.	Smoking cessation (at least 4–6 months in advance)
5.	Recommend pneumococcal and influenza vaccines
6.	Evaluation of sPAP by echocardiography
7.	Arterial blood gas analysis
8.	Evaluation of the use of anticoagulants
9.	Sputum culture
10.	Prophylactic treatment: antibiotic, corticosteroid, nebulizer

HRCT — high resolution computed tomography; sPAP — systolic pulmonary artery pressure

Premedication

Chronic obstructive pulmonary disease (COPD) exacerbation and pneumonia are the most common complications after the BLVR procedure [7]. In addition, acute inflammatory response to the procedure, and "coil-associated pneumonitis" have also been reported. Hence, many clinicians start corticosteroid (prednisolone 30 mg) and antibiotic (azithromycin 250 mg) prophylaxis in the preoperative period (1 day before) [10]. Corticosteroid treatment for 5 days and antibiotic therapy for 30 days after the procedure is recommended [10]. Despite insufficient supporting evidence in the literature, some BLVR treatment centers prefer β-lactam or macrolide use for 5–7 days postoperatively. In addition, some centers administer theophylline 200 mg, prednisolone 40 mg, levofloxacin 500 mg, and salbutamol/ipratropium nebulization 1 hour before BLVR [11].

Indication and protocol

The procedure is performed in patients with emphysema diagnosed by computed tomography who exhibit hyperinflated pulmonary functions [FEV_1: 15–45%, total lung capacity (TLC) > 100%, RV > 200%, and RV/TLC > 58%] [7, 9, 10]. Patients diagnosed with any other airway disease are not treated using this procedure. All coil implantations are performed using fi-

beroptic video bronchoscopy and fluoroscopic guidance. Ten standard (8–14 intervals) coils are implanted for each lung, and the second procedure is performed within 4–8 weeks. Patients without any complications are followed up in the hospital for an average of 1 day.

Anesthesia and intubation

Bronchoscopic lung volume reduction coil treatments are performed worldwide under general anesthesia. Generally, intubation with a 9-mm endotracheal tube and pressure-controlled ventilation at an inspiratory:expiratory ratio of 1:4 and respiratory frequency 10/min are preferred [10]. One study demonstrated I-gel supraglottic devices (SGD) (Intersurgical Ltd, Berkshire, UK) to be a safe alternative to endotracheal intubation in BLVR coil treatments [11]. I-gel SGD causes less bronchospasms, less mucosal/local trauma, and fewer hematomas than rigid bronchoscopy and endotracheal intubation, and the incidence of arytenoid dislocation is very low [12]. The size 8.5 of an endotracheal tube has a 57-mm cross-sectional area, while the new generation SGDs have a cross-sectional area of 127 mm [13]. This is very advantageous in that it makes the procedure easier and the complications of endotracheal intubation can be avoided.

Complications of endobronchial coil treatment

The complications of BLVR coil treatment can be divided into three groups based on when they occur: during the procedure, in the treatment recovery (TR) period (< 30 days), and within the follow-up phase (> 31 days). Complications in the TR and follow-up periods are summarized in Tables 2 and 3, respectively.

During the procedure

Previous work has documented procedure-related complications which include mild bleeding (13.3%), coil repositioning and lengthening of the procedure (10%), and termination of the procedure due to deterioration in hemodynamic parameters (2.0%) [14]. In the same study, 31.6% of patients had to undergo aspiration of bronchial secretion and 8.1% of them showed *Pseudomonas aeruginosa* colonization, the significance of which is not yet clear. In addition, bronchospasm, headache, hoarseness, paroxysmal atrial fibrillation, and phlebitis may develop due to anesthesia after BLVR coil treatment [15].

In the treatment recovery and follow-up periods

Various complications can be seen during the periods following the BLVR procedure. These include bleeding, chest pain, COPD exacerbation, pneumonia, pneumothorax, and respiratory failure. Treatment recommendations for these complications are given in Table 4.

Bleeding

The most common complication observed during the TR period is mild bleeding or hemoptysis. Studies report the observation of this compli-

Table 2. An overview of treatment recovery period (0 to 30 days) complications in principal studies

Author/study	Year	N	Baseline FEV_1 [L]	Baseline FEV_1 [%]	Hemoptysis	COPD exc.	Chest pain	Pneumonia	Pnx	Death
Slebos *et al.* [15]	2012	16	0.72 ± 0.16	28.7 ± 7.1	75.0	21.4	14.2	7.1	3.5	0.0
RESET study [16]	2013	23	0.72 ± 0.17	27.1 ± 8.0	0.0	5.0	—	5.0	5.0	0.0
Klooster *et al*. [17]	2014	10	0.58	22.0	25.0	15.0	30.0	0.0	5.0	0.0
Deslee *et al*. [18]	2014	60	0.83 ± 0.25	30.1 ± 6.3	53.9	13.0	24.3	9.5	3.4	0.0
Hartman *et al*. [19]	2014	38	—	27.0	74.0	—	—	—	5.2	—
Zoumot *et al*. [20]	2015	45	0.76 ± 0.20	28.3 ± 8.0	0.0	4.8	1.2	1.2	6.0	0.0
REVOLENS [21]	2016	50	0.75 ± 0.25	25.7 ± 7.5	2.0	8.0	2.0	10.0	6.0	2.0
RENEW [22]	2016	158	0.71 ± 0.20	25.7 ± 6.3	—	—	—	—	—	—
Gülsen *et al*. [14]	2017	40	0.68 ± 0.22	26.3 ± 9.1	10.0	—	25.0	—	—	0.0
Kontogianni [23]	2017	86	0.71 ± 0.21	27.7 ± 7.0	22.0*	18.5*	5.2*	28.1*	6.1*	3.5*
Simon *et al*. [24]	2018	33	0.46 ± 0.12	15.0 ± 3.0	—	—	—	—	—	—

*Adverse events within 3 months.
Data are shown as percentage. Events per procedure [14–18, 20, 21], events per patients [19, 23]
COPD — chronic obstructive pulmonary disease; exc. — exacerbation; FEV_1 — forced expiratory volume in 1 second; n — patients; pnx — pneumothorax

Table 3. An overview of follow-up (after > 31 days) complications in principal studies

Author/study	Year	COPD exc.	Pneumonia	Chest Pain	Hemoptysis	Pnx	Resp. failure	Death
Slebos *et al*. [15]	2012	50.0	10.7	7.1	0.0	0.0	—	0.0
RESET study [16]	2013	7.0	0.0	—	0.0	0.0	0.0	0.0
Klooster *et al*. [17]	2014	35.0	0.0	—	0.0	10.0	0.0	0.0
Deslee *et al*. [18]	2014	60.2	17.2	10.7	5.3	3.2	0.0	0.0
Hartman *et al*. [19]	2014	51.0 37.0 36.0	46.0 7.0 5.0	—	0.0 0.0 5.0	6.0 0.0 0.0	—	3.0 8.0 6.0
Zoumot *et al*. [20]	2015	6.0	1.2	1.2	0.0	3.6	—	11.1
REVOLENS [21]	2016	24.0	12.0	2.0	0.0	2.0	2.0	6.0
RENEW [22]	2016	39.3*	20.0*	—	3.9*	10.3*	3.9*	6.5*
Gülsen *et al*. [14]	2017	41.4	16.9	25.0	10.0	0.0	—	2.4
Kontogianni [23]	2017	12.3	7.9	0.0	3.5	1.7	2.6	—
Simon *et al.* [24]	2018	46.3**	5.6**	1.8**	77.7**	0.0**	0.0**	0.0**

*Adverse events within 12 months; **Adverse events within 3 months.
Data are shown as percentage. Events per procedure [14–18, 20, 21]. Events per patients [19, 23].
COPD — *chronic obstructive pulmonary disease*; exc. — exacerbation; FEV1 — forced expiratory volume in 1 second; n — patients; pnx — pneumothorax

Table 4. Possible complications and suggestions [10, 11, 15–27, 30–36]

Complication	Rates [%]	Suggestions
Aspergillus cavity	Rare	H, voriconazol
Bleeding,		
Mild	0–75.0	M, interruption of acetylsalicylic acid treatment,
Severe	1.5–3.5	arterial embolisation or surgical intervention
Bronchopleural fistula	Rare	H, VATS or thoracoscopic removal of coil
Bronchiectasis	Rare	Only M, if patient remained asymptomatic
Chest pain	0–25.0	M, if persist removal of suspected coils near the pleura
Coil-associated inflammation and opacities	Rare	broad-spectrum antibiotics + systemic corticosteroid (0.5 mg/kg)
COPD exacerbation	0–51.0	H, ± systemic corticosteroid
Hiccup	Rare	M, if persist removal of suspected coils near diaphragma
Pneumonia	0–46.0	H, broad-spectrum antibiotics ± systemic corticosteroid
Pneumothorax	0–10.3	M, or inserting thorax tube
Respiratory failure	0–3.9	H, NIV or intubation

COPD — chronic obstructive pulmonary disease; H — hospitalization; M — monitoring; NIV — non-invasive ventilation

cation in 0–75% of cases, whereas severe bleeding (> 150 mL) has rarely been noticed and appeared to resolve spontaneously in most cases [15–22]. Kontogianni *et al.* [23] reported severe bleeding in 3.5% of patients at the 1-year follow-up, and 3/4 of these patients required surgical intervention. In a study of bleeding complications, 65.3% of the subjects showing bleeding were in the TR period, and complications were more frequent in patients receiving acetylsalicylic acid treatment [24]. Bleeding improved spontaneously in 98.5% of these patients, and persistent hemoptysis ameliorated after bronchial arterial embolization in 1.5% of the subjects [25]. Therefore, while anticoagulant use is contraindicated for this procedure, patients receiving acetylsalicylic acid therapy should also be treated with caution.

Chest pain

Chest pain or discomfort is common in the TR period and gradually diminishes during the

follow-up. If the chest pain is continuous and pleuritic, the coil implanted close to the pleura should be considered as the causative factor and assessed for removal. However, it can only be removed during the procedure and in the TR period [14]. A case of coil removal due to ongoing chest pain in the tenth month has been reported [26]. However, complete reversibility of the coils is not possible.

COPD exacerbations

The most common complication observed in the follow-up period is COPD exacerbation. Slebos *et al.* reported that COPD exacerbations were more frequent in the first month (here defined as "TR period"), and decreased in frequency subsequently [15]. Nevertheless, in a 3-year study, 51.0%, 37%, and 36% of COPD exacerbations were reported over the first, second, and third year, respectively [19]. It is thought that the frequent occurrence of COPD exacerbations in patients undergoing BLVR coil treatment is caused by local mucosal injury in the subsegmental airways, local edema, and the triggered secondary bronchoconstriction [15]. In the REVOLENS study, 2 g of amoxicillin/clavulanic acid (in the case of allergy, 600 mg of clindamycin plus 5 mg/kg of gentamicin) was recommended immediately before the BLVR procedure [21]. Although there is no clear consensus on preoperative preparation and therapy, we believe that this treatment regimen may be improved, and may reduce some complications, including exacerbation of COPD.

Pneumonia

The second most common complication in BLVR coil treatments is pneumonia or related pneumonitis. In the literature, the incidence of pneumonia is reported to be 14.8% on average (range 0.0–46.0%) [7]. Therefore, the benefits of using steroids and antibiotic regimens in cases of pneumonia (or pneumonitis) in the TR period should also be investigated in further studies.

Pneumothorax

Another potential complication after BLVR coil treatments is pneumothorax. It is observed in 3.4–6.1% of patients during the TR period [15–20, 23], and in 0.0–11.6% during the follow-up period [15–17, 19–24]. Pneumothorax is a serious complication that can cause respiratory failure, need for surgery, and even death. Patients who develop pneumothorax must be hospitalized and monitored. Intercostal drainage or a thorax tube can be used if necessary [9]. Although there is an algorithm for predicting pneumothorax after BLVR valve treatment in the literature, there is no specific algorithm for pneumothorax after endobronchial coil treatment [27].

Respiratory failure

A possible complication of the BLVR procedure, respiratory failure was reported in 0.0–3.9% of patients after the TR period [16, 17, 21–24]. In contrast, in a meta-analysis conducted in 2015 involving 140 patients, respiratory failure was not reported [28]. These disparate results suggest the highly variable rates of respiratory failure, highlighting the need for further studies to evaluate contributing factors.

Rare and unexpected complications

There are some rare complications of BLVR coil treatments that may have serious consequences. These include *Aspergillus* cavitation (coil-related aspergilloma), bronchopleural fistula and penetration into the pleural space, bronchiectasis, coil-associated inflammatory response and opacities, and hiccups.

Aspergillus cavitation (coil-related aspergilloma)

Two case reports on this complication have been recently published [29, 30]. First case concerned the patient who underwent bilateral endobronchial coil treatment during the RENEW trial and developed a 27-mm cavity in the left upper lobe [29]. The patient was treated with voriconazole for 3 months and died due to decompensated respiratory failure. In the second case, the patient underwent endobronchial coil treatment for both upper lobes 3 years earlier [30]. Fungal cultures obtained during the procedure were positive for *Aspergillus* species, evaluated as colonization. *Aspergillus fumigatus* positivity was continued in the fungal cultures of the patient who continued spirometric improvement for the first 2 years. However, in the third year, computed tomography was performed because of worsening of dyspnea and frequent acute COPD exacerbations. Suspicious masses were observed in areas covering the distal end of the coils and the diagnosis was confirmed as aspergilloma. The patient was treated with voriconazole for about 14 months, and was discontinued due to cutane-

ous side effects. Aspergillus was not detected in ongoing cultures, clinical findings of the patient were stabilized and the follow-up continued. These two case reports highlight this rare complication, especially in the long term [29, 30].

Bronchopleural fistula and penetration into pleural space

This serious complication has been reported several times [23, 31–33]. This rare complication is due to the direct perforation of the bronchial wall and emphysematous tissue after coil implantation. It is usually observed in the first few days after the procedure. It may cause respiratory insufficiency, and in such cases, the coil should be removed thoracoscopically [34]. It is unclear whether this complication develops due to the proximity of the coils to the pleura; therefore, thoracic surgeons should be informed about the complication.

Bronchiectasis

Development of localized bronchiectasis a few months after endobronchial coil therapy has been reported in one case [35]. The cause of this complication and underlying mechanism are not yet known. The development of bronchiectasis may be an inflammatory response to a component of the coil or may be caused by tension in the subsegmental region, disrupting the blood supply to the bronchial artery and causing local ischemia [35]. In addition, the implantation of multiple coils into the same subsegment could have also led to this complication.

Coil-associated opacities and inflammatory response

Bronchoscopic lung volume reduction studies with lung sealant have revealed a new side effect of these treatments. This reaction is defined as the post-treatment acute inflammatory response [36, 37]. It usually includes chest pain or discomfort, cough, dyspnea, fever, negative microbiological findings, increased levels of inflammation markers (leukocytosis and high C-reactive protein levels), and low oxygen saturation. Similar findings have been found in cases of BLVR coil treatments. This phenomenon, described as coil-associated opacity (CAO), was first reported in 2016 in the RENEW trial [22]. The consolidations around the coils can mimic organized pneumonia and are usually non-infectious. Although the underlying mechanisms are not fully understood, it is generally accepted that this is a secondary inflammatory reaction due to stress and traction force in the lung tissue, airway closure, local airway irritation, or local ischemia [10, 21, 22]. It is difficult to differentiate from bacterial pneumonia, and some patients may not have fever and excess sputum. Corticosteroid therapy (0.5 mg/kg) is recommended in addition to standard pneumonia treatment [10].

Interestingly, in other lung volume reduction procedures such as thermal vapor ablation, local inflammatory response is an indication of the efficacy of treatment [38]. Similarly, in patients who developed CAO after endobronchial coil treatment, there was a significant decrease in the volume of the targeted and treated lobe after complete recovery and resolution. These patients are thought to be the best responders [10, 39].

A report of two cases by Perch *et al*. showed a 34% improvement in basal FEV_1 in the patient who responded well to CAO treatment [40]. In the second subject, CAO was not included in the preliminary diagnoses and the patient died after circulatory collapse. Autopsy revealed necrotizing inflammation and organized pneumonia in the tissues around the coil. This demonstrates that CAO can lead to life-threatening consequences if not diagnosed and treated early. This suggests that patients may have an acute inflammatory reaction due to BLVR treatment, and inflammation markers must be closely monitored. The high values for inflammation markers have the potential to mask other infections that may develop, causing new infections to be missed. The duration for which these laboratory values continue to remain high and the extent to which they can be treated are separate research topics.

In a different report of two patients with severe upper lobe emphysema, the study subjects were treated for community-acquired upper lobe pneumonia [41]. After pneumonia treatment and resolution, the most diseased and hyperinflated lung area lost lobar volume and significant improvement in respiratory function was reported. The natural and interesting outcome of these individuals who did not undergo BLVR was similar to that of patients who developed CAO after BLVR.

Deaths

Mortality was reported in 0.0–3.5% of patients after the TR period and 0.0–11.1% of the subjects during the follow-up [14–24]. In these studies, mortality was not thought to be entirely dependent on coil procedures, and deaths due to non-procedural/non-respiratory causes such as hemorrhagic stroke, severe urinary sepsis, esophageal cancer can also be observed [19]. However,

the cause of mortality is usually severe pneumonia, COPD exacerbation, respiratory failure and sepsis [14, 19–23].

Hiccups

Hiccups are a very rare complication. It is likely caused by the proximity of the coils to the diaphragm or the uptake of the diaphragm owing to the reduction in lower lobe volume. The incidence rate was reported to be 1.6% in one study, and spontaneous recovery has been documented [14]. In stubborn cases, removal of the coil may be considered.

Discussion

Bronchoscopic lung volume reduction coil treatments are an option especially for patients with severe hyperinflation and emphysema who do not respond to medical/supportive treatments. BLVR coil treatments have been shown to improve functional and clinical parameters in many studies [14, 15, 17, 20–24]. In the RENEW study, which included a 1-year follow-up, partial improvement in 6-MWT and respiratory functions were reported in those who received coil therapy compared to usual care, and any complication has been reported in 34.8% of those treated with coil therapy and 19.1% in usual care [22]. In the REVOLENS study, which included a 2-year follow-up, FEV_1 and dyspnea score (modified Medical Research Council) were not statistically significant compared to the initial value, while the quality of life score (Saint George's Respiratory Questionnaire), 6-minute walk test and residual volume values remained statistically significant [21]. Twenty-six patients had 45 serious adverse events (SAEs) in the first year, while 27 SAEs in twenty patients were observed in the second year. As a respiratory complication, 1 lung nodule, 1 lung transplantation, 4 pneumonia and 12 cases of COPD exacerbation were reported, while unexpected SAEs and pneumothorax did not develop [21]. Considering the potential complications, great care must be taken in the selection of the patients for these treatments. In addition, some studies did not classify complications as a recover period (first 30 days) or follow-up (after > 31 days), which naturally leads to a lack of exact rates for complications (e.g. 0–75% for bleeding).

Various complications have been reported during and after BLVR coil treatments (Figure 1). Patients should be informed about the complications that may develop and their written informed consent must be obtained prior to the procedure. Despite the observed complications, it can be said that this treatment is effective and safe considering the medium- to long-term outcomes [14–24]. The high COPD exacerbation rate in the studies suggests that the use of premedication, prophylactic antibiotics, and corticosteroids is warranted. Other observed complications have not proven to be preventable after premedication. In fact, some complications may be related to the experience of the endoscopist. In addition, we also recommend that patients should carefully monitor their current vaccination status (influenza and pneumococcal) because a large proportion of persons are at the COPD GOLD III or IV stage. We hypothesize that the incidence of some complications in vaccinated patients will be lower, although this hypothesis requires future testing.

Mortality rates in the follow-up period after BLVR coil therapy were reported to average at 3.9% (range 0.0–11.1%) [14–24]. A 3-year survival rate of 84% was found in the longest follow-up study of BLVR coil treatment [19]. All patients undergoing BLVR are at the COPD GOLD III and GOLD IV stages. Hence, these subjects already have a natural comorbidity. A 15-year survival rate of 7.3% (5.3% for GOLD III patients and 0.0% for GOLD IV patients) was found in all COPD groups in a recent study [42]. However, GOLD III and IV patients were also reported to have a life expectancy of 6.1 and 3.1 years, respectively, when hospitalized with exacerbation [42]. The situation is not different in individuals with emphysema. In a study of an emphysema patient group with a mean FEV_1 of 26.7 ± 7.0%, mortality was reported as 12.7 per 100 person-years over a mean follow-up of 3.9 years [43]. These results suggest that mortality rates with BLVR are likely lower than those in untreated patients with similar morbidity.

Patients with emphysema and GOLD IV COPD are potential or borderline candidates for lung transplantation. According to the guidelines of the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation (2014), persons with FEV_1 < 15–20% are considered candidates for lung transplantation [44]. However, when this value is < 25%, it is suggested that patients are included in the transplantation list [44]. In a published case report, bilateral BLVR coil therapy was applied to an end-stage emphysema patient enrolled in the lung transplantation list [45]. After treatment, the patient's FEV_1 increased from 19% to 21, and the RV decreased from 289% to 254%. Transplantation was postponed because of improvement

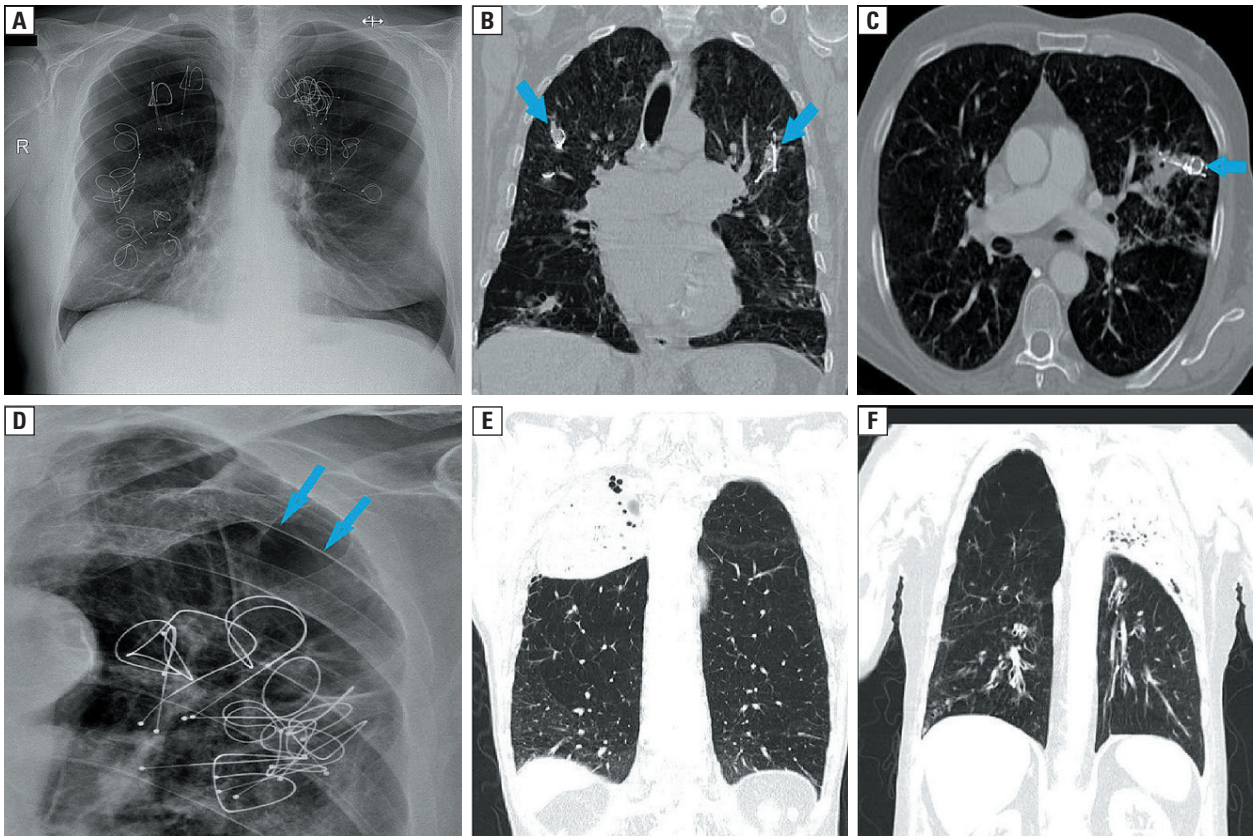

Figure 1. Successful bilateral endobronchial coil implantation (**A**), bilateral upper lobe coil-associated opacities (**B**), unilateral left upper lobe coil -associated opacities (**C**), left upper lobe coil implantation and pneumothorax (**D**), right upper lobe coil implantation and pneumonia (**E**), left upper lobe coil implantation and pneumonia (**F**)

in clinical symptoms and pulmonary function, and was performed after 3.5 years. In another study, BLVR coil treatments were found to be safe during the 12-month follow-up among transplant candidate patients with FEV_1 values below 25% [46]. This result is an example of how BLVR coil therapy can buy time for people awaiting lung transplantation.

Bacterial colonization in the airway is frequently observed in BLVR coil therapy patients and represents a significant opportunity for improved outcomes. In one study, colonization by *Pseudomonas* was reported in 8.1% of patients who were treated with BLVR coil treatment [14]. A separate 2017 study reported the detection of at least one potential pathogen in 47% of the BLVR coil patients. These pathogens, *Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae,* and *Pseudomonas aeruginosa*, were detected in 9%, 6%, 6%, and < 5% of cases, respectively [47]. Therefore, it is important to perform sputum examination before the first procedure. Although there is no definite contraindication in patients with *Pseudomonas aeruginosa* colonization, it should be kept in mind that this may be a relative contraindication if the patient has frequent exacerbations or uses antibiotics regularly. In a case report published by Casutt *et al.*, a patient who had previous *Pseudomonas* infection but had no growth in current sputum culture developed severe pneumonia after endobronchial coil treatment [48]. In the post-procedure sputum culture, *Aspergillus fumigatus* and *Pseudomonas aeruginosa* colonies were observed. Risk–benefit evaluation of BLVR treatments in patients who have previously had bacterial infection or colonization is recommended.

Medical devices manufactured from materials such as nickel-titanium alloy (nitinol) generally have an intrinsic antibacterial effect and resistance to bacterial formation [49]. However, *Acinetobacter*, *Alcaligenes*, *Pseudomonas*, *Comamonas*, *Stenotrophomonas,* and *Aspergillus* families can develop nickel resistance through plasmids and may contribute to CAO or pneumonia [50]. An example of this are the cases of *Aspergillus*-associated cavitation [29, 30]. It is thus clear that this issue requires further research.

Conclusions

Bronchoscopic lung volume reduction coil therapy is a minimally invasive nonsurgical procedure with potential complications in both the early and late follow-up periods. However, patients treated with BLVR have lower mortality rates than untreated patients with similar morbidity. Based on the findings of this review, we can estimate that premedication one day before and just before the procedure may reduce potential complications. Some medical centers apply and recommend 30-day macrolide treatment after the procedure. New generation SGD may be preferred to avoid complications due to endotracheal intubation. Moreover, further research is needed to identify risk factors, prevent potential complications, and a common consensus is required for routine preventive treatment.

Conflict of interest

The author has stated explicitly that there are no conflicts of interest in connection with this article.

References:

1. Minai OA, Benditt J, Martinez FJ. Natural history of emphysema. Proc Am Thorac Soc. 2008; 5(4): 468–474, doi: 10.1513/pats.200802-018ET, indexed in Pubmed: 18453357.
2. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 Guideline. Available at:https://goldcopd.org/wp-content/uploads/2020/03/GOLD-2020-POCKET-GUIDE-ver1.0_FINAL-WMV.pdf. [Last accessed at: 04.08.2020].
3. Altintas N. Update: non-invasive positive pressure ventilation in chronic respiratory failure due to COPD. COPD. 2016; 13(1): 110–121, doi: 10.3109/15412555.2015.1043520, indexed in Pubmed: 26418151.
4. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 — an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015; 34(1): 1–15, doi: 10.1016/j.healun.2014.06.014, indexed in Pubmed: 25085497.
5. Lammi MR, Marchetti N, Barnett S, et al. Heterogeneity of lung volume reduction surgery outcomes in patients selected by use of evidence-based criteria. Ann Thorac Surg. 2013; 95(6): 1905–1911, doi: 10.1016/j.athoracsur.2013.03.088, indexed in Pubmed: 23647860.
6. Decker MR, Leverson GE, Jaoude WA, et al. Lung volume reduction surgery since the National Emphysema Treatment Trial: study of Society of Thoracic Surgeons Database. J Thorac Cardiovasc Surg. 2014; 148(6): 2651–8.e1, doi: 10.1016/j.jtcvs.2014.02.005, indexed in Pubmed: 24631312.
7. Gülşen A. Bronchoscopic lung volume reduction: a 2018 review and update. Turk Thorac J. 2018; 19(3): 141–149, doi: 10.5152/TurkThoracJ.2018.18044, indexed in Pubmed: 30083406.
8. Ramaswamy A, Puchalski J. Bronchoscopic lung volume reduction: recent updates. J Thorac Dis. 2018; 10(4): 2519–2527, doi: 10.21037/jtd.2018.02.72, indexed in Pubmed: 29850160.
9. Herth FJF, Slebos DJ, Criner GJ, et al. Endoscopic lung volume reduction: an expert panel recommendation — update 2019. Respiration. 2019; 97(6): 548–557, doi: 10.1159/000496122, indexed in Pubmed: 30836374.
10. Welling JBA, Slebos DJ. Lung volume reduction with endobronchial coils for patients with emphysema. J Thorac Dis. 2018; 10(Suppl 23): S2797–S2805, doi: 10.21037/jtd.2017.12.95, indexed in Pubmed: 30210833.
11. Arevalo-Ludeña J, Arcas-Bellas JJ, Alvarez-Rementería R, et al. A comparison of the I-Gel supraglottic device with endotracheal intubation for bronchoscopic lung volume reduction coil treatment. J Clin Anesth. 2016; 31: 137–141, doi: 10.1016/j.jclinane.2016.02.016, indexed in Pubmed: 27185696.
12. Yu SH, Beirne OR. Laryngeal mask airways have a lower risk of airway complications compared with endotracheal intubation: a systematic review. J Oral Maxillofac Surg. 2010; 68(10): 2359–2376, doi: 10.1016/j.joms.2010.04.017, indexed in Pubmed: 20674126.
13. Grande B, Loop T. Anaesthesia management for bronchoscopic and surgical lung volume reduction. J Thorac Dis. 2018; 10(Suppl 23): S2738–S2743, doi: 10.21037/jtd.2018.02.46, indexed in Pubmed: 30210826.
14. Gulsen A, Sever F, Girgin P, et al. Evaluation of bronchoscopic lung volume reduction coil treatment results in patients with severe emphysema. Clin Respir J. 2017; 11(5): 585–592, doi: 10.1111/crj.12387, indexed in Pubmed: 26365390.
15. Slebos DJ, Klooster K, Ernst A, et al. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. Chest. 2012; 142(3): 574–582, doi: 10.1378/chest.11-0730, indexed in Pubmed: 22116796.
16. Shah P, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. The Lancet Respiratory Medicine. 2013; 1(3): 233–240, doi: 10.1016/s2213-2600(13)70047-x.
17. Klooster K, Ten Hacken NHT, Franz I, et al. Lung volume reduction coil treatment in chronic obstructive pulmonary disease patients with homogeneous emphysema: a prospective feasibility trial. Respiration. 2014; 88(2): 116–125, doi: 10.1159/000362522, indexed in Pubmed: 24902999.
18. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax. 2014; 69(11): 980–986, doi: 10.1136/thoraxjnl-2014-205221, indexed in Pubmed: 24891327.
19. Hartman JE, Klooster K, Gortzak K, et al. Long-term follow-up after bronchoscopic lung volume reduction treatment with coils in patients with severe emphysema. Respirology. 2015; 20(2): 319–326, doi: 10.1111/resp.12435, indexed in Pubmed: 25418910.
20. Zoumot Z, Kemp SV, Singh S, et al. Endobronchial coils for severe emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial. PLoS One. 2015; 10(4): e0122656, doi: 10.1371/journal.pone.0122656, indexed in Pubmed: 25853697.
21. Deslée G, Mal H, Dutau H, et al. Lung volume reduction coil treatment vs usual care in patients with severe emphysema: the REVOLENS randomized clinical trial. JAMA. 2016; 315(2): 175–184, doi: 10.1001/jama.2015.17821, indexed in Pubmed: 26757466.
22. Sciurba FC, Criner GJ, Strange C, et al. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. JAMA. 2016; 315(20): 2178–2189, doi: 10.1001/jama.2016.6261, indexed in Pubmed: 27179849.
23. Kontogianni K, Gerovasili V, Gompelmann D, et al. Coil therapy for patients with severe emphysema and bilateral incomplete fissures — effectiveness and complications after 1-year follow-up: a single-center experience. Int J Chron Obstruct Pulmon Dis. 2017; 12: 383–394, doi: 10.2147/COPD.S117655, indexed in Pubmed: 28176954.
24. Simon M, Harbaum L, Oqueka T, et al. Endoscopic lung volume reduction coil treatment in patients with very low FEV: an observational study. Ther Adv Respir Dis. 2018; 12: 1753466618760133, doi: 10.1177/1753466618760133, indexed in Pubmed: 29480070.
25. Simon M, Ittrich H, Harbaum L, et al. Bleeding complications after endoscopic lung volume reduction coil treatment: a retrospective observational study. Arch Bronconeumol. 2016; 52(12): 590–595, doi: 10.1016/j.arbres.2016.04.012, indexed in Pubmed: 27528576.

26. Dutau H, Bourru D, Guinde J, et al. Successful late removal of endobronchial coils. Chest. 2016; 150(6): e143–e145, doi: 10.1016/j.chest.2016.03.026, indexed in Pubmed: 27938769.
27. Valipour A, Slebos DJ, de Oliveira HG, et al. Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema — potential mechanisms, treatment algorithm, and case examples. Respiration. 2014; 87(6): 513–521, doi: 10.1159/000360642, indexed in Pubmed: 24777292.
28. Slebos DJ, Hartman JE, Klooster K, et al. Bronchoscopic coil treatment for patients with severe emphysema: a meta-analysis. Respiration. 2015; 90(2): 136–145, doi: 10.1159/000431384, indexed in Pubmed: 26112380.
29. Orton CM, Garner JL, Desai SR, et al. Aspergillus cavitation complicating endobronchial lung volume reduction coil placement. Am J Respir Crit Care Med. 2020; 201(3): e8–e9, doi: 10.1164/rccm.201906-1176IM, indexed in Pubmed: 31469578.
30. Plante A, Guinde J, Boudreau C, et al. A rare complication: development of an aspergilloma after endobronchial coil placement in a COPD patient. Respiration. 2020; 99(5): 423–425, doi: 10.1159/000503363, indexed in Pubmed: 31622972.
31. Gulsen A, Sever F, Girgin P, et al. Bronchopleural fistula and pneumothorax following lung volume reduction coil treatment in severe emphysema: A case report. 1.4 Interventional Pulmonology. 2015, doi: 10.1183/13993003.congress-2015.pa807.
32. Mongelli F, Cafarotti S, Di Giuseppe M, et al. Late onset of pneumothorax after bronchoscopic lung volume reduction due to migration of a nitinol coil. Eur J Cardiothorac Surg. 2018; 53(4): 884–885, doi: 10.1093/ejcts/ezx402, indexed in Pubmed: 29186411.
33. Marchetti G, McCracken DJ, Rahman NM. Endobronchial coil penetration into the pleural space. Thorax. 2018; 73(9): 890–891, doi: 10.1136/thoraxjnl-2018-211754, indexed in Pubmed: 29574418.
34. Franzen D, Straub G, Freitag L. Complications after bronchoscopic lung volume reduction. J Thorac Dis. 2018; 10(Suppl 23): S2811–S2815, doi: 10.21037/jtd.2018.06.66, indexed in Pubmed: 30210835.
35. Debray MP, Marceau A, Dombret MC, et al. Bronchiectasis complicating lung volume reduction coil treatment. Chest. 2017; 152(3): e57–e60, doi: 10.1016/j.chest.2017.04.189, indexed in Pubmed: 28889896.
36. Herth FJF, Eberhardt R, Ingenito EP, et al. Assessment of a novel lung sealant for performing endoscopic volume reduction therapy in patients with advanced emphysema. Expert Rev Med Devices. 2011; 8(3): 307–312, doi: 10.1586/erd.11.10, indexed in Pubmed: 21542703.
37. Kramer MR, Refaely Y, Maimon N, et al. Bilateral endoscopic sealant lung volume reduction therapy for advanced emphysema. Chest. 2012; 142(5): 1111–1117, doi: 10.1378/chest.12-0421, indexed in Pubmed: 22722233.
38. Gompelmann D, Eberhardt R, Ernst A, et al. The localized inflammatory response to bronchoscopic thermal vapor ablation. Respiration. 2013; 86(4): 324–331, doi: 10.1159/000354175, indexed in Pubmed: 23988888.
39. Michaud GC, Carbone C, Sciurba FC, et al. Coil associated inflammatory response syndrome (CAIRS) following endoscopic lung volume reduction with endobronchial coils in severe emphysema. Am J Respir Crit Care Med. 2018; 197: A1726.
40. Perch M, Johannesen H, Fiehn AM, et al. The "coil associated opacity" in endoscopic emphysema treatment. Friend or foe? Interventional Pulmonology. 2018, doi: 10.1183/13993003.congress-2018.pa5396.
41. Kayani K, Mahadeva R, Stinchcombe S, et al. Lung function improvements in emphysema following pneumonia. Respir Med Case Rep. 2019; 26: 1–5, doi: 10.1016/j.rmcr.2018.10.025, indexed in Pubmed: 30416955.
42. van Hirtum PV, Sprooten RTM, van Noord JA, et al. Long term survival after admission for COPD exacerbation: A comparison with the general population. Respir Med. 2018; 137: 77–82, doi: 10.1016/j.rmed.2018.02.015, indexed in Pubmed: 29605217.
43. Martinez FJ, Foster G, Curtis JL, et al. Predictors of mortality in patients with emphysema and severe airflow obstruction. Am J Respir Crit Care Med. 2006; 173(12): 1326–1334, doi: 10.1164/rccm.200510-1677OC, indexed in Pubmed: 16543549.
44. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 — an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015; 34(1): 1–15, doi: 10.1016/j.healun.2014.06.014, indexed in Pubmed: 25085497.
45. Grewal HS, Mehta AC. Emphysema management: from investigational endobronchial coils to lung transplantation. Am J Respir Crit Care Med. 2018; 198(3): e14, doi: 10.1164/rccm.201711-2352IM, indexed in Pubmed: 29676590.
46. Gulsen A. Importance of bronchoscopic lung volume reduction coil therapy in potential candidates for lung transplantation. Biosci Trends. 2018; 12(4): 395–402, doi: 10.5582/bst.2018.01134, indexed in Pubmed: 30158333.
47. Trudzinski FC, Seiler F, Wilkens H, et al. Microbiological airway colonization in COPD patients with severe emphysema undergoing endoscopic lung volume reduction. Int J Chron Obstruct Pulmon Dis. 2018; 13: 29–35, doi: 10.2147/COPD.S150705, indexed in Pubmed: 29296080.
48. Casutt A, Koutsokera A, Lovis A. Lung volume reduction coil treatment: is there an indication for antibiotic prophylaxis? Arch Bronconeumol. 2016; 52(2): 114–115, doi: 10.1016/j.arbres.2014.12.011, indexed in Pubmed: 25766124.
49. Ohtsu N, Suginishi S, Hirano M. Antibacterial effect of nickel-titanium alloy owing to nickel ion release. Applied Surface Science. 2017; 405: 215–219, doi: 10.1016/j.apsusc.2017.02.037.
50. Stoppel R, Schlegel HG. Nickel-resistant bacteria from anthropogenically nickel-polluted and naturally nickel-percolated ecosystems. Appl Environ Microbiol. 1995; 61(6): 2276–2285, doi: 10.1128/AEM.61.6.2276-2285.1995, indexed in Pubmed: 16535048.

Andrzej Emeryk[1], Justyna Emeryk-Maksymiuk[2]

[1]Department of Pediatric Pulmonology and Rheumatology Medical University in Lublin, Poland
[2]Chair of Internal Medicine and Department of Internal Medicine in Nursing Medical University in Lublin, Poland

Short-acting inhaled β2-agonists: why, whom, what, how?

Abstract

We showed the present data about the efficacy and safety of inhaled short-acting β2-agonists (SABA), such as salbutamol and fenoterol, in the management of obstructive diseases in children and adults. Our work discusses major mechanisms of action, clinical effects, possible side effects and indications of inhaled SABA. We presented current recommendations for the position of SABA in the therapy of obstructive diseases in children and adults, particularly in asthma and chronic obstructive pulmonary disease.

Key words: short-acting β2-agonist, salbutamol, fenoterol, inhalation, nebulization, asthma, COPD

Adv Respir Med. 2020; 88: 443–449

Introduction

Short-acting β2-agonists (SABA) stimulate β2-adrenergic receptor (β2-AR). They are called β2-mimetics or β2-agonists. First selective SABA widely used in clinical practice appeared more than 50 years ago. They were introduced to the global market in the following order: terbutaline (1966 yr.), salbutamol (1968 yr.) and fenoterol (1970 yr.) [1]. Next drugs, such as levalbuterol, reproterol, rimiterol, klenbuterol and pirbuterol, were introduced afterwards [2–4]. Short-acting β2-agonists are selective agonists of β2-AR, however they differ in their degree of selectivity. Salbutamol (albuterol) is the most used SABA in the world — in US it took 9th place on the list of prescribed medicines in 2016 (70 million of prescriptions) [5]. According to World Health Organization (WHO) salbutamol ranks among the most effective and safest medicines essential to health care systems [6]. Racemic salbutamol is an equal (1:1) mixture of R-salbutamol (levalbuterol) and S-salbutamol isomers. R-isomer of salbutamol is a pharmacologically active compound which exhibits many clinical effects, including potent bronchodilation [7]. Suppression of bronchoconstriction and bronchodilation occur 5 minutes after administration of inhaled salbutamol, but the duration of action does not exceed 4–6 hours (Figure 1) [8].

Drugs from this group provide effective protection against exercise-induced bronchoconstriction within 0.5–2.0 hours also against bronchoconstriction triggered by exposure to sensitizing allergen [9, 10]. Clinical studies show more potent bronchodilation and less side effects of R-salbutamol in comparison with racemic salbutamol [11–13]. High cost of levalbuterol justifies, however, its administration only in selected clinical conditions [13].

Salbutamol *versus* fenoterol

Two inhaled drugs from SABA group are available in Poland: salbutamol and fenoterol. Table 1 shows their most important properties.

Data in the table demonstrate that β2/β1 (selectivity index) stimulation index is 10 times greater for salbutamol than fenoterol. Having in mind similar stimulation of β2 receptors by both drugs (0.55 salbutamol *vs* 0.60 fenoterol), it means that salbutamol exerts more selective β2-AR stimulation *vs* fenoterol and both cause similar bronchodilation. Studies from the 1990s

Address for correspondence: Andrzej Emeryk, Department of Pediatric Pulmonology and Rheumatology Medical University in Lublin, Lublin, Poland; e-mail: andrzejemeryk@plusnet.pl
DOI: 10.5603/ARM.a2020.0132
Received: 08.02.2020
Copyright © 2020 PTChP
ISSN 2451–4934

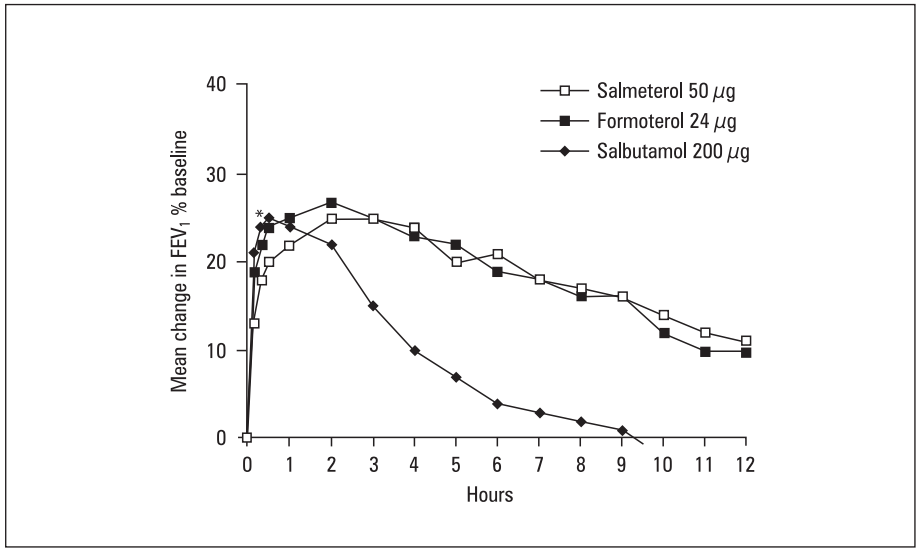

Figure 1. Effect of single dose of salbutamol, formoterol, and salmeterol on FEV_1 value in asthma patients [8]
FEV_1 — forced expiratory volume in the first second

Table 1. Comparison of short-acting β2-agonists' (salbutamol and fenoterol *vs* isoproterenol) ability to stimulate β-adrenergic receptors (β1, β2, β3) [14, 15]

	β1 inotropic activity (atrium)	β2 dilatory activity (bronchi)*	β3 lipolytic activity (adipocytes)	β2/β1 index
Isoproterenol	1,0	1,0	1,0	1,0
Salbutamol	0,0004	0,55	0,002	1375
Fenoterol	0,005	0,6	0,02	120

*Increase in FEV_1 (forced expiratory volume in the first second) ≥ 15% from baseline

proved similar or better clinical efficacy and better safety of salbutamol in comparison with inhaled fenoterol in different age groups of asthma patients [16, 17]. Better safety is also a result of the fact that salbutamol shows more features of β2-AR partial agonist than fenoterol. It determines that asthma patients using salbutamol have lower risk of death *vs* patients using fenoterol [17, 18]. It should be stressed that adverse effects of fenoterol increase in hypoxemia, which occurs during severe and prolonged episode of bronchoconstriction [19].

Clinical effects of SABA

Short-acting β2-agonists in conditions with bronchoconstriction exert many following clinical effects [1, 15]:

— bronchodilation (removal of bronchial smooth muscles constriction);
— prevention of bronchoconstriction induced by different bronchoconstrictive factors;
— reduction of capillary permeability (reduction of plasma exudate);
— suppression of sensory nerves activation;
— improvement of mucociliary clearance;
— dilatation of pulmonary vascular bed (decrease in pO_2);
— increased release of surfactant.

They can depend on the polymorphism of gene encoding β2-AR located on chromosome 5q31-q32 [20, 21]. Some studies showed relationship between response to SABA, course of asthma and the polymorphism of gene encoding β2-AR [22]. It is mainly about 2 polymorphisms: genotype Arg/Arg at codon 16 of gene encoding β2-AR and Gln/Gln at codon 27 of this gene. It was revealed that homozygotes for Arg/Arg at codon 16 of gene encoding β2-AR with chronic obstructive pulmonary disease (COPD) are predisposed to more severe clinical course of the disease [23]. Similar relationship was shown in patients with cystic fibrosis with altered response to SABA [24].

Short-acting β2-agonists usage can be associated with many side effects described may years ago [25]: tachycardia, skeletal muscle tremor, hypokalaemia, increased level of lactic acid in plasma (lactic acidosis), headaches, hyperglycaemia. Systemic side effects are observed rarely after inhalation administration and increased risk of cardiovascular side effects appear in patients with comorbid cardiovascular disease, especially in the elderly [26, 27]. It is worth mentioning that paradoxical bronchoconstriction after inhalation of SABA occurs in 4.4% of the general population [28].

There are additional possible side effects and adverse clinical effects when SABA are used in asthma. These effects occur in patients receiving SABA as monotherapy or/and if SABA are used very often or regularly without inhaled corticosteroids (ICS). It can lead to increased risk of the following adverse outcomes [29–35]:

— decrease in the number and sensitivity of β2-AR;
— diminished bronchial response to SABA or/ /and LABA;
— increased bronchial hyperresponsiveness;
— increased allergic reactions and eosinophilic airway inflammation;
— increased risk for asthma exacerbation (with regular or frequent use: ≥ 3 SABA canisters/ /year, average 1.7 puffs/day);
— increased risk of death in patients with asthma (≥ 11 SABA canisters/year);
— deterioration in spirometric parameters.

These facts which are known for many years and other new clinical evidences for efficacy and safety of SMART therapy (Single Maintenance and Reliver Therapy) changed the perception of the role and place of SABA in the management of asthma in last Global Initiative for Asthma report (GINA) 2019 [36], which will be discussed further below. Another way of limiting the SABA overuse relies on monitoring use of SABA by patients preferably with electronic inhalers [37, 38], including inhalers transmitting information to the health care system in real time [39].

Salbutamol in pressurised metered-dose inhaler in comparison to other pharmaceutical forms of SABA

Short-acting β2-agonists have different routes of administration (inhalation, oral and intravenous), because they are available in different pharmaceutical forms. Many forms of salbutamol are available [40]:

— inhalation aerosol (suspension) from pressurised metered-dose inhaler (pMDI) (children and adults);
— powder from dry powder inhaler (DPI), types: Diskus (children over 4 years and adults), Turbuhaler (children over 3 years and adults) and Easyhaler and (children over 4 years, adults);
— inhalation solution for nebulizers (children and adults);
— sirup (children over 2 years, adults);
— tablets (children over 2 years, adults);
— solution for injection (adults).

Inhalation is the most effective way of SABA therapy in airway diseases. Oral therapy can be alternative only exceptionally in small children, who do not accept inhalation or cannot inhale properly [38]. Additional parenteral therapy (salbutamol) is necessary rarely in patients with severe exacerbation of asthma, who do not respond do proper inhalation therapy [41].

Inhalation formulations of SABA most often used are listed in Table 2 [43].

According to table 2, four inhalation formulations of salbutamol are available: pMDI, pressurised metered-dose inhaler — breath actuated pMDI (pMDI-BA), DPI and inhalation solution for nebulizers; fenoterol is available only as pMDI. The expected therapeutic clinical effects and probability of side effects can depend on the choice of SABA inhalation method. Below we present the most important rules of SABA inhalation therapy:

Table 2. Inhalation formulations of SABA and SABA/ipratropium bromide combinations. Abbreviations according to [44]

Type of inhaler	pMDI	pMDI-BA	MDLI (respimat)	DPI	Nebulization
Salbutamol	+	+	–	+	+
Fenoterol	+	–	–	–	–
Salbutamol + ipratropium bromide	+*	–	+	–	+
Fenoterol + ipratropium bromide	+	–	+	–	+

pMDI — pressurised metered-dose inhaler; pMDI-BA — pressurised metered-dose inhaler — breath actuated); MDLI — metered dose liquid inhaler; DPI — dry powder inhaler

1. pMDI with properly fitted inhalation chamber is preferred method of SABA inhalation in children below 6 years, irrespective of severity of asthma attack, place of administration (home, admission ward, clinical ward, intensive care unit) [36, 45, 46].
2. Dose of salbutamol from pMDI depends mainly on the severity of asthma attack, not on patient age. According to GINA 2019 report during the first hour children below 6 years can receive up to 6 puffs, older children and adults can receive up to 12–30 puffs [36].
3. Salbutamol can be inhaled from DPI (e.g: Diskus and Easyhaler) in children above 6 years and adult with asthma, which provides similar clinical efficacy to pMDI [36]. Studies on administration of salbutamol from other DPI are ongoing [47].
4. Nebulization with pneumatic nebulizer — both intermittent and continuous — should be used in case of insufficient response or lack of response to SABA and life-threatening bronchoconstriction [36, 48, 49]. In adults with severe exacerbation of asthma continuous nebulized salbutamol more effectively improves lung function than intermittent nebulization [50].
5. Clinical effects of salbutamol nebulization to a considerable degree depend on the type of nebulizer: breath actuated pneumatic nebulizer provides better effect than continuous nebulization and mesh nebulizer in comparison to pneumatic nebulizer [51, 52].

Table 3. Current indications for SABA in children and adults [36, 55–64]*

Disease/state	Indications	Comment
Asthma	Attacks of dyspnoea, cough, and wheeze Disease exacerbations Prevention of exercise-induced bronchoconstriction Prevention of bronchoconstriction triggered by allergen exposure	Alternative to SMART therapy in patients < 12 years Always with ICS — evidence A
Obstructive bronchitis — so-called early childhood asthma	Exacerbation of bronchoconstriction	First-line treatment Number of doses should be adjusted to the patient's clinical condition
Stable COPD	Initial treatment — dyspnoea attack or/and respiratory difficulties As-needed SABA	— Only patients from group A — Reduction in symptoms and an increase in FEV_1 — evidence A — Combination of SABA + SAMA is superior to SABA or SAMA alone (symptoms and FEV_1) — evidence A
COPD — exacerbation	Acute exacerbation of disease SABA added to other medication	Increase the dose or frequency of SABA or combine SABA and SAMA in the initial treatment of acute exacerbation — evidence C
Bronchiolitis	Selected cases with confirmed positive clinical response to treatment	In most cases there are no indications to routine therapy
Cystic fibrosis	Pulmonary exacerbation with features of bronchoconstriction and confirmed positive clinical response or in patients with positive BDR test, before inhalation of hypertonic saline	Rather commonly used, however ecommendations are not explicit
Transient tachypnoea of the newborns		Very poor evidences for the efficacy
Chronic lung disease in premature babies	Prevention and treatment	Poor evidences for the efficacy
Familial dysautonomia	SABA + SAMA	1 study confirming SABA efficacy
Other diseases with reversible bronchoconstriction	Acute chest syndrome in sickle cell disease	Further studies are needed
Bronchodilator reversibility (BDR) test	Spirometric features of bronchoconstriction (FEV_1%FVC < 80 % predicted value, FEV_1%VC < 80% predicted value, PEF < 80% predicted value)	2–4 puffs of salbutamol pMDI + inhalation chamber as the standard of BDR test

*One shouldn't be afraid of administration of SABA (salbutamol) in the elderly (> 90 years) [65] FEV_1 — forced expiratory volume in the first second; ICS — inhaled corticosteroids; COPD — chronic obstructive pulmonary disease; SABA — short-acting β2-agonists; SAMA — short-acting muscarinic antagonists; SMART — Single Maintenance and Reliver Therapy

Table 4. Initial emergency (as-needed) pharmacotherapy of asthma according to GINA 2019 report [36]

Age group	Preferred management	Alternative management	Comments
Patients ≥ 12 years	Low dose ICS-formoterol — Step 1–5 treatment	SABA pMDI, pMDI-BA SABA pMDI + IC SABA DPI— Step 1–5 treatment	ICS: budesonide or beclometasone
Patients 6–11 years	SABA DPI SABA pMDI + IC SABA DPI — Step 1–5 treatment	Low dose ICS-formoterol — Step 3–5 treatment*	*Children receiving ICS-formoterol combination as maintenance
Patients 5 years and younger	SABA "as-needed" pMDI + IC — Step 1–4 treatment	SABA "as-needed" by nebulizer — Step 1–4 treatment	Proper use of the equipment and estimation of appropriate dose of the drug are required

DPI — dry powder inhaler; ICS — inhaled corticosteroids; IC — inhalation chamber; pMDI — pressurised metered-dose inhaler; SABA — short-acting β2-agonists

6. Parenteral, oral, or nebulized SABA are associated with increased risk of side effects (tachycardia, muscle tremor, headaches, hypokalaemia). In this respect inhalation from pMDI is the safest method [53, 54].
7. Short-acting β2-agonist (alternatively in combination with ipratropium bromide) in pMDI + IC or in nebulization is the first-line initial treatment of acute exacerbation of COPD [55]. Dose of SABA from pMDI: 1–2 puffs every hour for the first 2–3 hours of treatment, then 1–2 puffs every 2–4 hours depending on the response to the treatment [56].
8. Patients with COPD should receive air-driven nebulization of SABA, but not high-flow oxygen-driven nebulization to avoid hypercapnia in patients with chronic respiratory failure [57].

Indications to SABA

Short-acting β2-agonists have been very important drugs for many years used in the management of various bronchoconstrictive diseases in children and adults. Indications for their administration were collected in Table 3.

Current place of SABA in the management of asthma is defined by GINA 2019 report, which considerably changes former recommendations (tab. 4) [35]. Experts in this report do not recommend SABA monotherapy in all age groups (look tab. 3) because of patient's safety. Each SABA (regardless of its inhalation formulation) should be used simultaneously with ICS — from one or separate inhalers (or sometimes with oral/parenteral corticosteroid).

GINA 2019 report based on high-quality clinical studies recommends the following as-needed (emergency) step 1–5 treatment in patient ≥ 12 years: low dose ICS in combination with formoterol [36]. As-needed SABA from pMDI or DPI remains alternative option (worse regarding the efficacy and safety). In children 6–11 years preferred emergency management is administration of SABA from pMDI + inhalation chamber in combination with ICS (any medication) or oral corticosteroid [36]. Administration of SABA from pMDI + inhalation chamber: 4–10 puffs for every 20 minutes for the first hour of symptoms. Budesonide in combination with formoterol in SMART therapy model is alternative option for some children [36]. In group of children up to 5 years the only option of emergency treatment is SABA „as-needed" — from pMDI + inhalation chamber (preferred management) or in nebulization (alternative management) in all asthma steps [36].

References:

1. Tattersfield A.E. Current issues with beta2-adrenoceptor agonists: historical background. Clin Rev Allergy Immunol. 2006; 31(2–3): 107–118, doi: 10.1385/CRIAI:31:2:107, indexed in Pubmed: 17085787.
2. Baronti A., Grieco A., Vibelli C. A comparison between inhaled clenbuterol and salbutamol in chronic bronchitis with reversible airway obstruction. Eur J Respir Dis. 1980; 61(3): 143–150, indexed in Pubmed: 7002574.
3. Muittari A. A comparison of rimiterol and salbutamol by inhalation at high and low dose in asthmatic patients. Respiration. 1978; 35(3): 165–172, doi: 10.1159/000193873, indexed in Pubmed: 25466.
4. Rau J.L. Inhaled adrenergic bronchodilators: historical development and clinical application. Respir Care. 2000; 45(7): 854–863, indexed in Pubmed: 10926383.
5. Aitken M. Medicines Use and Spendingin the U.S. A Review of 2016 and Outlook to 2021. QuintilesIMS Instutite. 2017. Dostępne na stronie: https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/590c/6aa0/6970/2d2d/4182/0000/590c6aa069702d2d41820000.pdf. [dostęp: 12.08.2019].
6. World Health Organization. April 2015. Archived (PDF) from the original on 13 December 2016. Retrieved 8 December 2016.
7. Lipworth B.J., Clark D.J., Koch P. i wsp. Pharmacokinetics and extrapulmonary beta 2 adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. Thorax. 1997; 52(10): 849–852, doi: 10.1136/thx.52.10.849, indexed in Pubmed: 9404370.
8. van Noord J.A., Smeets J.J., Raaijmakers J.A. i wsp. Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action. Eur Respir J. 1996; 9(8):

1684–1688, doi: 10.1183/09031936.96.09081684, indexed in Pubmed: 8866595.
9. Inman M.D., O'Byrne P.M. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 1996; 153(1): 65–69, doi: 10.1164/ajrccm.153.1.8542164, indexed in Pubmed: 8542164.
10. Cockcroft D. Inhaled 2 -agonists and airway responses to allergen. J Allergy Clin Immunol. 1998; 102(5): S96–S99, doi: 10.1016/s0091-6749(98)70038-7.
11. Patel M., Thomson N.C. (R)-salbutamol in the treatment of asthma and chronic obstructive airways disease. Expert Opin Pharmacother. 2011; 12(7): 1133–1141, doi: 10.1517/14656566.2011.571210, indexed in Pubmed: 21453221.
12. Yuan J., Lu Z.K., Zhang Y. i wsp. Clinical outcomes of levalbuterol versus racemic albuterol in pediatric patients with asthma: Propensity score matching approach in a medicaid population. Pediatr Pulmonol. 2017; 52(4): 516–523, doi: 10.1002/ppul.23565, indexed in Pubmed: 27701831.
13. Yuan J., Lu K. Economic impact of levalbuterol versus albuterol in low-income population. Value Health. 2014; 17(7): A781, doi: 10.1016/j.jval.2014.08.376, indexed in Pubmed: 27202897.
14. Hochhaus G., Möllmann H. Pharmacokinetic/pharmacodynamic characteristics of the beta-2-agonists terbutaline, salbutamol and fenoterol. Int J Clin Pharmacol Ther Toxicol. 1992; 30(9): 342–362, indexed in Pubmed: 1358833.
15. Emeryk A., Lis G. B2-mimetyki w astmie. W: Astma i choroby obturacyjne oskrzeli u dziec. A. Emeryk, A. Bręborowicz, G. Lis (red.). Elsevier Urban&Partner. Wrocław 2010: 145–154.
16. Scalabrin D.M., Solé D., Naspitz C.K. Efficacy and side effects of beta 2-agonists by inhaled route in acute asthma in children: comparison of salbutamol, terbutaline, and fenoterol. J Asthma. 1996; 33(6): 407–415, doi: 10.3109/02770909609068185, indexed in Pubmed: 8968295.
17. Bremner P., Burgess C., Beasley R. i wsp. Nebulized fenoterol causes greater cardiovascular and hypokalaemic effects than equivalent bronchodilator doses of salbutamol in asthmatics. Respir Med. 1992; 86(5): 419–423, doi: 10.1016/s0954-6111(06)80009-0, indexed in Pubmed: 1462021.
18. Bremner P., Siebers R., Crane J. i wsp. Partial *vs* full beta-receptor agonism. A clinical study of inhaled albuterol and fenoterol. Chest. 1996; 109(4): 957–962, doi: 10.1378/chest.109.4.957, indexed in Pubmed: 8635377.
19. Bremner P., Burgess C.D., Crane J. i wsp. Cardiovascular effects of fenoterol under conditions of hypoxaemia. Thorax. 1992; 47(10): 814–817, doi: 10.1136/thx.47.10.814, indexed in Pubmed: 1481183.
20. Martinez F.D., Graves P.E., Baldini M. i wsp. Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. J Clin Invest. 1997; 100(12): 3184–3188, doi: 10.1172/JCI119874, indexed in Pubmed: 9399966.
21. NCBI NCBI Gene. 2019. Jul 23, [2018-11-19]. ADRB2 adrenoceptor beta 2 [Homo sapiens (human)]. Dostępne na stronie: www.ncbi.nlm.nih.gov/gene/154. [dostęp: 14.12.2019].
22. Hikino K., Kobayashi S., Ota E. i wsp. The influence of beta-2 adrenergic receptor gene polymorphisms on albuterol therapy for patients with asthma: protocol for a systematic review and meta-analysis. JMIR Res Protoc. 2019; 8(9): e14759, doi: 10.2196/14759, indexed in Pubmed: 31538939.
23. Emeryk-Maksymiuk J., Emeryk A., Krawczyk P. i wsp. Beta-2-adrenoreceptor polymorphism at position 16 determines the clinical severity of chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2017; 43: 1–5, doi: 10.1016/j.pupt.2017.01.005, indexed in Pubmed: 28093224.
24. Marson F.A.L., Bertuzzo C.S., Ribeiro A.F. i wsp. Polymorphisms in ADRB2 gene can modulate the response to bronchodilators and the severity of cystic fibrosis. BMC Pulm Med. 2012; 12: 50, doi: 10.1186/1471-2466-12-50, indexed in Pubmed: 22950544.
25. Lulich K.M., Goldie R.G., Ryan G. i wsp. Adverse reactions to beta 2-agonist bronchodilators. Med Toxicol. 1986; 1(4): 286–299, doi: 10.1007/bf03259844, indexed in Pubmed: 2878344.
26. Sears M. Adverse effects of -agonists. J Allergy Clin Immunol. 2002; 110(6): S322–S328, doi: 10.1067/mai.2002.129966.
27. Gupta P., O'Mahony M.S. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: recommendations for prescribing. Drugs Aging. 2008; 25(5): 415–443, doi: 10.2165/00002512-200825050-00005, indexed in Pubmed: 18447405.
28. Schissler A.J., Celli B.R. Prevalence of paradoxical bronchoconstriction after inhaled albuterol. Respir Med. 2018; 141: 100–102, doi: 10.1016/j.rmed.2018.06.028, indexed in Pubmed: 30053954.
29. Hancox R.J., Cowan J.O., Flannery E.M. i wsp. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. Respir Med. 2000; 94(8): 767–771, doi: 10.1053/rmed.2000.0820, indexed in Pubmed: 10955752.
30. Drazen J.M., Israel E., Boushey H.A. i wsp. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med. 1996; 335(12): 841–847, doi: 10.1056/NEJM199609193351202, indexed in Pubmed: 8778601.
31. Stanford R.H., Shah M.B., D'Souza A.O. i wsp. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol. 2012; 109(6): 403–407, doi: 10.1016/j.anai.2012.08.014, indexed in Pubmed: 23176877.
32. Sears M.R., Lötvall J. Past, present and future--beta2-adrenoceptor agonists in asthma management. Respir Med. 2005; 99(2): 152–170, doi: 10.1016/j.rmed.2004.07.003, indexed in Pubmed: 15715182.
33. Suissa S., Ernst P., Boivin J.F. i wsp. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med. 1994; 149(3 Pt 1): 604–610, doi: 10.1164/ajrccm.149.3.8118625, indexed in Pubmed: 8118625.
34. Aldridge R.E., Hancox R.J., Robin Taylor D. i wsp. Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma. Am J Respir Crit Care Med. 2000; 161(5): 1459–1464, doi: 10.1164/ajrccm.161.5.9906052, indexed in Pubmed: 10806139.
35. Aldridge R.E., Hancox R.J., Cowant J.O. i wsp. Eosinophils and eosinophilic cationic protein in induced sputum and blood: effects of budesonide and terbutaline treatment. Ann Allergy Asthma Immunol. 2002; 89(5): 492–497, doi: 10.1016/s1081-1206(10)62087-x, indexed in Pubmed: 12452208.
36. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), Update 2019. Dostępne na stronie: https://ginasthma.org/gina-reports/. [dostęp: 11.10.2019].
37. Taylor TE, Zigel Y, De Looze C, et al. Advances in audio-based systems to monitor patient adherence and inhaler drug delivery. Chest. 2018; 153(3): 710–722, doi: 10.1016/j.chest.2017.08.1162, indexed in Pubmed: 28887061.
38. Blakey JD, Bender BG, Dima AL, et al. Digital technologies and adherence in respiratory diseases: the road ahead. Eur Respir J. 2018; 52(5), doi: 10.1183/13993003.01147-2018, indexed in Pubmed: 30409819.
39. PROAIR® DIGIHALERTM (albuterol sulfate) inhalation powder. Dostępne na stronie: www.proairdigihaler.com/globalassets/proair_digihaler/Proair_Digihaler_PI.pd. [Dostęp: 10.06.2019 r.].
40. Salbutamo. Dostępne na stronie: www.mp.pl/pacjent/leki/subst.html?id=711. [Dostęp: 14.12.2019 r.].
41. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Clinical Practice Guidelines. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. Report No.: 07-4051. Dostępne na stronie: www.nhlbi.nih.gov/NHLBAC-Asthma-WG-Report.pdf. [Dostęp: 12.02.2018 r.].
42. Travers A.H., Milan S.J., Jones A.P. i wsp. Addition of intravenous beta(2)-agonists to inhaled beta(2)-agonists for acute asthma. Cochrane Database Syst Rev. 2012; 12: CD010179, doi: 10.1002/14651858.CD010179, indexed in Pubmed: 23235685.
43. Emeryk A., Emeryk-Maksymiuk J. Połączenie krótkodziałającego b2-mimetyka z krótkodziałającym lekiem antycholinergicznym u dzieci z obturacją oskrzeli. Terapia. 2018; 26: 4.
44. Emeryk A., Pirożyński M., Mazurek H. i wsp. Polski Przewodnik Inhalacyjny. Via Medica, Gdańsk 2015: 1–22.

45. Pollock M., Sinha I.P., Hartling L. i wsp. Inhaled short-acting bronchodilators for managing emergency childhood asthma: an overview of reviews. Allergy. 2017; 72(2): 183–200, doi: 10.1111/all.13039, indexed in Pubmed: 27588581.
46. Emeryk A., Doniec Z., Mazurek H. i wsp. Zasady stosowania komór inhalacyjnych u dzieci. Pediatria Polska. 2017; 92(3): 288–293, doi: 10.1016/j.pepo.2017.02.003.
47. Boshra M.S., Almeldien A.G., Salah Eldin R. i wsp. Total emitted dose of salbutamol sulphate at different inhalation flows and inhalation volumes through different types of dry powder inhalers. Exp Lung Res. 2018; 44(4-5): 211–216, doi: 10.1080/01902148.2018.1489015, indexed in Pubmed: 30346848.
48. Emeryk A., Bodajko-Grochowska A., Bartkowiak-Emeryk M. Postępowanie ambulatoryjne w zaostrzeniach astmy u dzieci poniżej 6. roku życia. Między standardami a życiem. Standardy Medyczne/Pediatria. 2017; 14: 808–818.
49. Lin A.T., Moore-Clingenpeel M., Karsies T.J. Comparison of two continuous nebulized albuterol doses in critically ill children with status asthmaticus. J Asthma. 2019 [Epub ahead of print]: 1–7, doi: 10.1080/02770903.2019.1623249, indexed in Pubmed: 31119958.
50. Rodrigo G. Asthma in adults (acute). BMJ Clin Evid. 2011; 4: 1513.
51. Lin Y.Z., Huang F.Y. Comparison of breath-actuated and conventional constant-flow jet nebulizers in treating acute asthmatic children. Acta Paediatr Taiwan. 2004; 45(2): 73–76, indexed in Pubmed: 15335114.
52. Lipworth B.J., Sims E.J., Taylor K. i wsp. Dose-response to salbutamol via a novel palm sized nebuliser (Aerodose Inhaler), conventional nebuliser (Pari LC Plus) and metered dose inhaler (Ventolin Evohaler) in moderate to severe asthmatics. Br J Clin Pharmacol. 2005; 59(1): 5–13, doi: 10.1111/j.1365-2125.2005.02168.x, indexed in Pubmed: 15606434.
53. Ducharme F.M., Dell S.D., Radhakrishnan D. i wsp. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. Can Respir J. 2015; 22(3): 135–143, doi: 10.1155/2015/101572, indexed in Pubmed: 25893310.
54. Hartman S., Merkus P., Maseland M. i wsp. Hypokalaemia in children with asthma treated with nebulised salbutamol. Arch Dis Child. 2015; 100(10): 970–972, doi: 10.1136/archdischild-2015-308427, indexed in Pubmed: 26044135.
55. Global Strategy for the Diagnosis, Management, andPrevention of Chronic Obstructive Pulmonary Disease 2020 Report. Dostępne na stronie: https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf. [Dostep: 14.01.2020 r.].
56. van Geffen WH, Douma WR, Slebos DJ, et al. Bronchodilators delivered by nebuliser versus pMDI with spacer or DPI for exacerbations of COPD. Cochrane Database Syst Rev. 2016(8): CD011826, doi: 10.1002/14651858.CD011826.pub2, indexed in Pubmed: 27569680.
57. Bardsley G, Pilcher J, McKinstry S, et al. Oxygen versus air-driven nebulisers for exacerbations of chronic obstructive pulmonary disease: a randomised controlled trial. BMC Pulm Med. 2018; 18(1): 157, doi: 10.1186/s12890-018-0720-7, indexed in Pubmed: 30285695.
58. Doniec Z., Mastalerz-Migas A., Bręborowicz A. i wsp. Rekomendacje postępowania w astmie wczesnodziecięcej dla lekarzy Podstawowej Opieki Zdrowotnej — KOMPAS POZ. Fam Med Prim Care Review. 2016; 8: 81–92.
59. Ventolin. Charakterystyka produktu leczniczego. Dostępne na stronie: http://leki.urpl.gov.pl/files/25_Ventolin_aerozol_inh_zaw.pdf. [dostęp: 14.12.2019].
60. Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev. 2014(6): CD001266, doi: 10.1002/14651858.CD001266.pub4, indexed in Pubmed: 24937099.
61. Dunn M, Muthu N, Burlingame CC, et al. Reducing albuterol use in children with bronchiolitis. Pediatrics. 2020; 145(1), doi: 10.1542/peds.2019-0306, indexed in Pubmed: 31810996.
62. Bar-Aluma BE, Efrati O, Kaufmann H, et al. A controlled trial of inhaled bronchodilators in familial dysautonomia. Lung. 2018; 196(1): 93–101, doi: 10.1007/s00408-017-0073-7, indexed in Pubmed: 29234869.
63. Barry PJ, Flume PA. Bronchodilators in cystic fibrosis: a critical analysis. Expert Rev Respir Med. 2017; 11(1): 13–20, doi: 10.1080/17476348.2017.1246358, indexed in Pubmed: 27718752.
64. Knight-Madden J, Hambleton I. Inhaled bronchodilators for acute chest syndrome in people with sickle cell disease. Cochrane Database of Systematic Reviews. 2016, doi: 10.1002/14651858.cd003733.pub4.
65. Melo SM, Oliveira LA, Rocha RD, et al. Bronchodilator test in extreme old age: Adverse effects of short-acting beta-2 adrenergic agonists with clinical repercussion and bronchodilator response. Rev Assoc Med Bras (1992). 2019; 65(11): 1343–1348, doi: 10.1590/1806-9282.65.11.1343, indexed in Pubmed: 31800894.

Monika Bal-Bocheńska[1, 2], Justyna Wyszyńska[1], Wojciech Kądziołka[2]

[1]Medical College of Rzeszów University, University of Rzeszów, Poland
[2]Clinical Provincial Hospital No. 1, Podkarpackie Center for Lung Diseases in Rzeszów, Poland

Early and interdisciplinary physiotherapy in a patient in the intensive care unit with a bronchopulmonary fistula after thoracic fenestration: a case report

Abstract

The aim of this study is to present the effects of the medical team's therapy with particular focus on early physiotherapy in a patient subjected to elective pneumonectomy due to pleural empyema and chest fenestration. Our patient was 48 years old and underwent an elective pneumonectomy due to pleural empyema and cicatrization atelectasis as a result of complications. A lack of lung recoil after chest fenestration was the indication to transfer the patient to the intensive care unit (ICU) from the operating theater. Respective rehabilitation is necessary to restore the function of the respiratory system. It should be an integral part of the treatment plan, must be implemented in a timely manner, and should continue until the patient's full recovery. This paper presents the effects of the medical team's work with the emphasis on early physiotherapy in a patient in the ICU that resulted in a shorter hospitalization and a full return to functional capacity.

Key words: bronchopulmonary fistula, ICU, physiotherapy, stimulation of breathing, thoracic fenestration

Adv Respir Med. 2020; 88: 450–453

Introduction

The intensive care unit (ICU) is a common place for patients to stay after thoracic surgery when they are in a life-threatening condition. The process of treating patients in the ICU requires holistic management from the entire medical team. Operated patients are often exposed to prolonged immobilization. Early rehabilitation is safe and helps to reduce physical and psychological complications in patients. The priority is to improve the patient's critical status caused by potentially reversible failure of bodily systems. Holistic therapy is an interdisciplinary specialty in clinical medicine which also includes physiotherapy. The presented case confirms that personalized therapy has a significant impact on the improvement of treatment results while patients return to functional capacity.

Case report

A male patient aged 48 had elective surgery performed due to right pleural empyema. The patient demonstrated protein-caloric wasting (body mass index: 17.36). He underwent pleural decortication, right-sided pneumonectomy due to cicatrization atelectasis with pulmonary gangrene (TBC) with lack of recoil, and fenestration of the chest on the right side. The anterolateral sections of ribs III–IX were removed. The procedure was complicated by large blood loss (2500 mL) and hemorrhagic shock. The patient under, the influence of general anesthetics, was transferred from the Thoracic Surgery Operating Theater to the ICU.

Physiotherapy in the patient with a bronchopleural fistula after thoracic fenestration was introduced on the 5th day. The early implementation of the process allowed to limit the iatrogenic effects of immobilization. The process of physiotherapy

Address for correspondence: Justyna Wyszyńska, Institute of Health Sciences, Medical College of Rzeszów University, Rzeszów, Poland; e-mail: justyna.wyszynska@onet.pl
DOI: 10.5603/ARM.a2020.0128
Received: 22.04.2020
Copyright © 2020 PTChP
ISSN 2451–4934

in the critically ill patient was personalized and adapted to his health condition. The management covered three comprehensive domains:

— preservation of the full range of motion in the joints and prevention of contractures;
— counteracting muscle weakening and muscle wasting;
— improvement of circulatory and respiratory function.

Resection of the lung parenchyma was, in this case, an elective treatment. A proper rehabilitation was necessary to restore efficient functioning of the respiratory system. The patient, who was in a medium-severe condition, conscious, and alert and oriented, was ventilated and infused with Levonor solution to assist circulation. The prolonged state of hypokinesia, which negatively affected the anatomy of the human body, was countered with personalized kinesiotherapy. Passive exercise and functional positioning counteracted the decrease of muscle strength while, at the same time, proprioceptive stimulation influenced the central nervous system. Buerger's exercises were also introduced covering a three-minute rotation of lower limb positioning in the following order: passive ischaemia, hyperemia, and rest.

On the 10th day, bronchoaspiration was performed and small amounts of mucopurulent secretion were sucked out until the stump of the bronchi was sealed. Fully assisted partial verticalization was performed and a normal orthostatic change in vital parameters was noted. The effects came unexpectedly fast. From the 11th day on, rehabilitation could be performed in the sitting position. On the 12th day of the ICU stay, morphine was discontinued and assisted ventilation was withdrawn leaving the patient on passive therapy with nasal cannula 6 L/min. Exercises based on symmetrical pelvic movements in closed chains for the limbs were introduced in which the head and trunk are extended to enhance the sitting position during exercises of the shoulder girdle on the right side. In order to maintain proper ventilation, stimulation of respiration using different pathways was used. On the 14th day, the patient was able to maintain the stabilization of the lower trunk independently in a position with feet resting and stabilized on the ground. Achieving a higher position allowed for the inclusion of exercises enhancing the muscular strength of the lower limbs using a bedside cycle ergometer (Figure 1). The patient was verticalized every day. On the 15th day, tracheostomy was performed due to a need for prolonged ventilation. The patient was ventilated again. In addition, the therapist introduced manual work by stimulating the abdominal muscles to use indirect work on the respiratory system because after thoracic surgery, direct work on the surface of the ribs and sternum was impossible.

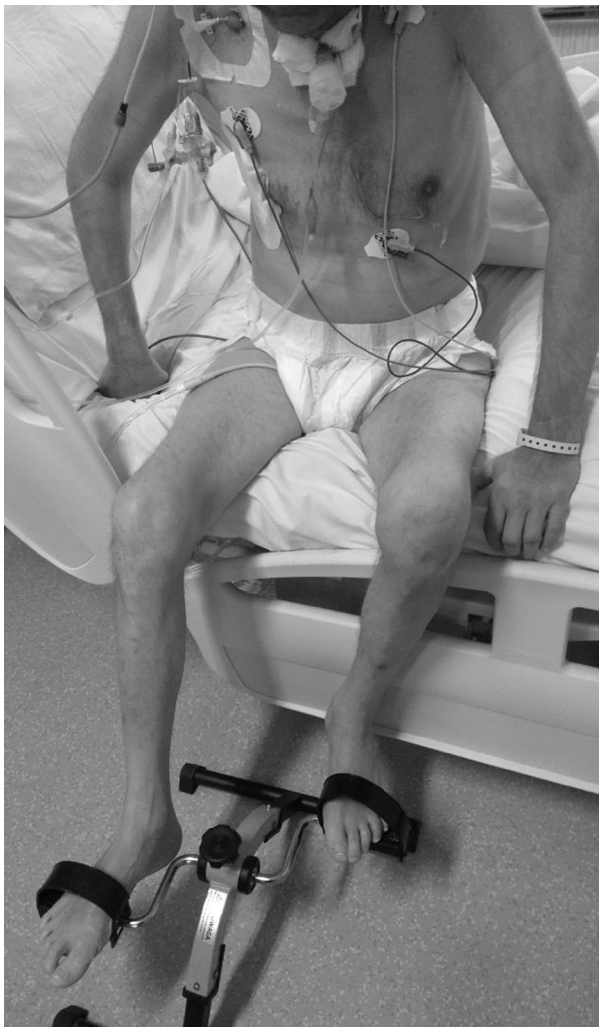

Figure 1. Training with a bedside cycle ergometer (informed consent to publication was obtained from patient)

Rehabilitation was carried out 6 days a week continuing the plan of the program. On the 19th day, the patient was in logical contact without sedation and was disconnected from the respirator. He remained on his own breathing through the tracheotomy tube. The next verticalizations took place in full circulatory and respiratory capacity, with an oxygen saturation of 94–99%. The bone window created in the thorax wall allowed for open healing of the abscess (Figure 2). In addition to parenteral feeding through a central port, an easily digestible diet rich in protein was introduced. The daily verticalization of the patient from the 14th day of hospitalization prevented the development of contractures of the short muscles of the feet and Achilles tendons. Verticalization of

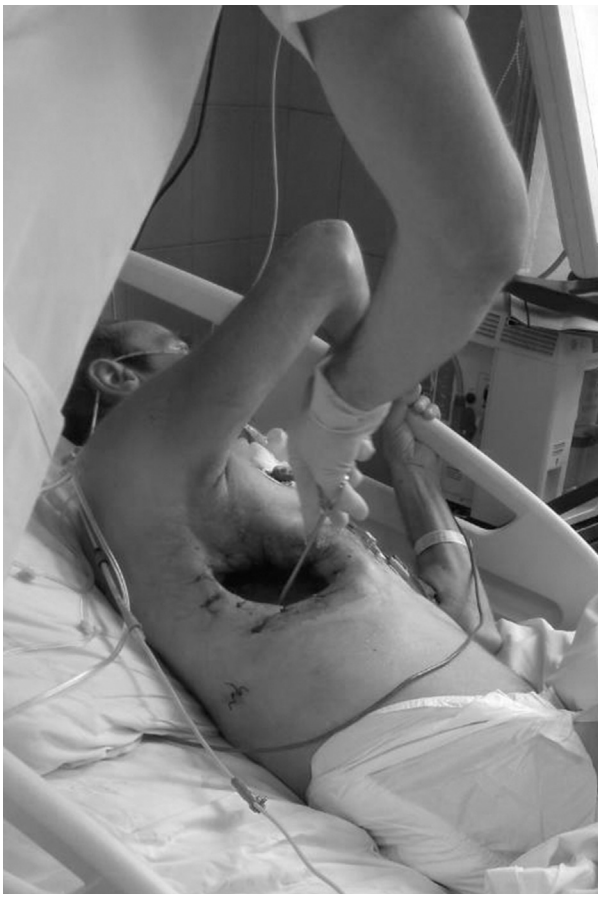

Figure 2. Dressing change (informed consent to publication was obtained from patient)

the patient in stages forced him to be active and involved. In the first period, he stabilized his feet, knee joints, pelvis, and shoulder girdle. At the end of the rehabilitation process, after applying appropriate knee joint fixation, the patient stood independently aided only by support at one location (on the sacral bone). In the afternoon, the patient performed simple self-assisted exercises of the upper limbs in a sitting position. Rehabilitation of the critically ill patient was conducted under constant monitoring of the bodily systems: blood pressure, ECG, saturation, and capnometry. On the 26th day, a cardiopulmonary and respiratory capable patient with passive oxygen therapy was transferred to the Department of Thoracic Surgery where he stayed for the next 10 days.

After the fenestration was closed, pleural sterilization was performed through a drain with an iodine solution and a dressing change. The chest was asymmetrical. The rehabilitation process was continued and exercises with blue Thera-band were introduced. The patient was educated about the purposefulness of carrying out resistance exercises with tools such as a water bottle or Trifflo apparatus. The correct performance of these exercises aided in the evacuation of bronchial tree secretions. From the very first day in the Thoracic Surgery department, the most important thing in the rehabilitation process was the patient's independent activity. The exercises in the ICU were initially assisted on by a therapist. As the patient's muscle strength and education improved, they began to be initiated by the patient himself and were performed several times a day after receiving proper instructions from the physiotherapist. An increase in the strength of the respiratory muscles was observed in the following days. There was also a significant increase in chest circumference and a reduction in dyspneic episodes during resisted breathing exercises. Building trust and a sense of security in a critically ill patient is an important foundational step that initiates good therapy perspectives, especially when taking into account the long duration of rehabilitation at all stages of treatment.

The patient was discharged home from the Clinical Thoracic Surgery Department after 36 days in the Provincial Clinical Hospital — Center for Lung Diseases in a stable condition. He was fully capable and independent. The patient remained in the care of the Thoracic Surgery Outpatient Clinic where he had regular follow-ups.

Discussion

Interdisciplinary rehabilitation undertaken in the ICU is an indispensable element of the holistic treatment process of patients. According to Parker *et al.*, programmed physiotherapy contributes to a reduction in the occurrence of possible disorders acquired by surgical patients in the ICU [1]. Dhand reports that polyneuropathy, myopathy, and prolonged neuromuscular blockade are now considered a frequent cause of newly acquired disease syndromes in these patients [2]. Early rehabilitation is associated with increased functional capacity and muscle strength in critically ill patients. The cyclical nature of verticalization affects the patient's perceived quality of life. In addition, Chapman *et al.* demonstrated that keeping the patient in a semi-high position not only protects him from aspiration of offending agents in the alimentary tract, but also protects against ventilator-associated pneumonia [3]. Ibáñez *et al.* presented similar conclusions emphasizing the significant impact of early rehabilitation in critically ill patients which reduced the time of their hospitalization in the ICU [4]. Other studies have shown that early physical mobilization

can be performed in critically ill patients even when they require mechanical ventilation thanks to movement patterns based on Proprioceptive Neuromuscular Facilitation (PNF) [5]. It is emphasized that actions to improve the state of critically ill patients should be carried out while observing the results of monitoring systems including blood pressure, ECG, and oxygen saturation [6]. It has been shown that an increase in respiratory function is associated with the use of resistance and strengthening exercises which influence the increase in the efficiency of the critically ill organism [7]. The effectiveness of respiratory rehabilitation based on the elements of the PNF method to increase respiratory functions was also demonstrated by authors who carried out research using resistance and strengthening respiratory exercises in neurological patients in ICUs [8, 9]. Park *et al.* recommended indirect work on the respiratory system when direct work on the ribs is impossible so that the abdominal muscles are stimulated [10]. It was also demonstrated that bedside cycling can improve rehabilitation in critically ill patients as it ensures low-intensity movement and introduces activity to patients after pneumonectomy which affects the individual improvement of the body's capacity [11]. Our paper joins the growing collection of literature that suggests that early training cycles on a bedside bike can safely be carried out with critically ill patients. Camargo Pires-Neto *et al.* confirmed that a single 20-minute cycling session commenced within the first 72 hours showed no safety concern as long as patients received low-dose infusions of a vasoactive drug to limit the increase in cardiac output [12]. Cycling specifically targets the legs and requires movements that involve hip flexion which is important because these are parts of the body that are most susceptible to muscle atrophy and weakness when lying in bed [13]. Maintaining muscular strength may improve functional outcome as both paresis acquired at ICU and decreased muscle strength were independently associated with poor hospital results [14]. Early rehabilitation had a significant impact on the functional state, muscle strength, mechanical ventilation time, gait capacity on discharge, and overall quality of life [15].

The analysis of the material as well as the authors' own experiences allow for the formulation of several conclusions regarding early thoracic-surgical rehabilitation of the patient at the ICU. The main goal of rehabilitation is to prevent complications resulting from immobilization by instilling early and functional mobilization of the patient which shortens hospitalization and accelerates the return of functional capacity by improving the patient's quality of life.

Conflict of interest

None declared.

References:

1. Parker A, Sricharoenchai T, Needham DM. Early rehabilitation in the intensive care unit: preventing physical and mental health impairments. Curr Phys Med Rehabil Rep. 2013; 1(4): 307–314, doi: 10.1007/s40141-013-0027-9, indexed in Pubmed: 24436844.
2. Dhand UK. Clinical approach to the weak patient in the intensive care unit. Respir Care. 2006; 51(9): 1024–40; discussion 1040, indexed in Pubmed: 16934166.
3. Chapman AR, Litton EL. Primary prevention in the intensive care unit: a prospective single-centre study of the risk factors for invasive pneumococcal disease. Anaesth Intensive Care. 2017; 45(4): 448–452, doi: 10.1177/0310057X1704500406, indexed in Pubmed: 28673213.
4. Ibáñez J, Peñafiel A, Raurich JM, et al. Gastroesophageal reflux in intubated patients receiving enteral nutrition: effect of supine and semirecumbent positions. JPEN J Parenter Enteral Nutr. 1992; 16(5): 419–422, doi: 10.1177/0148607192016005419, indexed in Pubmed: 1433774.
5. Conceição TM, Gonzáles AI, Figueiredo FC, et al. Safety criteria to start early mobilization in intensive care units. Systematic review. Rev Bras Ter Intensiva. 2017; 29(4): 509–519, doi: 10.5935/0103-507X.20170076, indexed in Pubmed: 29340541.
6. Arias-Fernández P, Romero-Martin M, Gómez-Salgado J, et al. Rehabilitation and early mobilization in the critical patient: systematic review. J Phys Ther Sci. 2018; 30(9): 1193–1201, doi: 10.1589/jpts.30.1193, indexed in Pubmed: 30214124.
7. Liaw MY, Lin MC, Cheng PT, et al. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. Arch Phys Med Rehabil. 2000; 81(6): 752–756, doi: 10.1016/s0003-9993(00)90106-0, indexed in Pubmed: 10857519.
8. Seo K, Cho M. The effects on the pulmonary function of normal adults proprioceptive neuromuscular facilitation respiration pattern exercise. J Phys Ther Sci. 2014; 26(10): 1579–1582, doi: 10.1589/jpts.26.1579, indexed in Pubmed: 25364117.
9. Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. Cardiopulm Phys Ther J. 2012; 23(1): 5–13, indexed in Pubmed: 22807649.
10. Park SY, Park IK, Hwang Y, et al. Immediate postoperative care in the general thoracic ward is safe for low-risk patients after lobectomy for lung cancer. Korean J Thorac Cardiovasc Surg. 2011; 44(3): 229–235, doi: 10.5090/kjtcs.2011.44.3.229, indexed in Pubmed: 22263157.
11. Needham DM, Truong AD, Fan E. Technology to enhance physical rehabilitation of critically ill patients. Crit Care Med. 2009; 37(10 Suppl): S436–S441, doi: 10.1097/CCM.0b013e3181b6fa29, indexed in Pubmed: 20046132.
12. Camargo Pires-Neto R, Fogaça Kawaguchi YM, Sayuri Hirota A, et al. Very early passive cycling exercise in mechanically ventilated critically ill patients: physiological and safety aspects--a case series. PLoS One. 2013; 8(9): e74182, doi: 10.1371/journal.pone.0074182, indexed in Pubmed: 24040200.
13. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci. 2002; 57(12): M772–M777, doi: 10.1093/gerona/57.12.m772, indexed in Pubmed: 12456735.
14. Arias-Fernández P, Romero-Martin M, Gómez-Salgado J, et al. Rehabilitation and early mobilization in the critical patient: systematic review. J Phys Ther Sci. 2018; 30(9): 1193–1201, doi: 10.1589/jpts.30.1193, indexed in Pubmed: 30214124.
15. Yeampattanaporn O, Mekhora K, Jalayondeja W, et al. Immediate effects of breathing re-education on respiratory function and range of motion in chronic neck pain. J Med Assoc Thai. 2014; 97 Suppl 7: S55–S59, indexed in Pubmed: 25141528.

Nitesh Gupta, Abanti Das, Pranav Ish, Rohit Kumar, Ankit Sharma, Shibdas Chakrabarti

Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India

A case of an 81-year-old with cough and dyspnea

Abstract

It is uncommon to diagnose usual interstitial pneumonitis as a unilateral presentation. We present a case of an 81-year-old current smoker who presented with exertional dyspnea and dry cough. The patient had right sided UIP pattern in the CT chest along with hiatus hernia. The etiology for the unilateral lung involvement was postulated to be due to the hiatus hernia leading to gastro--esophageal reflux disease (GERD) which caused micro aspirations leading to lung injury and fibroblast activation. Whether this can be prevented by anti-reflux medications needs further research. Our patient was managed with pirfenidone, metered dose inhalers containing tiotropium and proton-pump inhibitors. Thus, a high index of suspicion for underlying gastro-esophageal reflux must be kept in such patients to arrive at an early diagnosis and start treatment.

Key words: unilateral UIP, GERD, hiatus hernia

Adv Respir Med. 2020; 88: 454–457

Introduction

Usual interstitial pneumonitis (UIP) pattern is often seen in idiopathic pulmonary fibrosis, rheumatoid arthritis associated interstitial lung disease, chronic hypersensitivity pneumonitis, asbestosis along with progressive fibrosing interstitial lung diseases. The pattern is described with bilateral subpleural basal reticular opacities with honeycombing, with or without traction bronchiectasis. Occasionally, there can be a unilateral presentation of this pattern leading to diagnostic dilemma. We present a case of an elderly male patient who had an unilateral UIP with an interesting underlying probable etiology.

Case report

An 81-year-old man, current smoker with 30 pack-years smoking history, presented to the out-patient department with complaints of gradually progressive exertional dyspnea for 4 months associated with dry cough, more in the evening. There was no history of fever, hemoptysis, loss of weight or appetite. The patient was on proton-pump inhibitors (PPI) irregularly since last 6 years for gastroesophageal reflux disease (GERD). There were no other comorbidities. He denied history of joint pains, Raynaud phenomenon, skin tightening, dry eyes, dry mouth or any skin rash. The patient had no other drug intake, relevant family history and has negative autoimmune markers.

Examination of the chest revealed right sided end-inspiratory Velcro-like crackles. Arterial blood gas analysis revealed the following parameters: pH — 7.41, pO_2 — 63, pCO_2 — 39 and bicarbonate (HCO_3) — 24. A spirometry was suggestive of FEV1/FVC (forced expiratory volume in one second/forced vital capacity) of 63, FEV1 — 40% and FVC — 65%; signifying obstruction with possible restriction, which was confirmed by a low total lung capacity. The chest X-ray and chest CT scans are attached (Figures 1–5).

The case was discussed in multidisciplinary discussion and both the radiologist and pulmonologist opined that it fulfils the criteria of usual interstitial pneumonia pattern. The etiology of unilateral involvement was postulated as gastroesophageal reflux disease (GERD) with recurrent aspirations in view of the nocturnal cough, use of PPI and a large hiatus hernia evident on CT

Address for correspondence: Pranav Ish, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India; e-mail: pranavish2512@gmail.com

DOI: 10.5603/ARM.a2020.0158
Received: 20.02.2020
Copyright © 2020 PTChP
ISSN 2451–4934

scan. A study done by Raghu *et al*. has shown that GERD prevalence is up to 87% in idiopathic pulmonary fibrosis (IPF) with only half of them having symptoms [1]. Another study suggested that nearly 66% of patients with IPF had reflux and symptoms did not help to diagnose it [2]. Hence, in the absence of symptoms, diagnosing GERD early and identifying it as a risk factor for initiation and progression of IPF is difficult. However, GERD associated with recurrent aspirations, preferably on the right side can lead to lung injury and fibroblast activation which may be responsible for unilateral IPF. Whether this can be prevented by anti-reflux medications needs further research. Our patient was discharged on pirfenidone, metered dose inhalers containing tiotropium and proton-pump inhibitors. He did not give consent to surgical lung biopsy.

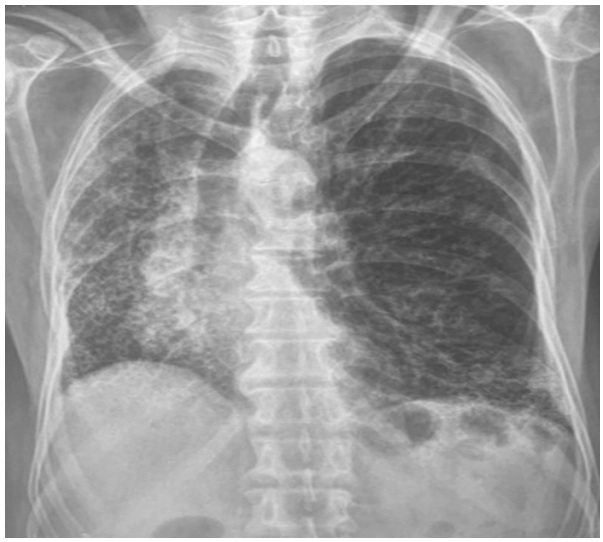

Figure 1. Frontal chest radiograph showing volume loss in the right hemithorax with ipsilateral cardio-mediastinal shift. Diffuse reticular opacities with preferential involvement of the right side and an apico-basal gradient on the left side

Thus, a final diagnosis of unilateral usual interstitial pneumonitis (UIP) with underlying hiatus hernia causing GERD was made. In view of negative drug history, autoimmune history and investigations, occupational or exposure history, a diagnosis of unilateral IPF was considered.

Discussion

The literature on unilateral IPF and its plausible mechanisms is sparse [2]. A study of 14 asymmetrical IPF when compared to symmetrical IPF revealed similar clinical characteristics, including more frequent occurrence in men, elderly population with history of smoking with a trend towards increased mortality over an eight-year follow-up. The etiology of the unilateral nature of the disease could not be ascertained as GERD, prior radiation therapy to the chest and smoking history was not found to be significantly different. The authors, however, admitted to the small sample size to be able to find any causative etiologies [3].

Another large study of asymmetrical IPF investigated 96 patients, out of which 32 had asymmetrical IPF, but none had unilateral disease. This study found GERD and micro-aspirations as a plausible mechanism of the asymmetrical disease, which was supported by the increased right lung involvement [4]. A case of a middle-aged man with unilateral UIP revealed associated pulmonary artery sarcoma which can be the un-

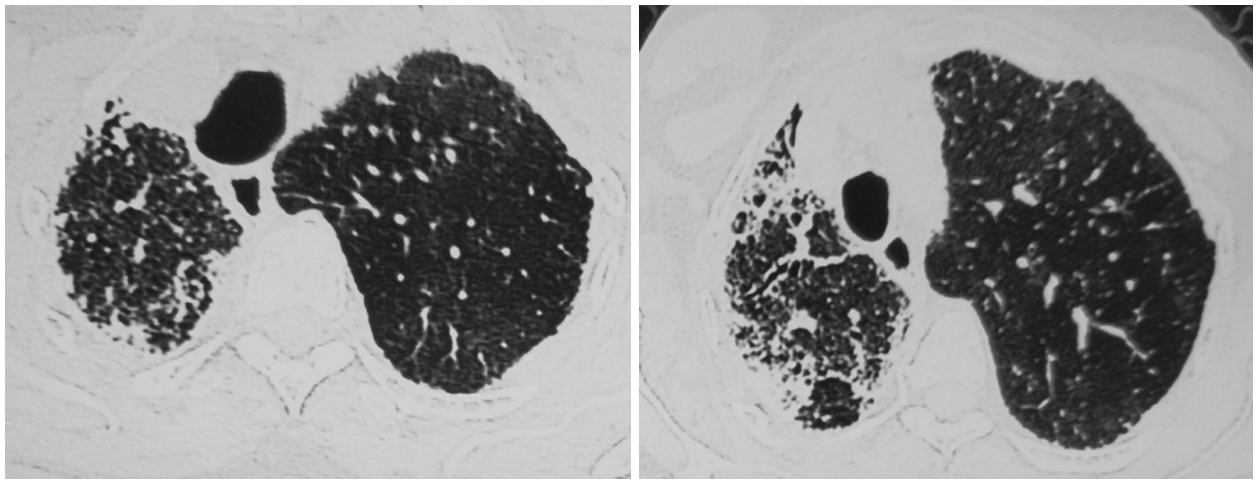

Figure 2. Axial sections through the upper lung zone show relative sparing of the lung apices and preferential involvement of the right side with compensatory hyperinflation on the left side. There is mild peripheral subpleural reticulations and traction bronchiolectasis

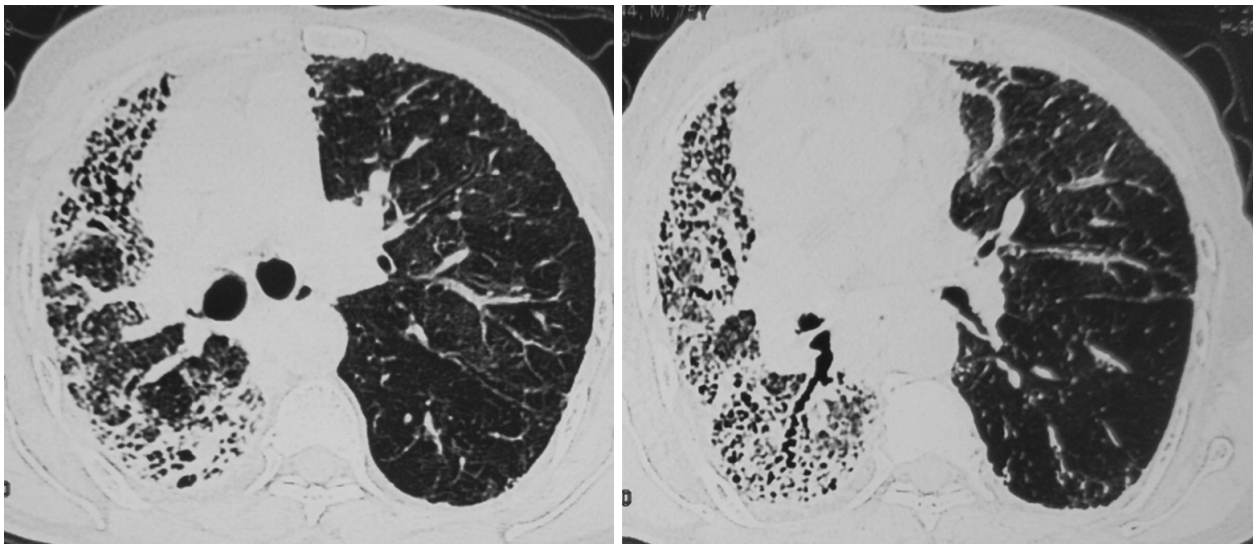

Figure 3. Axial sections through the carina and bronchus intermedius show apicobasal gradient with prominent traction bronchiectasis, fibrotic opacities, interlobular septal thickening on the right side with associated volume loss

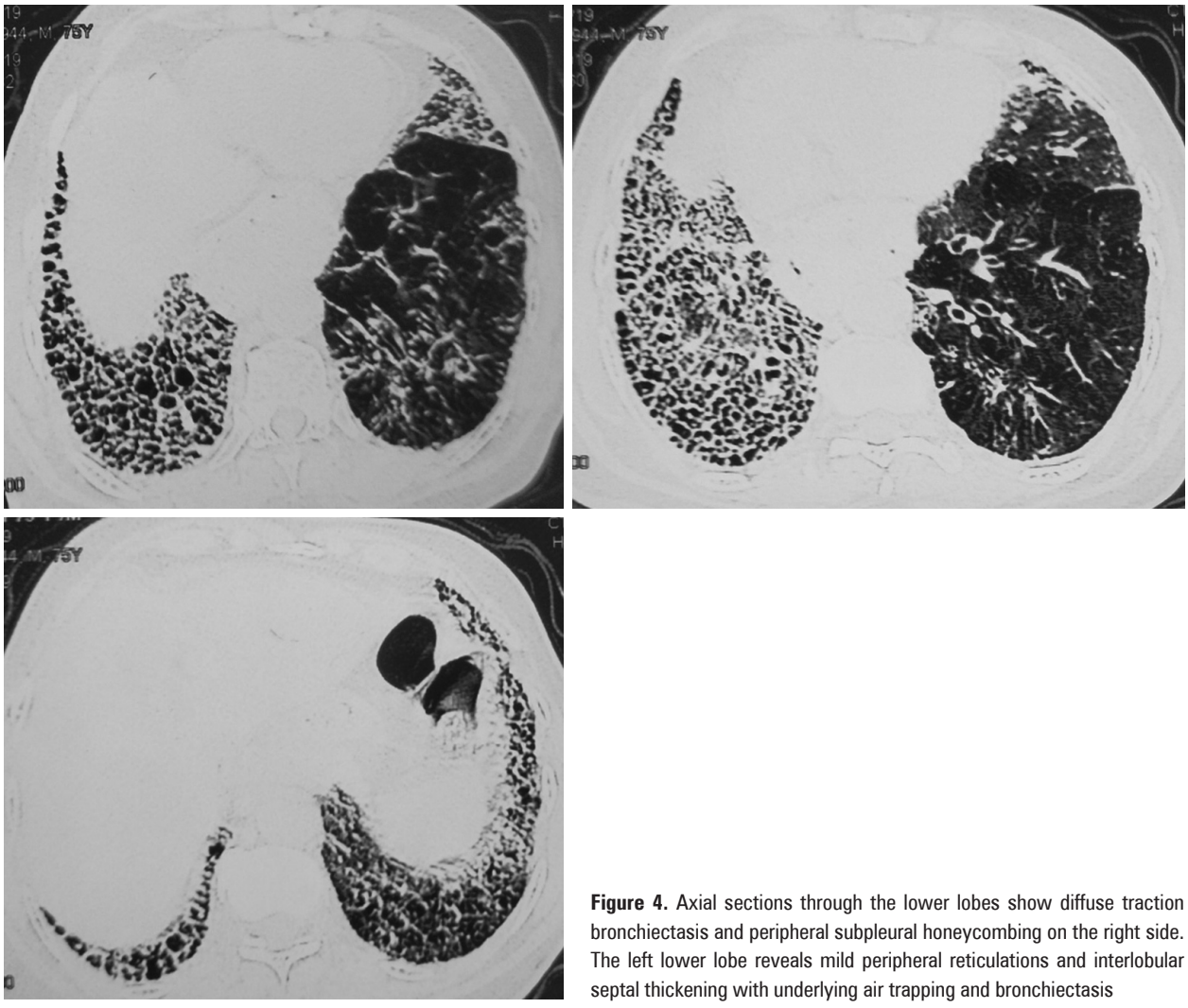

Figure 4. Axial sections through the lower lobes show diffuse traction bronchiectasis and peripheral subpleural honeycombing on the right side. The left lower lobe reveals mild peripheral reticulations and interlobular septal thickening with underlying air trapping and bronchiectasis

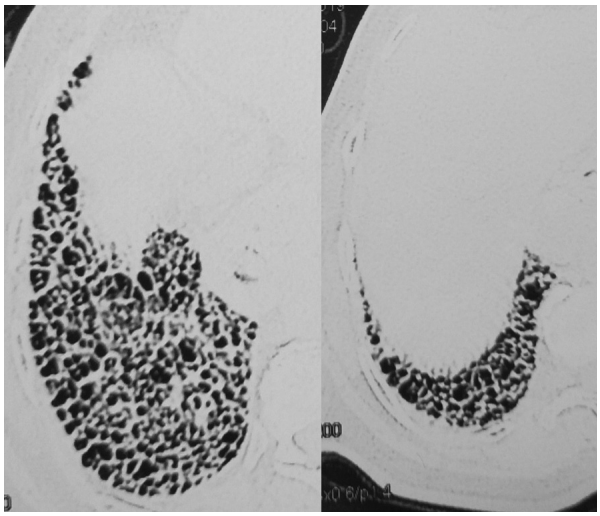

Figure 5. Magnified images of the right lower hemithorax showing peripheral subpleural honeycombing with basal predominance

derlying etiology in view of chronic pulmonary ischemia or the tumor producing some fibrogenic factors [5].

Two case reports of unilateral UIP were reported to be associated with connective tissue disorders — a young female with systemic sclerosis had GERD as the possible etiology of unilateral right sided UIP and a 70-year-old female with Sjogren syndrome with unilateral UIP who presented with an exacerbation [6, 7]. There is an interesting case report of Sweyer James Macleod syndrome (SJMS) presenting with unilateral UIP. The authors postulated that SJMS depletes the lung of source of myofibroblast which include epithelial cells and myofibroblasts. This leads to a protective effect for that lung, and eventually, the patient develops unilateral UIP only in the contralateral side [8].

Conclusion

To conclude, the existing literature on unilateral UIP is limited to case reports and case series, in view of its uncommon occurrence. However, a high index of suspicion must be kept for underlying possible causes like GERD resulting from hiatus hernia in such patients.

Conflict of interest

None declared.

References:

1. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006; 27(1): 136–142, doi: 10.1183/09031936.06.00037005, indexed in Pubmed: 16387946.
2. Sweet MP, Patti MG, Leard LE, et al. Gastroesophageal reflux in patients with idiopathic pulmonary fibrosis referred for lung transplantation. J Thorac Cardiovasc Surg. 2007; 133(4): 1078–1084, doi: 10.1016/j.jtcvs.2006.09.085, indexed in Pubmed: 17382656.
3. Callahan SJ, Xia M, Murray S, et al. Clinical characteristics in patients with asymmetric idiopathic pulmonary fibrosis. Respir Med. 2016; 119: 96–101, doi: 10.1016/j.rmed.2016.08.028, indexed in Pubmed: 27692155.
4. Tcherakian C, Cottin V, Brillet PY, et al. Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. Thorax. 2011; 66(3): 226–231, doi: 10.1136/thx.2010.137190, indexed in Pubmed: 20880868.
5. Chong S, Kim TS, Chung MP, et al. Unilateral usual interstitial pneumonia associated with sarcoma of the pulmonary artery. AJR Am J Roentgenol. 2007; 189(4): W221–W223, doi: 10.2214/AJR.05.1011, indexed in Pubmed: 17885035.
6. Lesnyak VN, Danilevskaya OV, Averyanov AV, et al. Unilateral pulmonary fibrosis and systemic sclerosis. Am J Respir Crit Care Med. 2014; 190(9): 1067–1068, doi: 10.1164/rccm.201407-1253IM, indexed in Pubmed: 25360729.
7. Takahashi T, Satoh M, Satoh H. Unilateral acute exacerbation of pulmonary fibrosis in association with Sjögren's syndrome. Intern Med. 1996; 35(10): 811–814, doi: 10.2169/internalmedicine.35.811, indexed in Pubmed: 8933193.
8. Abdulla O, Cain J, Howells J. Swyer-James-MacLeod syndrome with unilateral pulmonary fibrosis: a case report. BJR Case Rep. 2017; 3(4): 20160105, doi: 10.1259/bjrcr.20160105, indexed in Pubmed: 30363238.

Jolita Palacionyte[1], Vilma Hofertiene[2], Kristina Bieksiene[1], Skaidrius Miliauskas[1]

[1]Department of Pulmonology, Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Kaunas, Lithuania
[2]Department of Radiology, Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Kaunas, Lithuania

Massive hemoptysis due to anastomosis between the left phrenic artery and pulmonary arteries/veins

Abstract

Massive hemoptysis is a serious medical condition or emergency which needs immediate treatment. It typically appears in the bronchial arteries and can be caused by a wide range of pulmonary diseases. This report is based on a very rare case of a patient bleeding from an anastomosis between the left phrenic artery and pulmonary arteries/veins. In this case, the chest computed tomography had detected changes which required doctors to perform a successful embolization.

Key words: hemoptysis, phrenic artery, pulmonary artery, anastomosis, embolization

Adv Respir Med. 2020; 88: 458–461

Introduction

Hemoptysis, or the expectoration of blood, can range from the blood-streaking of sputum to the presence of gross blood in the absence of any accompanying sputum. Hemoptysis has a broad differential diagnosis, but the cause can be determined in the majority of patients [1]. Before assuming that the source of bleeding is from the lower respiratory tract, the possibility that the blood may be coming from a non-pulmonary source, such as the upper airway or the gastrointestinal tract, should be considered [2]. Hemoptysis is commonly caused by bronchiectasis, chronic bronchitis, and lung cancer [3]. Other rare causes of hemoptysis include pulmonary hamartomas, a congenital unilateral absence of the left pulmonary artery, and primary pulmonary hypertension [4]. Bronchopulmonary sequestration also can be a cause of hemoptysis.

When a patient presents with massive hemoptysis, the initial steps are to correctly position the patient, establish a patent airway, ensure adequate gas exchange and cardiovascular function, and control the bleeding [5]. Recently, non-bronchial systemic arteries have been reported as an important source of bleeding in patients with massive hemoptysis [6]. The Pulmonology Department of Kaunas Clinics, which is also connected to the Lithuanian University of Health Sciences, had a case where a 47-year-old male was hospitalized because of continued coughing up of blood over the course of, approximately, a few months. The diagnosed cause was both unexpected and rare.

Case report

A 47-year-old male had complained about continuing weakness, night sweats, and coughing up of blood (up to 200 mL per day). The patient had a history of chronic pancreatitis. He had no history of chronic bronchitis, bronchiectasis, tuberculosis, lung cancer, or other diseases. He had been smoking for roughly 30 years (approximately 10 cigarettes per day). Moreover, the man had been working as a welder for a long time. The patient reported no family history of any "lung problems".

The patient had been treated at the department of pulmonology 10 months ago. The man suffered from a low-risk pulmonary embolism,

Address for correspondence: Jolita Palacionyte, Department of Pulmonology, Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Kaunas, Lithuania; e-mail: jolita.palacionyte@kaunoklinikos.lt
DOI: 10.5603/ARM.a2020.0136
Received: 10.04.2020
Copyright © 2020 PTChP
ISSN 2451–4934

left lung abscess, and pneumonia. The prescribed medicine was heparin (of a low molecular weight) and later, rivaroxaban, an oral factor Xa inhibitor (for a 3 month period). In addition, the patient had also received therapy in the form of antibiotics. Finally, after the stationary period, the man started coughing up a small amount of blood. This continued for about a week, but eventually disappeared. Then, 3 months ago, the coughing up of blood had returned and the patient was subsequently hospitalized in Panevezys regional hospital. An examination of the chest was carried out with the help of a computed tomography (CT) scan and it showed that the lower lobe of the left lung had changes (infiltration with air bronchograms), and the middle lobe and the basal segments of the right lung had ground-glass opacities. Furthermore, a flexible bronchoscopy showed no changes and the microscopy of the bronchial specimens showed no acid resistant sticks (ARS). Finally, *Mycobacterium tuberculosis* was not found to be growing in bronchial specimens. The treatment had been carried out with the help of antibiotic therapy and the anemia had been corrected with red blood cell (RBC) transfusions.

After the stationary treatment, the man continued to cough up blood over the next few months and was admitted to our hospital for the third time. During the last visit, the patient's health was normal, and his hemodynamics were also stable. The breath sound was vesicular without changes, and the breathing frequency was 16 breaths per minute. SpO_2 was measured to be at 96 percent without any additional oxygen. There were no significant changes in other systems.

Based on the complaints, the disease anamnesis, and the data of the objective analysis, the patient was diagnosed with hemoptysis and chronic pancreatitis.

The blood analysis had showed anemia [hemoglobin (Hb) of 98 g/L with a slightly increased C–reactive protein (CRP) level of 23.8 mg/L]. Moreover, a slightly increased amount of liver enzymes [aspartate aminotransferase (AST) — 112 IU/L and alanine aminotransferase (ALT) — 39 IU/L] was also noted. The indicators of blood coagulation were within normal ranges. Finally, a fibro-bronchoscopy (FBS) was carried out because of an unclear source of bleeding from the respiratory tract. During FBS, a small amount of blood was observed in the lingula bronchus, and no active bleeding was found.

The bloody coughing continued throughout the treatment period so, therefore, a CT of the chest was performed. The chest CT revealed a heterogenous ill-defined consolidation and ground glass opacities in the lower lobe of the left lung (Figure 1). Contrast-enhanced CT showed a wide left branch of the phrenic artery and abnormal contrast enhancement in the basal segments of the left lung. These changes were considered to be anastomoses between the left phrenic artery and pulmonary arteries and veins. (Figure 2). Therefore, in order to stop the unnatural blood circulation, angiography and embolization of the left phrenic artery was performed (Figure 2).

Overall, this treatment was successful, and the symptoms were eliminated. At follow-up over one year after successful treatment, the coughing

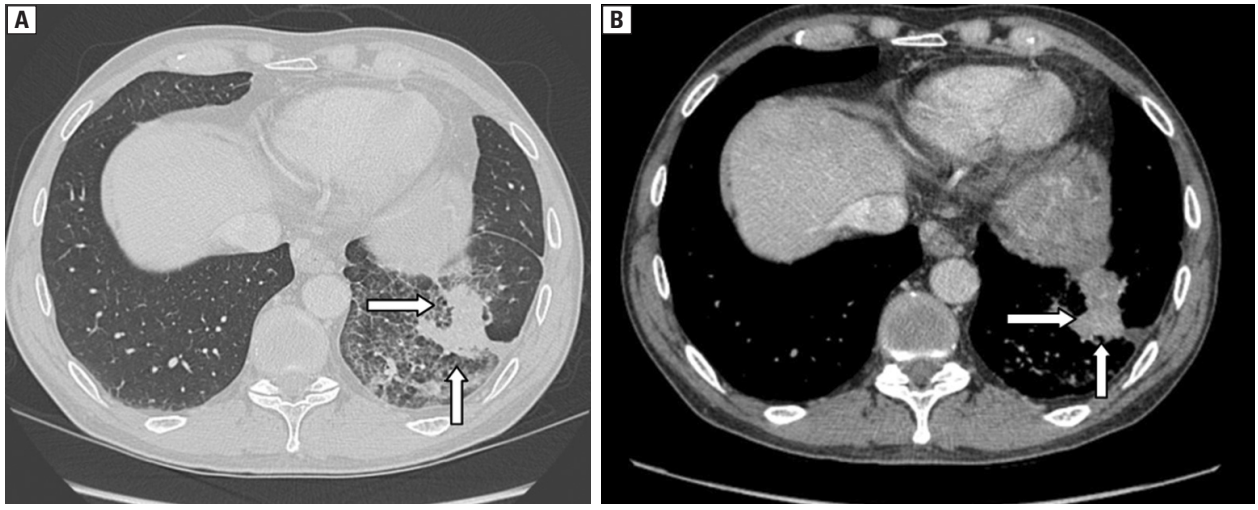

Figure 1. Computed tomography axial images demonstrate a heterogenous consolidation and ground glass opacities in the lower lobe of the left lung: **A**. Lung window (the lesion — white arrows); **B.** Soft-tissue window (the lesion — white arrows)

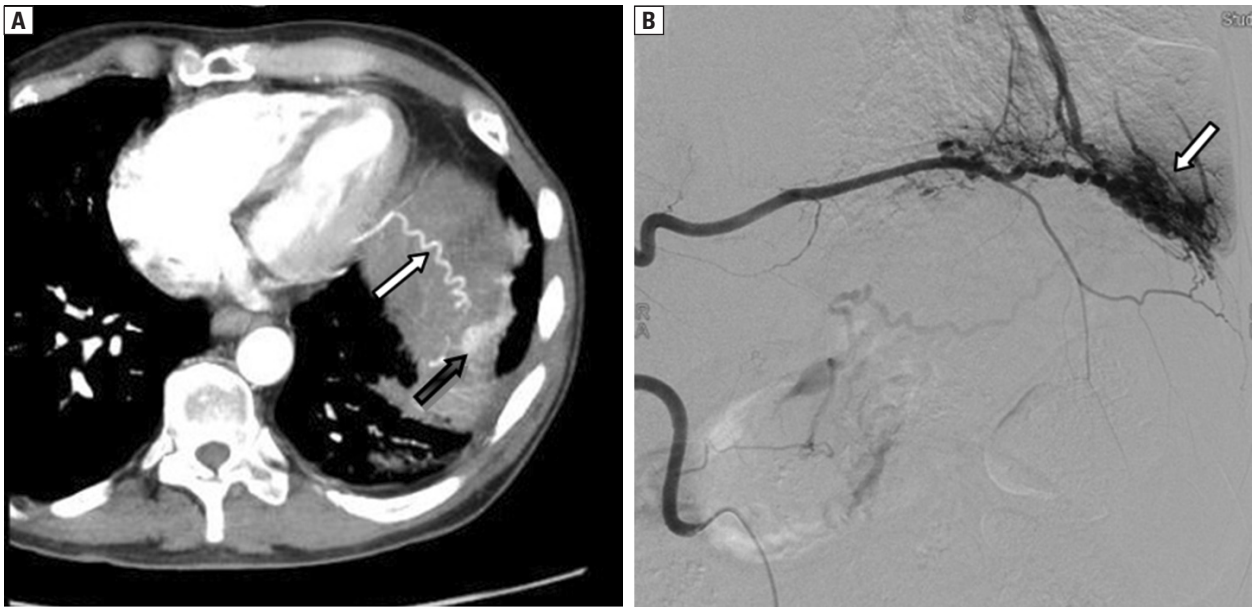

Figure 2. Contrast-enhanced computed tomography images: **A.** Maximum intension projection (MIP) — the white arrow shows a wide left branch of phrenic artery; the black arrow shows abnormal contrast enhancement in the basal segments of the left lung; **B.** Angiography (white arrow) confirmed an abnormal vascular anastomosis between the left inferior phrenic artery and pulmonary arteries and veins

up of blood did not recur. The patient feels well and can engage in routine activities.

Discussion

This report presents a clinical case of a middle-aged male patient who had coughed up blood for a long time. However, the final diagnosis was unexpected and rare.

Blood arising from the bronchial arteries has a high perfusion pressure and as a result, is a more common source of massive hemoptysis than blood from the pulmonary circulation [7]. Less than 10% of all cases of hemoptysis originate from the pulmonary arteries [8]. In the remaining 10% of cases, the internal mammary, intercostal, and inferior phrenic artery are typically involved in hemoptysis [9]. This case of hemoptysis was caused by an anastomosis between the left phrenic artery and pulmonary arteries/veins. Transpleural systemic-pulmonary artery anastomoses may develop in patients with bronchiectasis, cystic fibrosis, tuberculosis, or chronic pneumonia [9]. In the case presented, a man had an anastomosis between the left inferior phrenic artery and pulmonary arteries and veins in the form of a fistula which was the source of bleeding in the left lower lobe. The literature describes several clinical cases of hemoptysis caused by fistula formation between the phrenic artery and pulmonary artery. Yakushiji *et al.* published a similar clinical case with massive hemoptysis when an elderly woman had a right inferior phrenic artery-to-pulmonary artery fistula [10].

In our case, the localization of the vascular anastomosis was the same. For this reason, we think that the left lung abscess which was detected and treated in the hospital 10 months ago was the reason this pulmonary vascular anastomosis. A left lung abscess could have caused pulmonary sequestration, which in turn would explain why the male patient presented with recurrent hemoptysis.

Pulmonary sequestration is a rare congenital malformation that is uncommonly diagnosed during adulthood [11]. Most pulmonary sequestrations arise in the left lung and receive blood supply from the systemic circulation, most commonly from the thoracic or abdominal aorta [11]. Initially, intrathoracic sequestration was thought to be a congenital anomaly and the "accessory lung bud theory" was considered to be the basis for its development [12]. Current concepts, however, suggest that it could be an acquired disease and may be attributed to obliterative bronchitis and obstruction of the lower lobe bronchus secondary to repeated necrotizing infections of the lung [12]. We think that our patients pulmonary sequestration developed after the left lung abscess. Chest CT findings are useful for the diagnosis of pulmonary sequestration as those can show cystic areas or areas of consolidation with the abnormal artery usually being mostly in the lower lobe [13].

Conclusion

Massive hemoptysis is a serious medical condition which needs immediate treatment. The present clinical case demonstrates that effective transcatheter embolization is a well-established and effective non-surgical procedure for the management of massive hemoptysis.

Conflict of interest

None declared.

References:

1. Weinberger SE. Etiology and evaluation of hemoptysis in adults. Available at: https://www-uptodate-com.ezproxy.dbazes.lsmuni.lt/contents/etiology-and-evaluation-of-hemoptysis-in adults?search=hemoptysis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. [Last accessed at: 02.02.2018].
2. Ingbar DH. Massive hemoptysis: causes. Available at: www-uptodate-com.ezproxy.dbazes.lsmuni.lt/contents/massive-hemoptysis-causes?search=hemoptysis&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=5. [Last accessed: 02.12.2018].
3. Cordovilla R, Bollo de Miguel E, Nuñez Ares A, et al. Diagnosis and treatment of hemoptysis. Arch Bronconeumol. 2016; 52(7): 368–377, doi: 10.1016/j.arbres.2015.12.002, indexed in Pubmed: 26873518.
4. Gu W, Sun Lh, Fang Sr, et al. Clinical analysis of the rare causes of hemoptysis: a report of 4 cases. Zhonghua Jie He He Hu Xi Za Zhi. 2007; 30(5): 343–346, indexed in Pubmed: 17651639.
5. Ingbar DH. Overview of massive hemoptysis. Available at: https://www-uptodate-com.ezproxy.dbazes.lsmuni.lt/contents/overview-of-massive-hemoptysis?search=hemoptysis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. [Last accessed at: 02.12.2018].
6. Noë GD, Jaffé SM, Molan MP. CT and CT angiography in massive haemoptysis with emphasis on pre-embolization assessment. Clin Radiol. 2011; 66(9): 869–875, doi: 10.1016/j.crad.2011.03.001, indexed in Pubmed: 21658690.
7. Grippi MA, Elias JA, Fishman JA, et al. Fishman's, pulmonary diseases and disorders. McGraw Hill, Philadelphia 2015.
8. Khalil A, Fedida B, Parrot A, et al. Severe hemoptysis: From diagnosis to embolization. Diagn Interv Imaging. 2015; 96(7-8): 775–788, doi: 10.1016/j.diii.2015.06.007, indexed in Pubmed: 26141487.
9. Webb WR, Jacobs RP. Transpleural abdominal systemic artery-pulmonary artery anastomosis in patients with chronic pulmonary infection. AJR Am J Roentgenol. 1977; 129(2): 233–236, doi: 10.2214/ajr.129.2.233, indexed in Pubmed: 409155.
10. Yakushiji E, Ota S, Komatsu T, et al. Massive hemoptysis due to right inferior phrenic artery-to-right pulmonary artery fistula in the right middle lobe of the lung. Intern Med. 2017; 56(6): 687–689, doi: 10.2169/internalmedicine.56.6783, indexed in Pubmed: 28321071.
11. Petty L, Joseph A, Sanchez J. Case report: Pulmonary sequestration in an adult. Radiol Case Rep. 2018; 13(1): 21–23, doi: 10.1016/j.radcr.2017.09.029, indexed in Pubmed: 29487633.
12. Arjun P, Palangadan S, Haque A, et al. Intralobar sequestration. Lung India. 2017; 34(6): 559, doi: 10.4103/lungindia.lungindia_51_17.
13. Naoko O, Yukiyasu T, Yuko K, et al. Thoracoscopic segmentectomy for intralobar sequestration in adult: a case report. Surg Case Rep. 2018; 4: 51.
14. Lin Y, Chen Z, Yang X, et al. Bronchial and non-bronchial systemic arteries: value of multidetector CT angiography in diagnosis and angiographic embolisation feasibility analysis. J Med Imaging Radiat Oncol. 2013; 57(6): 644–651, doi: 10.1111/1754-9485.12058, indexed in Pubmed: 24283551.
15. Ghanaati H, Shakouri Rad A, Firouznia K, et al. Bronchial artery embolization in life-threatening massive hemoptysis. Iran Red Crescent Med J. 2013; 15(12): e16618, doi: 10.5812/ircmj.16618, indexed in Pubmed: 24693401.
16. Walker CM, Rosado-de-Christenson ML, Martínez-Jiménez S, et al. Bronchial arteries: anatomy, function, hypertrophy, and anomalies. Radiographics. 2015; 35(1): 32–49, doi: 10.1148/rg.351140089, indexed in Pubmed: 25590386.
17. Sidhu M, Wieseler K, Burdick TR, et al. Bronchial artery embolization for hemoptysis. Semin Intervent Radiol. 2008; 25(3): 310–318, doi: 10.1055/s-0028-1085931, indexed in Pubmed: 21326520.
18. Xi Y, Liu D, Yang C, et al. [Cause of massive hemoptysis in critical patients and the effect of bronchial artery embolization]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2018; 30(7): 671–676, doi: 10.3760/cma.j.issn.2095-4352.2018.07.011, indexed in Pubmed: 30045796.
19. Gu W, Sun Lh, Fang Sr, et al. [Clinical analysis of the rare causes of hemoptysis: a report of 4 cases. Zhonghua Jie He He Hu Xi Za Zhi. 2007; 30(5): 343–346, indexed in Pubmed: 17651639.

A rare initial presentation of miliary tuberculosis

Somya Ish[1], Vidushi Rathi[2], Pranav Ish[2], Himanshu Garkoti[1], Deepa Sharma[1]

[1]Department of Ophthalmology, Dr *Ram Manohar Lohia* Hospital, New Delhi, India
[2]Department of Pulmonary, Critical Care And Sleep Medicine, Vardhaman Mahavir Medical College & Safdarjung Hospital, New Delhi, India

A sixteen-year-old female presented with a gradual decrease of vision in the left eye for two weeks. She did not report any fever, weight loss, discharge, or redness of the eye. The chest X-ray of the patient was normal. On ocular examination, the best corrected visual acuity in the right eye was 6/6. In the left eye, the best acuity was noted when fingers were counted close to the face. Anterior segment examination of both the eyes was normal with normally reacting pupils. The fundus examination of the right eye was normal. In the left eye, a well-defined, subretinal, elevated, and oval-shaped lesion was located on the macula. It had a 1.5 mm disc diameter (DD) that had overlying dilated vessels and adjacent oedema with subretinal haemorrhage which was suggestive of a possible tuberculoma (Figure 1A). Optical coherence tomography (OCT) of the macula of the left eye revealed elevation of all the retinal layers along with parafoveal subretinal fluid and one intraretinal cystic space (Figure 1B). There was a history of pulmonary tuberculosis two years ago which was microbiologically diagnosed and adequately treated for six months.

The patient subsequently developed malaise, weight loss, and a positive tuberculin skin test. A repeat chest X-ray done 1 week after the initial presentation was suggestive of miliary tuberculosis (Figure 1C). There were no neurological deficits or symptoms of higher mental dysfunction. A non-contrast CT of the head was performed and the results were normal. A sputum sample was examined using the cartridge-based nucleic acid amplification test (CBNAAT) and returned positive for mycobacterium tuberculosis with no rifampicin resistance. The patient was treated with antitubercular therapy (ATT) alongside systemic steroids and showed symptomatic improvement.

Ocular TB is a rare presentation (1% of all cases of TB) and can involve any part of the eye [1]. The most common intraocular manifestations of tubercular posterior uveitis include multiple choroidal tubercles and, less commonly, as a large solitary tuberculoma located at the posterior pole [2], which was seen in our case. Moreover, a solitary tuberculoma is often seen in the chronic course of the disease and, uncommonly, as the initial manifestation of miliary tuberculosis. Even though the exact mechanism remains unclear, the choroid

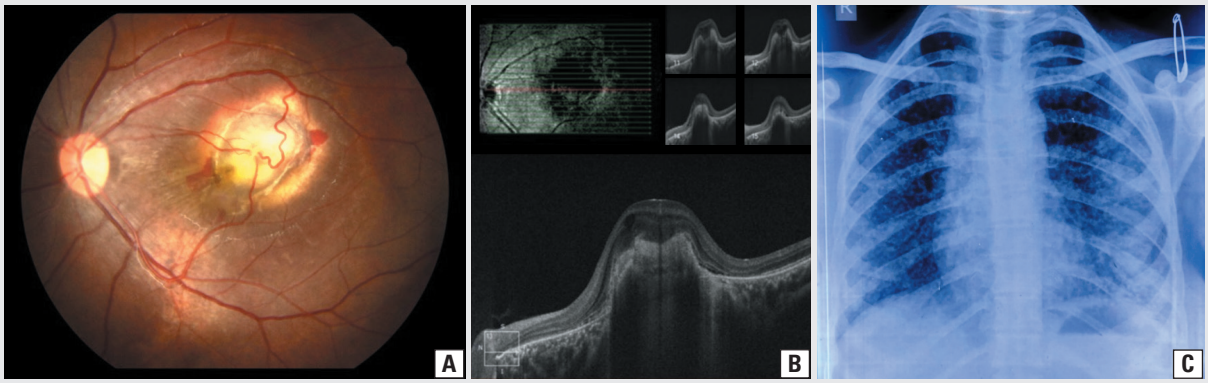

Figure 1. A. Fundoscopic examination of the left eye revealing a well-defined, subretinal, elevated, and oval-shaped lesion that was located on the macula. It had a 1.5 mm disc diameter (DD) that had overlying dilated vessels and adjacent oedema with subretinal haemorrhage, which was suggestive of a possible tuberculoma; **B.** Optical coherence tomography (OCT) of the macula of the left eye demonstrating an elevation of all the layers of the retina with parafoveal subretinal fluid and one intraretinal cystic space; **C.** Chest X-ray posterior-anterior view showing miliary shadows bilaterally suggestive of miliary tuberculosis

Address for correspondence: Pranav Ish, Department of Pulmonary, Critical Care And Sleep Medicine, Vardhaman Mahavir Medical College & Safdarjung Hospital, New Delhi, India; e-mail: pranavish2512@gmail.com
DOI: 10.5603/ARM.a2020.0127
Received: 22.01.2020
Copyright © 2020 PTChP
ISSN 2451–4934
Conflict of interest: None

tubercles may suggest direct hematogenous infection, whereas the vasculitis and choroiditis are more likely to be the result of immune hypersensitivity [3]. According to previously reported cases, affected patients often have healed pulmonary tuberculosis, although rarely choroidal manifestations may lead to the subsequent diagnosis of pulmonary tuberculosis [4]. This is what occurred in our case. Choroidal tuberculoma has also been reported as an isolated presentation with no extra-ocular tuberculosis [5].

This case highlights the truly systemic nature of disseminated tuberculosis. A high index of suspicion by doctors of various specialities can help in making an early diagnosis with an appropriate treatment plan to prevent morbidity.

References:

1. Bodaghi B, LeHoang P. Ocular tuberculosis. Curr Opin Ophthalmol. 2000; 11(6): 443–448, doi: 10.1097/00055735-200012000-00010, indexed in Pubmed: 11141639.
2. Arej N, Fadlallah A, Chelala E. Choroidal tuberculoma as a presenting sign of tuberculosis. Int Med Case Rep J. 2016; 9: 365–368, doi: 10.2147/IMCRJ.S119703, indexed in Pubmed: 27956845.
3. Shakarchi FI. Ocular tuberculosis: current perspectives. Clin Ophthalmol. 2015; 9: 2223–2227, doi: 10.2147/OPTH.S65254, indexed in Pubmed: 26648690.
4. Jabbour NM, Faris B, Trempe CL. A case of pulmonary tuberculosis presenting with a choroidal tuberculoma. Ophthalmology. 1985; 92(6): 834–837, doi: 10.1016/s0161-6420(85)33952-0, indexed in Pubmed: 4034179.
5. Mansour A, Haymond R. Choroidal tuberculomas without evidence of extraocular tuberculosis. Graefe's Archive for Clinical and Experimental Ophthalmology. 1990; 228(4): 382–383, doi: 10.1007/bf00920066.

A young non-smoker with high ADA pleural effusion. It's not always tuberculosis

Gopal Chawla[1], Amrit Pal Kansal[2], Kunal Deokar[1]

[1]All India Institute of Medical Sciences, Jodhpur, Rajasthan, India
[2]Government Medical College, Patiala, India

Lung cancer is posing an ever-increasing medical and social problem due to its increasing morbidity and mortality. Here, we report a case of a young male who was originally being treated for a tubercular pleural effusion but was ultimately diagnosed with non-small cell carcinoma. While considering the diagnosis of pleural effusion in a country like India, where tuberculosis (TB) is endemic, it is not surprising that many clinicians prefer to consider pulmonary tuberculosis ahead of malignancy in the differential diagnosis, especially in a young patient.

A 26-year-old non-smoking and immunocompetent male presented with complaints of an intermittent fever, cough with mild expectoration, right-sided chest pain which increased on deep inspiration, and dyspnea for two months. His routine blood investigations were within normal limits and a general physical examination was also normal. His chest X-ray revealed a pleural effusion with left lower zone heterogeneous infiltration. He was started on anti-tubercular therapy on the basis of a lymphocytic and high ADA (67.7 IU) pleural effusion. However, even after one month, he did not respond to the treatment. Repeated diagnostic thoracentesis showed small and large clusters of malignant squamous epithelial cells exhibiting an increased nuclear-cytoplasmic ratio and nuclear hyperchromatism on MGG and PAP stained cytological smears. IHC was positive for p63 suggesting squamous cell carcinoma with the primary location possibly being in the lung. CECT showed a mass measuring 4 × 6 cm in the right lower lobe with a bronchus cut-off sign along with a mild pleural effusion and mediastinal lymphadenopathy (Figure 1). On bronchoscopy, multiple nodules were seen in the right lower lobe bronchus. Endobronchial lung biopsy confirmed the diagnosis of squamous cell carcinoma. The patient was diagnosed with a pT2bN1M1a stage IV squamous cell carcinoma according to the International Union Against Cancer staging system.

Lung cancer in young people is uncommon. It has been reported that only 1.2% to 2.7% of patients diagnosed with lung cancer are less than 40 years of age. In the younger group, women are more highly represented than in the older group. Adenocarcinomas are more frequent than squamous cell carcinomas among young and newer smokers [1].

Cigarette smoking is a major risk factor for lung cancer in young people. Factors other than smoking include environmental(second-hand) tobacco smoke, indoor air pollution (e.g. coal and cooking fumes), a family history of lung cancer, occupational and environmental agents (e.g. radon, asbestos, and heavy metals), preexisting lung diseases, and/or human papillomavirus infection [2]. The young man here, however, had not been significantly exposed to any of these factors. Therefore, other factors such as environmental carcinogens or genetic susceptibility might have contributed to the development of lung cancer.

Young patients with lung cancer often have advanced stages at presentation, and this was similar to what we witnessed in our present case. It has been suggested that this is due to the high malignant nature and/or the delayed diagnosis resulting from a low degree of suspicion of cancer, but this relationship is not significant [1]. It is speculated that younger patients can be managed in a more aggressive fashion than older patients because of their better overall medical conditions [2].

It is unknown why younger patients with carcinoma more commonly present with advanced disease. Because bronchogenic carcinoma in this age group is rare, both public and professional awareness is limited. Young patients may not suspect serious illness and often ignore any type of symptoms. Moreover, physicians often may not suspect an underlying carcinoma despite persistent pulmonary symptoms or abnormal findings on chest roentgenograms. The mean duration of symptoms before diagnosis is usually 4–5 months [3].

Therefore, repeated cytology should be performed in cases of pleural effusion that are not responsive to treatment even if the first cytology sample is negative and excludes the possibility of lung cancer. If non-small cell bronchogenic carcinoma is diagnosed and signs of distant metastasis are lacking, further exploration is

Address for correspondence: Gopal Chawla, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; e-mail: dr.gopalchawla@gmail.com
DOI: 10.5603/ARM.a2020.0144
Received: 29.03.2020
Copyright © 2020 PTChP
ISSN 2451–4934
Conflict of interest: None declared

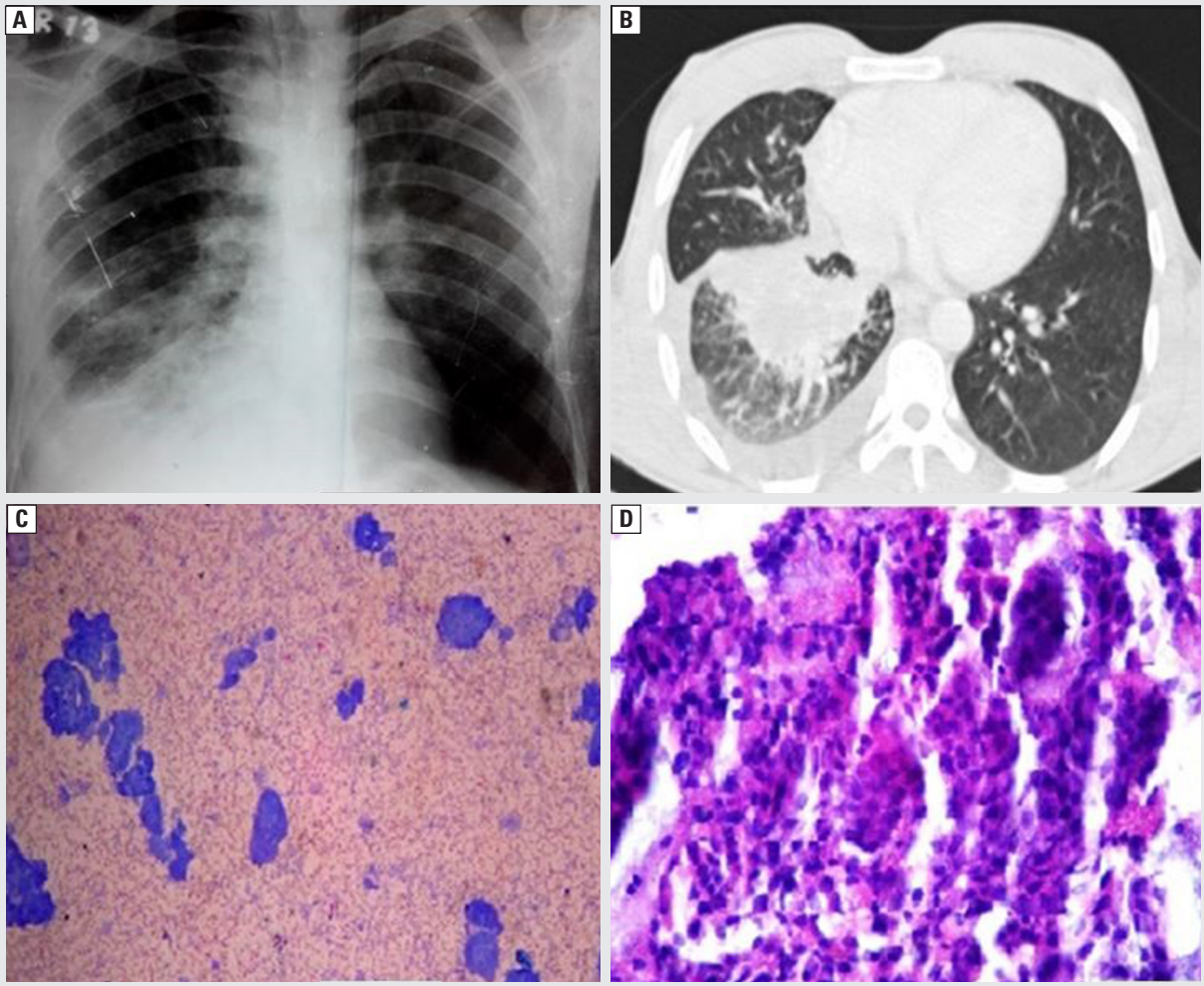

Figure 1. A. Chest X-ray showing a right pleural effusion with atelectasis; **B.** CT scan showing a mass lesion with pleural effusion; **C.** Microscopic 10× picture of the pleural effusion with small and large clusters of atypical cells; **D.** Endobronchial biopsy 10× showing atypical cells

necessary because improved survival depends on surgical resection. Because the rarity of the disease in this particular age group often delays the diagnosis, it is very important for all clinicians to consider the possibility of lung cancer in young patients where presentation or follow-up is atypical. Suspicion along with aggressive treatment may lead to an earlier diagnosis and a better prognosis.

References:

1. Ramalingam S, Pawlish K, Gadgeel S, et al. Lung cancer in young patients: analysis of a surveillance, epidemiology, and end results database. J Clin Oncol. 1998; 16(2): 651–657, doi: 10.1200/JCO.1998.16.2.651, indexed in Pubmed: 9469354.
2. Sekine I, Nishiwaki Y, Yokose T, et al. Young lung cancer patients in Japan: different characteristics between the sexes. Ann Thorac Surg. 1999; 67(5): 1451–1455, doi: 10.1016/s0003-4975(99)00171-x, indexed in Pubmed: 10355430.
3. Subramanian J, Govindan R. Lung cancer in never smokers: a review. J Clin Oncol. 2007; 25(5): 561–570, doi: 10.1200/JCO.2006.06.8015, indexed in Pubmed: 17290066.

Pneumomediastinum and subcutaneous emphysema after noninvasive ventilation in a COVID-19 patient

Natale Vazzana, Silvia Ognibene, Francesco Dipaola

Department of Internal Medicine, C. Magati Hospital, Scandiano, AUSL Reggio Emilia, Italy

An 80-year-old man was admitted because of persistent fever and dyspnea. Two days before he presented at the emergency department with a 5-day history of non-productive cough and fever. Chest X-ray revealed bilateral alveolar infiltrates. Blood tests showed mild leukocytosis, increased C-reactive protein and normal procalcitonin. Oxygen saturation was 96% at ambient air. High-resolution chest tomography (HRCT) showed bilateral ground-glass opacities. SARS-CoV-2 infection was diagnosed via nucleic acid test on nasopharyngeal swab. Hydroxychloroquine was started and he was discharged to home isolation. In the following 48 hours his symptoms did not improve. At second presentation, oxygen saturation was decreased to 93%, body temperature was 39.9°C, and respiratory rate was 30 breaths/min. Physical examination was notable for crackles in both lung bases. He was admitted to our COVID-19 ward and supplemented with oxygen through a non-rebreather face mask. Antiviral therapy (lopinavir/ritonavir) was added to ongoing hydroxychloroquine for 10 days. Intravenous (IV) antibiotics (ceftriaxone plus azithromycin) were also administered from day (D)2 to D7, and ceftriaxone alone was extended until D12. He was also receiving thromboprophylaxis (fondaparinux 2.5 mg/day) since admission. Although fever decreased within the first 5 days, his respiratory status progressively worsened, with a decrease in PaO2/FiO2 to less than 150. Steroid was started at D6 (IV methylpredinisolone 60 mg/die) with little improvement. Noninvasive ventilation was then applied (PPEP 6–8 cmH2O), but it was stopped after 48 hours because of poor compliance. Repeated HRCT scan showed increased ground-glass opacities and parenchymal consolidations (Figure 1). Pneumomediastinum was also observed, together with subcutaneous emphysema (Figure 1). Conservative treatment was applied, and antibiotic therapy was resumed because of fever relapse. In the following days, he received conventional oxygen supplementation, fever disappeared, but no further improvement of respiratory function was observed. He was ultimately transferred to a long-term care unit, where he continued receiving supportive and palliative treatment.

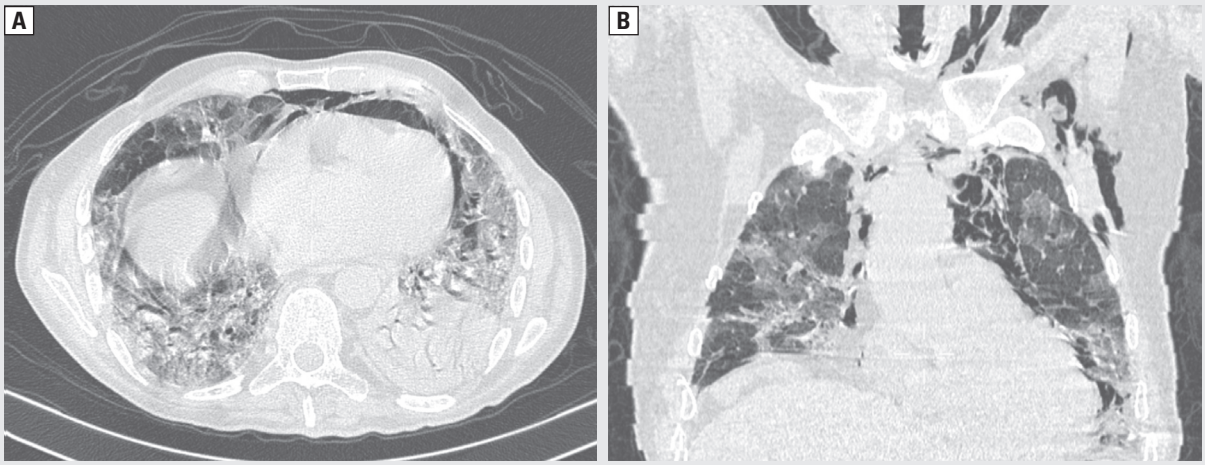

Figure 1. A. HRCT scan showing multiple ground-glass opacities with thickening of interlobular and intralobular septa (crazy-paving pattern) and a parenchymal consolidation in the left lower lobe. Pneumomediastinum was also observed around the heart, with the presence of connective tissue septae; **B.** Pneumomediastinum extended upward between the mediastinal pleura, the aortic arch and the superior mediastinum, together with subcutaneous emphysema extending to the soft tissue of the cervico-axillary region, and the lateral thoracic wall

Address for correspondence: Natale Vazzana, Department of Internal Medicine, C. Magati Hospital, AUSL Reggio Emilia, Italy; e-mail: natale.vazzana@ausl.re.it
DOI: 10.5603/ARM.a2020.0141
Received: 18.04.2020
Copyright © 2020 PTChP
ISSN 2451–4934
Conflict of interest: None declared

Pneumomediastinum is an uncommon complication of mechanical ventilation [1]. Spontaneous pneumomediastinum has also been observed in association with several structural lung diseases, including chronic obstructive lung disease, asthma, and interstitial lung diseases [1, 2]. More recently it has been reported complicating the course of COVID-19 [3]. Both spontaneous and ventilation-associated pneumomediastinum has been observed in patients with SARS, with high peak LDH level associated with its development [4]. In the presence of diffuse alveolar damage, free air could leak from ruptured alveoli, dissecting along the bronchovascular sheaths towards the mediastinum (Macklin effect) [1]. Symptoms and signs include chest pain, worsening dyspnea, subcutaneous emphysemas, mediastinal (Hamman's) crunch on heart auscultation [1]. Pneumomediastinum is generally a self-limiting condition [2]. More rarely it could be life-threatening by mimicking cardiac tamponade [1]. Here, we reported a case of pneumomediastinum in a patient with severe COVID-19-related pneumonia necessitating noninvasive ventilation. Prompt recognition is required during ventilatory support as it may promote its progression [5]. In both SARS and COVID-19, pneumomediastinum has been associated with a more severe course [3, 4], possibly reflecting massive alveolar and interstitial pulmonary injury. The occurrence rate of pneumomediastinum among ventilated COVID-19 patients is still unknown. Further data are needed to identify the mechanisms, frequency, risk factors and prognostic role of this rare complication of COVID-19.

References:

1. Kouritas VK, Papagiannopoulos K, Lazaridis G, et al. Pneumomediastinum. J Thorac Dis. 2015; 7(Suppl 1): S44–S49, doi: 10.3978/j.issn.2072-1439.2015.01.11, indexed in Pubmed: 25774307.
2. Iyer VN, Joshi AY, Ryu JH. Spontaneous pneumomediastinum: analysis of 62 consecutive adult patients. Mayo Clin Proc. 2009; 84(5): 417–421, doi: 10.1016/S0025-6196(11)60560-0, indexed in Pubmed: 19411438.
3. Kong N, Gao C, Xu MS, et al. COVID-19 with spontaneous pneumomediastinum. Lancet Infect Dis. 2020; 20(4): 510–3577, doi: 10.1016/S1473-3099(20)30156-0, indexed in Pubmed: 32164830.
4. Chu CM, Leung YY, Hui JYH, et al. Spontaneous pneumomediastinum in patients with severe acute respiratory syndrome. Eur Respir J. 2004; 23(6): 802–804, doi: 10.1183/09031936.04.00096404, indexed in Pubmed: 15218989.
5. Ruggeri P, Girbino G. Fatal pneumomediastinum associated with use of noninvasive mechanical ventilation. Respirol Case Rep. 2014; 2(4): 126–128, doi: 10.1002/rcr2.73, indexed in Pubmed: 25530859.

Niayesh Mohebbi[1], Atefeh Abedini[2], Reza Iashgari[3], Fatemeh Razavi[2], Mohammad Varahram[4], Arda Kiani[5]

[1]Clinical Pharmacy Department, Tehran University of Medical Sciences, Tehran, Iran
[2]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Brain Engineering Research Center, Institute for Research in Fundamental Sciences, Tehran, Iran
[4]Mycobacteriology Research Centre, National Research Institute of Tuberculosis and Lung Disease, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Vascular microthrombosis associated with increased interleukin-6. A severe acute respiratory distress syndrome in COVID-19 patients treated with tocilizumab

To the Editor

Thrombosis is an important pathology in the deterioration of COVID-19 patient [1–3]. In the course of the COVID-19 outbreak at the Masih Daneshvari hospital in Iran, we observed different cases of cerebrovascular thrombosis, deep vein thrombosis, and cases of pulmonary microthrombosis despite therapeutic dosing with enoxaparin. These thrombotic cases were detected by transbronchial lung biopsy mostly in COVID-19 infected patients with high interleukin-6 (IL-6) levels. This proposes that respiratory failure and hypoxemia might be associated with microthrombosis in the small vessels of the pulmonary tract. Moreover, we detected monocytosis accompanied by lymphopenia in most of the cases. Monocytosis can additionally potentiate the activation of coagulation pathways through tissue factor release [4–6].

As a matter of fact, IL-6 is a master influencer in inflammatory cytokine drama and correlates with a macrophage activation syndrome that presents in severe COVID-19 cases [7].

Besides all of the proinflammatory characteristics of IL-6, we want to point out its probable role in thrombosis. IL-6 inhibits ADAMTS-13 activity which causes less cleavage of ultra large von Willebrand factors (ULVWF) and results in a hypercoagulative state [4, 8]. Furthermore, IL-6 stimulates a systemic procoagulant effect by raising the levels of fibrinogen, plasminogen activator inhibitor-1, and C-reactive protein [5].

Seeing as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease does not yet have satisfactory treatment options, all health care systems are trying various approaches to save their patients. Tocilizumab, an IL-6 receptor antagonist, is one of the therapeutic strategies in severe cases with increased levels of IL-6 that can be used in order to control this cytokine release syndrome [7]. Surprisingly, however, we detected an increased occurrence in thrombotic events in patients who received tocilizumab. In spite of tocilizumab's mechanism of action, there was evidence of increased levels of IL-6 after treatment with tocilizumab, which could be a possible explanation for the thrombosis [9]. This rise in IL-6 level after tocilizumab administration was seen in all of the cases in our center.

Consequently, we recommend measuring the level of IL-6 following tocilizumab administration. In the case of an increased level, hemoperfusion with cytokine-absorbing columns and continuous renal replacement therapies are suggested in order to decrease the risk of throm-

Address for correspondence: Arda Kiani, Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran; e-mail: ardakiani@sbmu.ac.ir
DOI: 10.5603/ARM.a2020.0123
Received: 05.06.2020
Copyright © 2020 PTChP
ISSN 2451–4934

bosis. Although, plasmapheresis removes IL-6, it may also remove tocilizumab as well, but it can be an alternative method if the preferred one is not available.

All possible approaches with the potential to decrease IL-6 levels or negate IL-6's effects can be considered for research. For instance, based on evidence in relapsing thrombotic thrombocytopenic purpura, N-acetylcysteine may be another option for the prevention of thrombosis by reducing the size and activity of ULVWF [10].

Conflict of interest

None declared.

References:

1. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 75(23): 2950–2973, doi: 10.1016/j.jacc.2020.04.031, indexed in Pubmed: 32311448.
2. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 2020; 46(6): 1105–1108, doi: 10.1007/s00134-020-06059-6, indexed in Pubmed: 32347323.
3. Sungurlu S, Kuppy J, Balk RA. Role of antithrombin III and tissue factor pathway in the pathogenesis of sepsis. Crit Care Clin. 2020; 36(2): 255–265, doi: 10.1016/j.ccc.2019.12.002, indexed in Pubmed: 32172812.
4. Lee DD, Schwarz MA. Cell-Cell communication breakdown and endothelial dysfunction. Crit Care Clin. 2020; 36(2): 189–200, doi: 10.1016/j.ccc.2019.11.001, indexed in Pubmed: 32172808.
5. Libby P, Simon DI. Inflammation and thrombosis: the clot thickens. Circulation. 2001; 103(13): 1718–1720, doi: 10.1161/01.cir.103.13.1718, indexed in Pubmed: 11282900.
6. Toussaint S, Gerlach H. Activated protein C for sepsis. N Engl J Med. 2009; 361(27): 2646–2652, doi: 10.1056/NEJMct0808063, indexed in Pubmed: 20042756.
7. McGonagle D, Sharif K, O'Regan A, et al. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020; 19(6): 102537, doi: 10.1016/j.autrev.2020.102537, indexed in Pubmed: 32251717.
8. Bernardo A, Ball C, Nolasco L, et al. Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand factor multimers under flow. Blood. 2004; 104(1): 100–106, doi: 10.1182/blood-2004-01-0107, indexed in Pubmed: 15026315.
9. Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008; 112(10): 3959–3964, doi: 10.1182/blood-2008-05-155846, indexed in Pubmed: 18784373.
10. Cabanillas G, Popescu-Martinez A. N-Acetylcysteine for relapsing thrombotic thrombocytopenic purpura: more evidence of a promising drug. Am J Ther. 2016; 23(5): e1277–e1279, doi: 10.1097/MJT.0000000000000386, indexed in Pubmed: 26720166.

Gopal Chawla[1], Karan Madan[2], Hariharan Iyer[2], Pawan Tiwari[2], Vijay Hadda[2], Anant Mohan[2], Saurabh Mittal[2]

[1]All India Institute of Medical Sciences, Rajasthan, Jodhpur, India
[2]All India Institute of Medical Sciences, Ansari Nagar, Delhi, India

Removal of a self-expanding metallic Y stent in the management of reversible central airway obstruction due to mediastinal lymphoma

Dear Editor

In adults, central airway obstruction (CAO) can occur due to several benign and malignant etiologies either due to an endobronchial growth or extrinsic compression [1]. Mediastinal neoplasms may cause significant CAO due to extrinsic compression, and the clinical presentation is often accompanied by respiratory distress. Airway stenting is a well-established method for the immediate relief of symptoms as well as the restoration of airway patency in extrinsic lesions [1, 2]. Y-shaped self-expandable metallic stents (Y-SEMS) are commonly utilized in the management of malignant airway obstruction [3, 4]. The placement of SEMS in malignant CAO is usually with palliative intent with the expectation that the stent provides symptomatic relief during the expected duration of survival of the patient. SEMS, once deployed, are rarely removed in malignant CAO. Here, we describe a case where we were able to successfully remove a metallic stent in a patient treated for malignant airway obstruction following chemotherapy.

A 45-year-old male patient presented with a history of facial swelling for 15 days associated with voice hoarseness and rapidly worsening respiratory distress for two days. A chest radiograph (Figure 1A) revealed a well-defined homogenous opacity in the right paratracheal region. A CT scan of the thorax (Figure 1B and 1C) demonstrated a large heterogenous mediastinal mass encasing the superior vena cava causing narrowing of the lower trachea and bilateral proximal bronchi. A diagnostic flexible bronchoscopy examination with a pediatric bronchoscope revealed critical narrowing in the mid trachea. Because of rapidly worsening symptomatic CAO with a likely malignant etiology, a rigid bronchoscopy was performed under general anesthesia. A tracheobronchial Y SEMS (Ottomed, 18 mm × 60 mm) was deployed successfully and tracheobronchial luminal patency was restored. The patient had immediate relief of symptoms. Subsequently, a CT guided percutaneous biopsy of the mediastinal mass was performed and was suggestive of Non-Hodgkin's Lymphoma, B cell immune-phenotype (CD20+, BCL 6+). The patient was started on chemotherapy (CHOP-R regimen) and kept under close follow-up with serial radiographs and bronchoscopic examinations. After the 2nd cycle, the chest radiograph was suggestive of regression of the mass and the tracheobronchial lumen was seen entirely (Figure 1D). As the patient had clinical and radiological improvement, stent removal was planned. Rigid bronchoscopy was performed under general anesthesia. The patient was intubated with a size 12 mm tracheobronchoscope (Karl Storz, Germany), the proximal tracheal limb of the Y-SEMS was grasped with rigid stent placement forceps, gently twisted, and removed by proximal pulling. The stent was pulled into the lumen of the rigid bronchoscope with gradual, continuous rotating movements which separated

Address for correspondence: Saurabh Mittal, All India Institute of Medical Sciences, Ansari Nagar, Delhi, India; e-mail: saurabh_kgmu@yahoo.co.in
DOI: 10.5603/ARM.a2020.0146
Received: 09.06.2020
Copyright © 2020 PTChP
ISSN 2451–4934

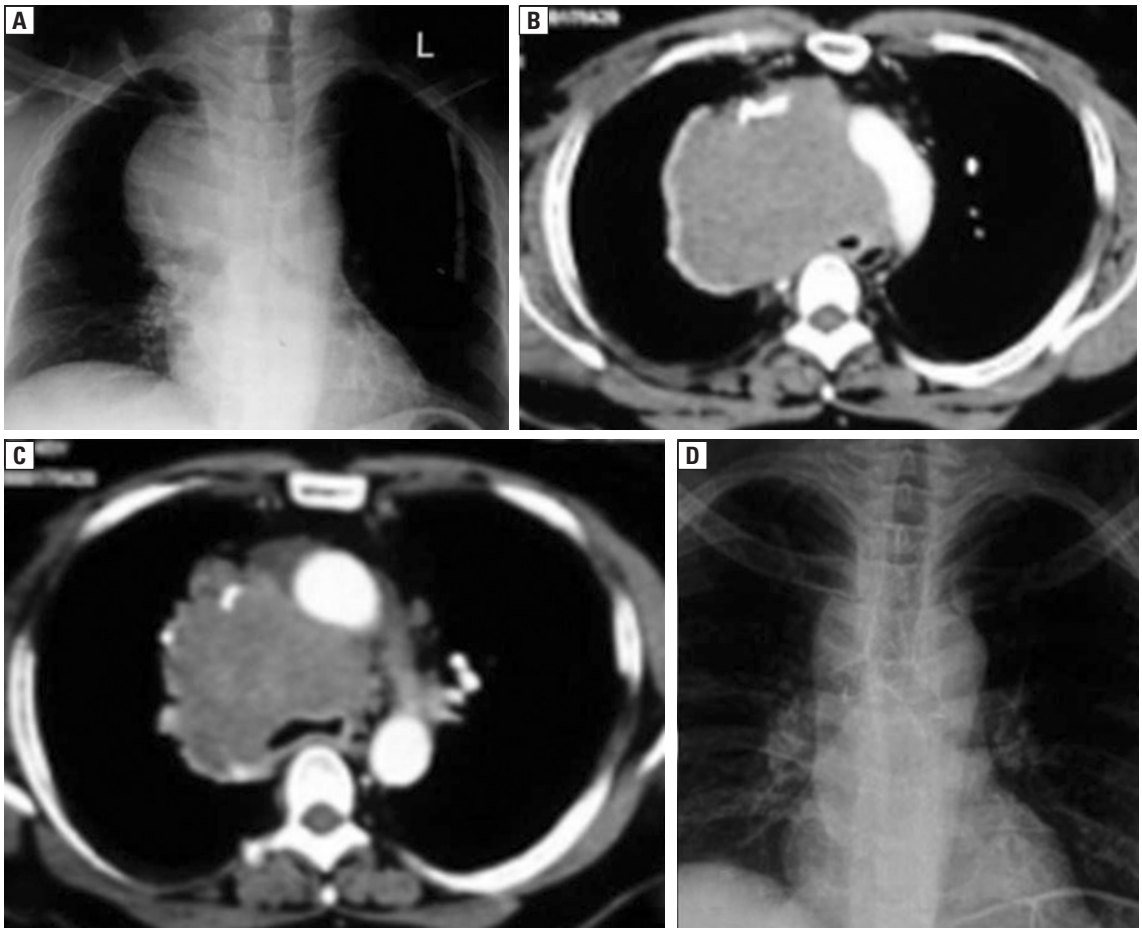

Figure 1. A. Baseline chest radiograph showing a large right paratracheal mass with tracheal compression; **B.** and **C.** CT thorax (mediastinal window) demonstrating a large mediastinal mass causing compression of the lower trachea and proximal main bronchi; **D.** Chest radiograph following chemotherapy showing reduction in the size of the right paratracheal opacity with clearly visible tracheal and both main bronchial lumina

the stent from the tracheal wall. Subsequently, the retrieved stent, which was in the lumen of the rigid bronchoscope, was removed fully along with the bronchoscope. A flexible bronchoscopy examination following removal of the stent showed minimal granulation tissue in the right main bronchus with complete luminal patency of the distal segments. The patient completed the chemotherapy cycles and was free of respiratory symptoms.

Long-term placement of airway SEMS may be associated with a complication such as granulation tissue formation, and the incidence of complications such as these increases over time. Metal stents often incite exuberant granulation tissue growth which itself can lead to obstruction at either end of the stent. Because of the risk of stent-associated airway complications, it is generally advised that airway stent insertion should be considered as a last option (some authors comment that the best stent is one that was never placed). Of the available stents (SEMS and Silicon), advantages of SEMS include ease of placement (may be performed under conscious sedation using a flexible bronchoscope), lower incidence of migration, and better adaption to irregular and compressed airways. Disadvantages of SEMS include possible complications like formation of granulation tissue, stent obstruction, fracture, erosion into surrounding tissue, and bacterial colonization. Lemaire et al. retrospectively reviewed the use of SEMS in a single institution and reported complications in 23 of 172 stent placements for malignant airway obstruction (tumor growth in nine, excessive granulation in seven, stent migration in five, and restenosis in two) [5]. These complications may require stent removal. Stent removal in the setting of stent-associated complications is difficult and potentially hazardous to the patient. Their removal can induce further serious complications such as a mucosal tear, hemorrhage, retained stent fragments, pneumothorax, re-obstruction, and ventilation failure in severe cases. In a sin-

gle-institution review of the placement of covered SEMS for benign airway disease, complications requiring stent removal were reported in 10 out of 39 patients [6]. Granulation tissue formation was the most common complication and required repeated interventions.

In this patient, considering the clinical scenario and urgency, Y-SEMS insertion was performed. Placement of a silicone stent could have been an option, but the diagnosis of lymphoma was not known at the time of SEMS placement. At the same time, insertion of silicone Y stents has particular problems in significant airway obstruction, as in this patient. The silicone stent is technically difficult to place in a complex airway as it requires the negotiation of a large rigid bronchoscope across the stenosis [7]. The advantage of a silicone stent is low granulation tissue and ease of removal if required.

In conclusion, the reversibility of the underlying pathology and the potential for stent removal should be considered at the time of stent placement. This case highlights the role of SEMS placement and removal in a patient with suspected malignant airway obstruction in a clinical situation where the underlying malignancy is adjudged to be well responsive to therapy.

Conflict of interest

None declared.

References:

1. Ernst A, Feller-Kopman D, Becker HD, et al. Central airway obstruction. Am J Respir Crit Care Med. 2004; 169(12): 1278–97.
2. Ost DE, Ernst A, Grosu HB, et al. Therapeutic bronchoscopy for malignant central airway obstruction: success rates and impact on dyspnea and quality of life. Chest. 2015; 147(5): 1282–1298, doi: 10.1378/chest.14-1526, indexed in Pubmed: 25358019.
3. Madan K, Dhooria S, Sehgal IS, et al. A multicenter experience with the placement of self-expanding metallic tracheobronchial y stents. J Bronchology Interv Pulmonol. 2016; 23(1): 29–38, doi: 10.1097/LBR.0000000000000250, indexed in Pubmed: 26705009.
4. Madan K, Shrestha P, Garg R, et al. Bronchoscopic management of critical central airway obstruction by thyroid cancer: Combination airway stenting using tracheal and inverted-Y carinal self-expanding metallic stents. Lung India. 2017; 34(2): 202–205, doi: 10.4103/0970-2113.201297, indexed in Pubmed: 28360477.
5. Lemaire A, Burfeind WR, Toloza E, et al. Outcomes of tracheobronchial stents in patients with malignant airway disease. Ann Thorac Surg. 2005; 80(2): 434–7; discussion 437, doi: 10.1016/j.athoracsur.2005.02.071, indexed in Pubmed: 16039180.
6. Noppen M, Stratakos G, D'Haese J, et al. Removal of covered self-expandable metallic airway stents in benign disorders: indications, technique, and outcomes. Chest. 2005; 127(2): 482–487, doi: 10.1378/chest.127.2.482, indexed in Pubmed: 15705985.
7. Sehgal IS, Dhooria S, Madan K, et al. Placement of tracheobronchial silicone Y-stents: Multicenter experience and systematic review of the literature. Lung India. 2017; 34(4): 311–317, doi: 10.4103/0970-2113.209241, indexed in Pubmed: 28671160.

Eunice Maria Ferreira Eira Marques Dias, Margarida Valério, Cidália Rodrigues

Centro Hospitalar Coimbra, Coimbra, Portugal

Capacity of exercise in sarcoidosis: what is the importance of cardiopulmonary exercise test in these patients?

Dear Editor

Sarcoidosis is a heterogeneous multisystem granulomatous disease of unknown etiology [1]. Pulmonary involvement is frequent (90%). Diagnosis relies on three criteria: a) a compatible clinical and radiologic presentation; b) pathologic evidence of noncaseating granulomas; and c) exclusion of other diseases with similar findings, such as infections or malignancy [2]. The original staging of sarcoidosis has been developed from lung involvement as determined only by chest X-ray (CXR): stage 0 — normal cxr with proven extrapulmonary sarcoidosis; stage I — bilateral hilar lymphadenopathy without parenchymal disease; stage II — bihilar lymphadenopathy with parenchymal disease; stage III — parenchymal involvement without lymphadenopathy; stage IV — fibrosis [3]. Pulmonary function tests (at rest) and imaging methods are the most commonly used examinations and diagnostic tests in the follow-up and evaluation of the therapeutic response [4]. Dyspnea and exercise in sarcoidosis are often poorly correlated with resting lung function. Measurement of peak exercise capacity is likely to be helpful in assessing and monitoring the disease [5].

The authors performed a retrospective analysis of the files of 35 patients (13 men and 22 women) with pulmonary sarcoidosis who underwent an incremental cardiopulmonary exercise test (CPET) in a cycle ergometer at the Pulmonology Department of Coimbra Hospital and University Center from January 2008 to June 2018. The compromise of exercise capacity and the limiting factor during maximum CPET were evaluated, along with its relationship with the pulmonary function tests (PFT) and radiological stages of the disease.

The following changes in PFT were described: obstructive respiratory disorder [forced ventilatory volume in one second (FEV_1) / forced vital capacity (FVC) < 0.70], restrictive respiratory disorder [FVC < 80% predicted and total lung capacity (TLC) < 80% predicted] and reduced diffusion capacity of carbon monoxide ($T_{L,CO}$ < 80% predicted) [6].

CPET was interpreted according with suggested normal guidelines by the American Thoracic Society/American College of Chest Physicians [7] and ERS statement on standardisation of CPET in chronic lung diseases [8]. Criteria of normality for interpretation CPET are the following: $VO2_{max}$ or $VO2_{peak}$ > 84% predicted (normal exercise capacity); anaerobic threshold (AT) > 40% $VO2_{max}$ predicted (wide range of normal 40–80%); maximum heart rate (HRmax) > 90% age predicted; heart rate reserve (HRR) < 15 beats/min; blood pressure < 220/90 mm Hg; O_2 pulse > 80%; ventilatory reserve (VR): 72 ± 15% (wide normal range); respiratory frequency (FR) < 60 breaths/min; VE/VCO_2 (at AT) > 34; VD/VT < 0.3; pO_2 > 80 mm Hg; $P(A\text{-}a)O_2$ < 35 mm Hg.

The causes of exercise limitation in CPET found in this study were the following: alteration in gas exchange, due to desaturation (> 4% from baseline or decrease of 10 mm Hg from initial PO2), due ventilatory limitation translated by dynamic hyperinflation and due to cardiovascular limitation with frequent dysrhythmias during exercise. Physical deconditioning were defined by decreased $VO2_{max}$ or $VO2_{peak}$, reduced or normal VO2 at AT and decreased or normal peak HR.

Address for correspondence: Eunice Maria Ferreira Eira Marques Dias, Centro Hospitalar Coimbra, Coimbra, Portugal; e-mail: eunicedias7@gmail.com
DOI: 10.5603/ARM.a2020.0157
Received: 10.06.2020
Copyright © 2020 PTChP
ISSN 2451–4934

Table 1. Pulmonary function tests (PFT) results in 35 sarcoidosis patients and correlation between the results of PFT and cardiopulmonary exercise test (CPET)

Stage	PFT disorders	CPET alterations					
		Normal	Physical deconditioning	Hypertensive response	Gas exchange limitation	Ventilatory limitation	Cardiovascular limitation
I (7 patients)	Normal (7)	1	5	1			
II (13 patients)	Normal (5)		4	1			
	Restrictive + ↓ $T_{L,co}$ (1)				1		1
	Obstructive + ↓ $T_{L,co}$ (1)					1	
	Obstructive (1)						1
	↓ $T_{L,co}$ (5)	1	4				
III (9 patients)	Normal (6)		3	1		2	
	Obstructive (1)					1	
	Obstructive + ↓ $T_{L,co}$ (1)					1	
	↓ $T_{L,co}$ (1)		1		1		
IV (6 patients)	Normal (3)					1	1
	Restrictive (1)				1		
	Restrictive + ↓ $T_{L,co}$ (1)				1		
	↓ $T_{L,co}$ (1)		1				

$T_{L,co}$ — diffusing capacity for carbon monoxide

The mean age of the patients was 43.1 ± 12.5 years. Regarding smoking habits, 24 subjects (68.6%) were non-smokers and 11 (31.4%) smokers or ex-smokers. Twenty-three patients (65.7%) had complaints of dyspnea and the rest were asymptomatic. Seven persons (20.0%) were in stage I of the disease, 13 (37.1%) in stage II, 9 (25.7%) in stage III and 6 (17.1%) in stage IV. Twenty-one patients (60%) were on corticosteroid therapy or had already finished. As for the results of the functional respiratory study, 14 patients (40.0%) had changes (Table 1).

All performed maximum incremental CPET, limited by symptoms, on a cycle ergometer. Only 3 individuals (8.6%) stopped early due to a hypertensive response.

Exercise capacity was normal (% $VO2_{peak}$ > 84% predicted) in 2 patients (5.7%), 1 in stage I and the other in stage II. The remaining 33 patients (94.3%) had decreased exercise capacity. The average % $VO2_{peak}$ (predicted) in each stadium was as follows: I — 66.83 ± 9.83; II — 61.42 ± 8.41; III — 63.22 ± 16.70; IV — 65.83 ± 8.77 (without statistically significant difference, p = 0.57). The majority of patients (n = 31, 88.6%) reached the anaerobic threshold.

The causes of exercise limitation were the following: a) alteration in gas exchange in 4 (12.1%) patients; b) ventilatory limitation in 6 (18.2%) individuals; c) cardiovascular limitation in 3 (9.1%) patients. In the remaining cases, exercise was restricted by physical deconditioning.

The correlation between the results of PFT and CPET are shown in Table 1. In stage I (n = 7), all patients had normal PFT, however, only 1 person had normal CPET (% $VO2_{peak}$ 97% predicted).

In stage II (n = 13), 1 patient had no exercise limitation (% $VO2_{peak}$ 110% predicted). One person with restrictive disorder and decreased $T_{L,CO}$ had exercise limitations due to alterations in gas exchange and cardiovascular limitations. One patient with obstructive disorder and decreased $T_{L,CO}$ had limitations due to ventilatory changes with dynamic hyperinflation and 1 individual with obstructive disorder had cardiovascular changes during exertion.

In stage III (n = 9), 2 patients with normal PFT had exercise limitation due to ventilatory alteration with dynamic hyperinflation. Two patients with obstructive disorder (one also with decreased $T_{L,CO}$) had ventilatory changes in CPET.

In stage IV (n = 6), the 3 patients with normal PFT had exercise limitation (1 due to alterations in gas exchange, 1 due to ventilatory limitations and 1 due to cardiovascular changes). Two patients with restrictive disorder in PFT (one of them also with decreased $T_{L,CO}$) had limited gas exchange.

Thus, the results of this study showed the predominant role of CPET in the evaluation of patients with sarcoidosis, since it allowed to identify changes that were not noticeable in exams at rest. It allowed for a better understanding of the underlying pathophysiological changes and the most correct adjustments of therapies.

As an asset in the integration of clinical, imaging and respiratory function results, CPET is, however, an exam that is not systematically requested in patients with sarcoidosis, justifying the small number of our sample. In subjects with cardiovascular limitation without previous known cardiac changes, it was possible to raise the hypothesis of cardiac involvement by sarcoidosis, highlighting the need for a directed study.

Ultimately, it should be noted that in view of the clinical, imaging and functional dissociation, CPET allowed decisions to be made regarding therapy in patients with changes.

Conflict of interest

None declared.

References:

1. Kallianos A, Zarogoulidis P, Ampatzoglou F, et al. Reduction of exercise capacity in sarcoidosis in relation to disease severity. Patient Prefer Adherence. 2015; 9: 1179–1188, doi: 10.2147/PPA.S86465, indexed in Pubmed: 26316723.
2. Wessendorf TE, Bonella F, Costabel U. Diagnosis of sarcoidosis. Clin Rev Allergy Immunol. 2015; 49(1): 54–62, doi: 10.1007/s12016-015-8475-x, indexed in Pubmed: 25779004.
3. Strookappe B, De Vries J, Elfferich M, et al. Predictors of fatigue in sarcoidosis: The value of exercise testing. Respir Med. 2016; 116: 49–54, doi: 10.1016/j.rmed.2016.05.010, indexed in Pubmed: 27296820.
4. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and management of sarcoidosis. Am Fam Physician. 2016; 93(10): 840–848, indexed in Pubmed: 27175719.
5. de Boer S, Kolbe J, Wilsher ML. Comparison of the modified shuttle walk test and cardiopulmonary exercise test in sarcoidosis. Respirology. 2014; 19(4): 604–607, doi: 10.1111/resp.12276, indexed in Pubmed: 24666931.
6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26(5): 948–968, doi: 10.1183/09031936.05.00035205, indexed in Pubmed: 16264058.
7. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003; 167(2): 211–277, doi: 10.1164/rccm.167.2.211, indexed in Pubmed: 12524257.
8. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26(5): 948–968, doi: 10.1183/09031936.05.00035205, indexed in Pubmed: 16264058.