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NCT

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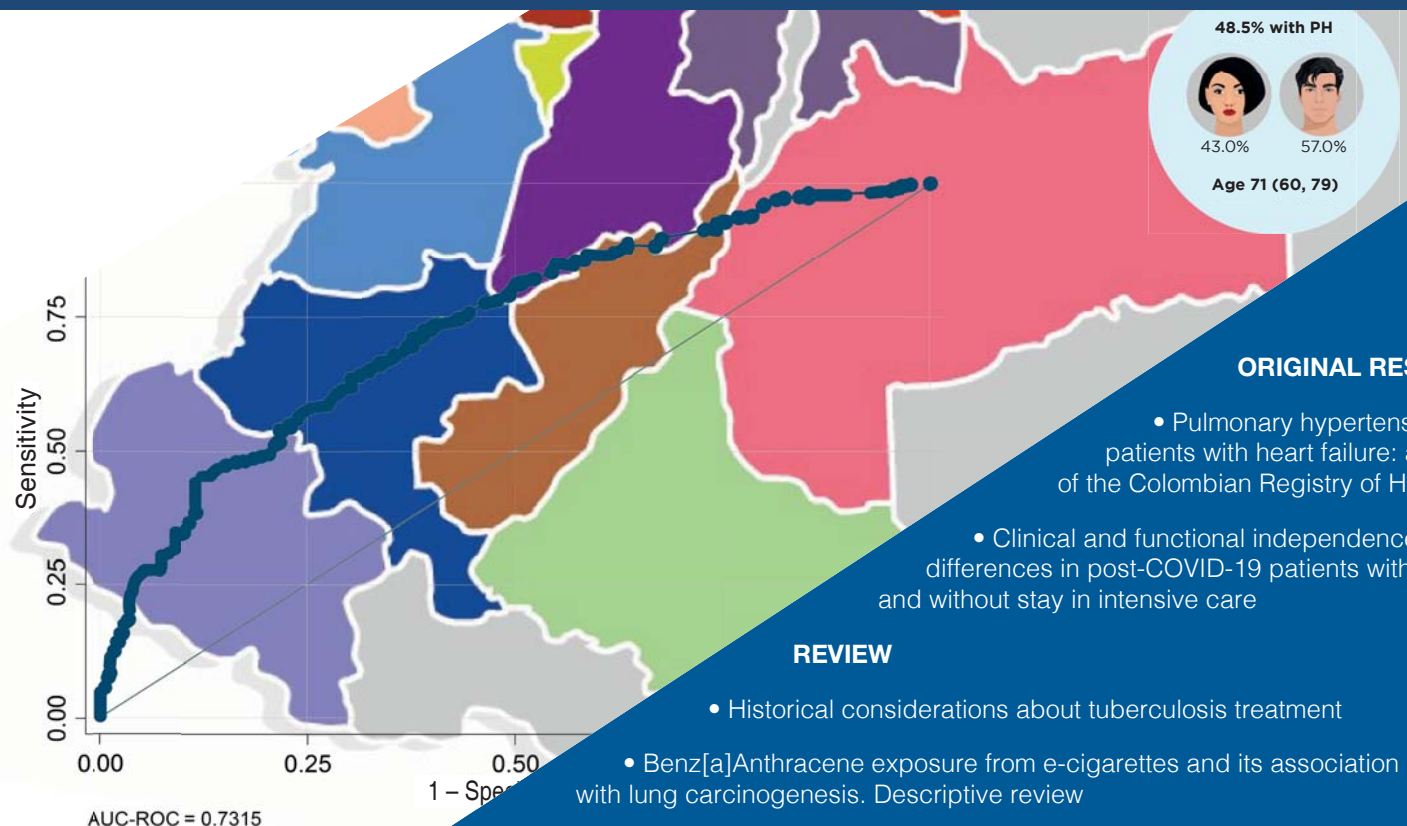
HEART FAILURE AND PULMONARY HYPERTENSION: FIRST LATIN AMERICAN STUDY



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Address correspondence to: Dr. Juan Carlos Vázquez García, Editor-in-Chief of the journal Neumología y Cirugía de Tórax, Office of Library and Editorial, National Institute of Respiratory Diseases Ismael Cosío Villegas: Calzada de Tlalpan 4502, district Section XVI, Mexico City, 14080.
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Editorial
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Heart failure and pulmonary hypertension: first Latin American study

Falla cardíaca e hipertensión pulmonar: primer estudio latinoamericano

Andrés Palomar-Lever*

*Centro Médico ABC, Mexico City.

In this NCT issue appears the article by Murillo-Benítez, et al.[1] on pulmonary hypertension (PH) in patients with heart failure from the Colombian Heart Failure Registry *(RECOLFACA)*. This Latin American registry includes adult outpatients with heart failure from the 60 centers of reference in Colombia over a two-year period. The authors evaluated the demographic characteristics, the comorbidities and as primary outcome the mortality by all causes, they used a Cox proportional hazards regression model to assess the primary outcome in patients with heart failure and PH. The authors included a large sample of 2,528 patients and in 1,833 echocardiographic reports were available to confirm or rule out the presence of PH; in 48% of the cases the echocardiographic criteria for PH diagnosis was met. In addition, they analyzed the impact of comorbidities, including chronic obstructive pulmonary disease (COPD), valve disease, atrial fibrillation, kidney disease, thyroid disease, anemia, use of blood thinners, vasodilators and diuretics, which were useful predictors to identify heart failure and PH, as well as a higher prevalence in patients with heart failure and preserved ejection fraction (HFpEF) with PH.

The systematic study of the patients with PH allows us to classify them into five different groups according to their hemodynamic definition (pre-capillary or post-capillary), also related to the type of vascular damage and the mechanism of PH vascular damage. The most frequent group is group II, associated with left-sided heart disease. In the last classification, this group distinguishes a new subgroup of patients with PH associated with an obstruction, congenital or acquired, of the inflow and outflow of the left ventricle. The other subgroups have remained as they were, systolic or diastolic dysfunction of the left ventricle and valve disease. In the case of heart failure, its involvement in pulmonary circulation is known; initial studies in the 1930s, focused on the mitral stenosis, reported histological damages to the pulmonary vasculature secondary to sustained increases in venous pressure, consisting of arterial remodeling, hypertrophy of the media, intimal proliferation, microthrombosis, thickening of the adventitia and fibrinoid necrosis. In 1958, Wood proposed the hemodynamic classification of PH, in which the mean pulmonary pressure is passively increased by an increase in the left atrial pressure. Recently, group II PH has become a topic of primary interest in terms of its pathophysiology and specific therapy in early stages of heart failure, categorizing two phenotypes according to their ejection fraction, preserved or reduced, and that related to comorbidities. HP is rated as pre-capillary when the pulmonary artery wedge pressure (PAWP) is ≤ 15 mmHg and post-capillary when the PAWP is >15 mmHg, post-capillary HP can be subclassified into pure post-capillary with normal diastolic-PAWP gradient and combined pre and post-capillary with diastolic-PAWP gradient ≥ 7 mmHg.

The echocardiography performed by experienced operators is the most useful tool for detecting PH, when there is clinical suspicion, as well as in patients from family risk groups, for example, patients with scleroderma, among others. In this study, the diagnosis of PH was made based

Correspondence:
Dr. Andrés Palomar-Lever
Centro Médico ABC, Mexico City.
E-mail: andrespalomar@hotmail.com

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on 2D echocardiographic and color Doppler findings with a calculated systolic pulmonary pressure above 35 mmHg. In addition, cases with reduced ejection fraction when it was < 40% were considered. However, there were no hemodynamic measurement variables. Demographic findings demonstrated that patients with heart failure and PH had a higher prevalence of COPD, thyroid disease, chronic kidney disease, valve diseases, anemia, and higher prescription of diuretics and anticoagulants, as well as a higher brain natriuretic peptide, compared to patients without PH. Patients with HFpEF and PH were more frequently female, with a higher prevalence of COPD, thyroid disease, and valve diseases. The diagnosis of PH in patients with heart failure was not associated with increased mortality at follow-up. This negative result is possible due to the requirement for a larger sample, the lack of hemodynamic study and possibly the lack of more echocardiographic information such as right ventricular function parameters, measurement of left atrial diameters and ventricular interaction data.

This is the first Latin American study that we are aware of that shows the demographic characteristics, comorbidities and mortality predictors of patients with heart failure and the presence of PH.

REFERENCE

1. Murillo-Benítez NE, Rivera-Toquica A, Saldarriaga C, Campbell-Quintero S, Morales-Rodríguez LN, López-Ponce de León JD, *et al.* Hipertensión pulmonar en pacientes con falla cardíaca: análisis del Registro Colombiano de Falla Cardíaca. Neumol Cir Torax. 2023;82(4):203-211. https://dx.doi.org/10.35366/117936

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Pulmonary hypertension in patients with heart failure: analysis of the Colombian Registry of Heart Failure

Hipertensión pulmonar en pacientes con falla cardíaca: análisis del Registro Colombiano de Falla Cardíaca

Nelson E. Murillo-Benítez,[1] Alex Rivera-Toquica,[2] Clara Saldarriaga,[3] Sebastián Campbell-Quintero,[4] Lisbeth N. Morales-Rodríguez,[5] Juan D. López-Ponce de León,[6] Andrés F. Buitrago,[7] Erika Martínez-Carreño,[8] Jorge A. Sandoval-Luna,[9] Alexis Llamas,[10] Gustavo A. Moreno-Silgado,[11] Julián Vanegas-Eljach,[12] Ricardo Gómez-Palau,[13] Luis E. Echeverría,[14] Juan E. Gómez-Mesa,[6,15]

[1]Angiography of the West, Department of Cardiology, Cali, Colombia; [2]Heart Medical Center, Cardiology Department, Pereira, Colombia; Rosales Clinic, Cardiology Department, Pereira, Colombia; Technological University of Pereira, Cardiology Department, Pereira, Colombia; [3]VID Cardio Clinic, Cardiology Department, Medellín, Colombia; [4]Medilaser Clinic, Cardiology Department, Florencia, Colombia; [5]Medilaser Clinic, Cardiology Department, Tunja, Colombia; [6]Valle de Lili Foundation, Cardiology Department, Cali, Colombia; [7]Santa Fe de Bogotá Foundation, Cardiology Department, Bogotá, Colombia; [8]Sanitas Iberoamerica Clinic Institution, Cardiology Department, Barranquilla, Colombia; [9]Siglo XXI Cardiology, Cardiology Department, Ibagué, Colombia; [10]Las Américas Clinic, Cardiology Department, Medellín, Colombia; [11]Hospicardio S.A.S., Cardiology Department, Montería, Colombia; [12] Alma Máter Hospital, Cardiology Department, Medellín, Colombia; [13]Imbanaco Clinic, Cardiology Department, Cali, Colombia; [14]Cardiovascular Foundation of Colombia, Cardiology Department, Floridablanca, Colombia; [15]Icesi University, Department of Health Sciences, Cali, Colombia.

ABSTRACT. Introduction: the diagnosis of pulmonary hypertension is associated with greater deterioration of heart failure, as well as a risk of adverse outcomes. **Objective:** the objective of this study was to analyze the prevalence of pulmonary hypertension and evaluate its prognosis in patients from the Colombian Registry of Heart Failure-RECOLFACA. **Material and methods:** RECOLFACA included adult outpatients with a diagnosis of heart failure belonging to 60 medical centers in Colombia in the period 2017-2019. The primary outcome was all-cause mortality. A Cox proportional hazards regression model was used to evaluate the factors associated with the primary outcome in patients with HF and pulmonary hypertension. A p value < 0.05 was considered significant. **Results:** of the 2,528 patients included in RECOLFACA, 1,833 were analyzed in this study because they had sufficient echocardiography reports to confirm or rule out the diagnosis of pulmonary hypertension. 48.6% met the diagnostic criteria for pulmonary hypertension. The

RESUMEN. Introducción: el diagnóstico de hipertensión pulmonar se asocia con mayor deterioro de falla cardiaca, así como un riesgo de desenlaces adversos. **Objetivo:** analizar la prevalencia de hipertensión pulmonar y evaluar su pronóstico en pacientes del Registro Colombiano de Falla Cardíaca (RECOLFACA). **Material y métodos:** RECOLFACA incluyó pacientes ambulatorios adultos con diagnóstico de falla cardíaca pertenecientes a 60 centros médicos en Colombia en el período 2017-2019. El desenlace primario fue mortalidad por todas las causas. Se utilizó un modelo de regresión de riesgos proporcionales de Cox para evaluar los factores asociados al desenlace primario en pacientes con falla cardíaca e hipertensión pulmonar. Se consideró significativo un valor de $p < 0.05$. **Resultados:** de los 2,528 pacientes incluidos en RECOLFACA, en este estudio se analizaron 1,833 porque tenían reportes de ecocardiografía suficientes para confirmar o descartar el diagnóstico de hipertensión pulmonar. El 48.6% cumplían con criterios diagnósticos de hipertensión

Correspondence:
Dr. Juan Esteban Gómez-Mesa
Departamento de Cardiología, Fundación Valle del Lili, Cali, Colombia; Departamento de Ciencias de la Salud, Universidad Icesi, Cali, Colombia.
ORCID: 0000-0002-6635-6224
E-mail: juan.gomez.me@fvl.org.co

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diagnoses of chronic obstructive pulmonary disease, atrial fibrillation, valvular heart disease, HF and the use of diuretics and anticoagulants were useful predictors for the identification of those patients with HF with preserved ejection fraction and pulmonary hypertension (AUC-ROC: 0.73). **Conclusions:** pulmonary hypertension is common in patients with heart failure, regardless of their ejection fraction. The differential characteristics of patients with heart failure according to the diagnosis of pulmonary hypertension were highlighted for the first time in a Latin American population. However, additional studies are required evaluating other echocardiographic parameters as predictors of pulmonary hypertension and adverse outcomes in this context.

Keywords: heart failure, pulmonary hypertension, mortality.

pulmonar. Los diagnósticos de enfermedad pulmonar obstructiva crónica, fibrilación auricular, valvulopatías, falla cardíaca y el uso de diuréticos y anticoagulantes fueron predictores útiles para la identificación de aquellos pacientes con falla cardíaca con fracción de eyección preservada e hipertensión pulmonar (AUC-ROC: 0.73). **Conclusiones:** la hipertensión pulmonar es frecuente en pacientes con falla cardíaca, independientemente de su fracción de eyección. Se destacaron por primera vez en una población latinoamericana las características diferenciales de los pacientes con falla cardíaca de acuerdo con el diagnóstico de hipertensión pulmonar. No obstante, se requieren estudios adicionales que evalúen otros parámetros ecocardiográficos como predictores de hipertensión pulmonar y desenlaces adversos en este contexto.

Palabras clave: falla cardíaca, hipertensión pulmonar, mortalidad.

Abbreviations:

AUC = Area Under the Curve.
COPD = chronic obstructive pulmonary disease.
HF = heart failure.
HFpEF = heart failure with preserved ejection fraction.
LVEF= left ventricular ejection fraction.
HR = Hazard Ratio.
PH = pulmonary hypertension.
95% CI = 95% confidence interval.
NT-proBNP = N-terminal pro b-type natriuretic peptide.
NYHA = New York Heart Association.
PASP = pulmonary artery systolic pressure.
Q1 = quartile 1.
Q3 = quartile 3.
RECOLFACA = Colombian Registry of Heart Failure.
ROC = Receiver Operating Characteristic.

INTRODUCTION

Heart failure (HF) represents a chronic non-communicable disease of high prevalence worldwide and is considered one of the most relevant public health problems today.[1,2] Its genesis and evolution of adjacent pathophysiological mechanisms promote the appearance of other conditions such as atrial fibrillation (AF), insulin resistance and pulmonary hypertension (PH). The latter is secondary to the increase in filling pressures of the left ventricle chronically as a consequence of HF, increases pulmonary venous pressures and triggers processes of vasoconstriction and arterial remodeling, resulting in greater pulmonary vascular resistance and, consequently, in pre-capillary PH.[3,4] Previous studies suggest that patients with PH and HF present a worse prognosis than those only diagnosed with HF, highlighting the positive value of pharmacological and mechanical interventions in the reversibility of PH and the prognosis of these patients.[5,6]

The study of PH in the context of patients with HF has shown relevant aspects that represent a high impact on survival; however, further research is still required in understanding the phenomenon.[7] An important focus of attention results from the relationship of PH and preserved ejection fraction (HFpEF) in Latin American population whose characteristics, prevalence and implications may differ with respect to other populations and impact on therapeutic management.[8-10] It is necessary to evaluate this interaction, firstly, because the presence of elevated pulmonary venous pressures in patients with pEF is associated with a differential hemodynamic process, closely related to the severity of diastolic dysfunction, as has been observed in patients with aortic stenosis; secondly, because the factors associated with adverse outcomes in Latin American patients have not been evaluated so far.[3,4,11] For this reason, the objective of this study is to describe and analyze the clinical, echocardiographic and outcome characteristics of patients diagnosed with HF and with PH from the Colombian Registry of Heart Failure (RECOLFACA).

MATERIAL AND METHODS

Study design and population. The RECOLFACA is a prospective cohort study conducted in 60 medical institutions, heart failure clinics and outpatient centers in Colombia. Patient recruitment began in February 2017 and ended in October 2019, including outpatients older than 18 years with a clinical diagnosis of HF who had at least one hospitalization for HF in the 12 months prior to recruitment. The specific inclusion and exclusion criteria, together with the additional methodological characteristics of the registry, were previously described.[12,13] This study was reviewed and approved by the Biomedical Research Ethics Committee of the Valle del Lili Foundation, approval number 174-2017.

Data collection. Information on sociodemographic, clinical, and laboratory variables was recorded at baseline. The severity of HF was assessed using the New York Heart Association (NYHA) classification. In addition, a diagnosis of ischemic disease was recorded if the patient underwent a coronary revascularization procedure or had a history of prior myocardial infarction. The recording of left ventricular ejection fraction (LVEF) ≥ 40% allowed the identification and classification of HF with HFpEF, while those with LVEF < 40% were considered to have HF with reduced

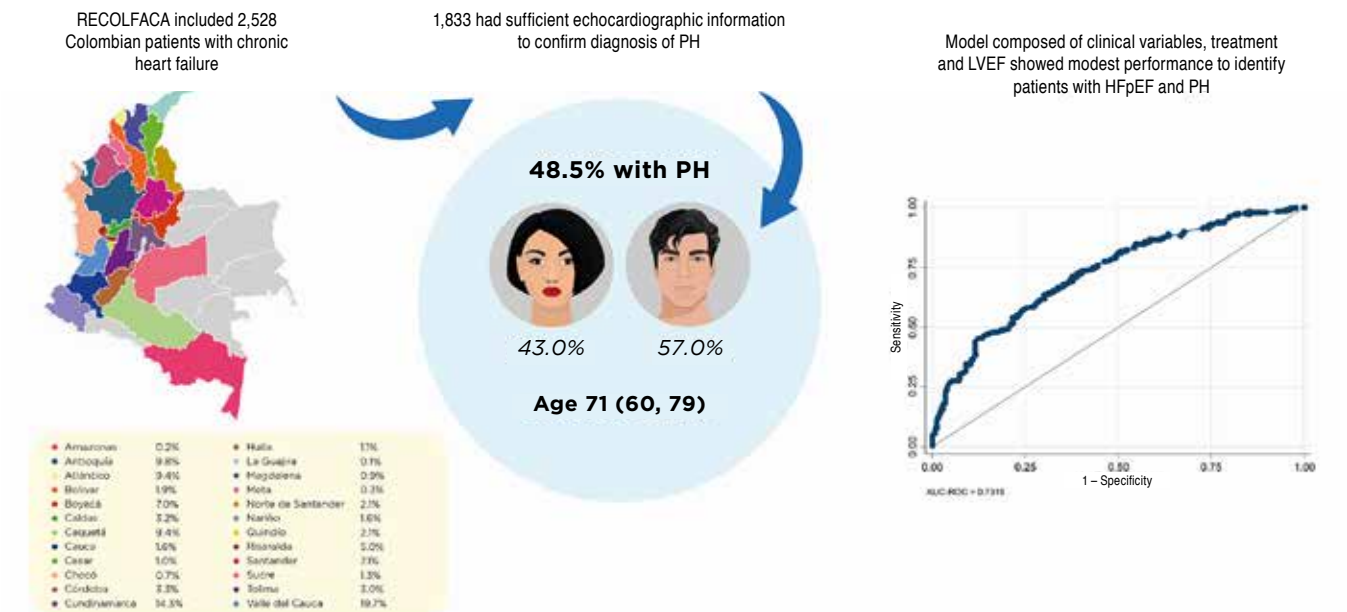
ejection fraction (HFrEF). The diagnosis of PH was defined according to the results of 2D echocardiography and color Doppler, specifically in those patients with a pulmonary artery systolic pressure (PASP) > 35 mmHg. On the other hand, chronic kidney disease was defined as an estimated glomerular filtration rate of < 60 mL/min/1.73 m^2 according to the MDRD formula. Clinical comorbidities evaluated were: arterial hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, atrial fibrillation (AF) diagnosed based on a 12-lead electrocardiogram (ECG) or documented history of this condition, anemia defined as the presence of a hemoglobin value < 13 g/dL for men and < 12 g/dL for women, and dyslipidemia defined as elevated total cholesterol [≥ 200 mg/dL] or low-density lipoprotein-bound cholesterol [LDL] [≥ 100 mg/dL], or triglycerides ≥ 150 mg/dL, or receiving lipid-lowering medications at enrollment. Other clinical diagnoses such as valvulopathy, chronic obstructive pulmonary disease (COPD), type 2 diabetes, cancer, liver failure, dementia, thyroid disease and Chagas disease were reported, according to how they were completed in the RECOLFACA database.

Outcomes. The main outcome of the study was all-cause mortality. Data on this outcome were collected using a questionnaire applied by each participating institution in an outpatient follow-up conducted six months after recruitment. Each institution also reviewed each patient's clinical records to assess specific data on outcomes.

Statistic analysis. Baseline characteristics were described as medians and quartiles if the variable was continuous. For categorical variables, proportions and percentages were recorded. Differences between patients with HF and PH (HF + PH) and those with HF without PH were assessed using Pearson's χ^2 tests and Fisher's exact test if they were categorical variables. The Mann-Whitney U test was used for continuous variables. The cumulative incidence of mortality events was calculated with their respective 95% confidence intervals (95% CI). Survival analyses were performed using the Kaplan-Meier method, the life table, and Cox proportional hazard models. A univariate and multivariate analysis was performed using Cox proportional regression models to assess the association between PH and mortality. On the other hand, a multivariate logistic regression model was adjusted to evaluate the clinical conditions associated with the diagnosis of PH in patients with pEFHF. For this purpose, we fit a stepwise logistic regression model. A p-value < 0.05 (two-tailed test) was considered statistically significant. All analyses were performed using the STATA statistical package version 15 (Station College, Texas, USA).

RESULTS

The RECOLFACA included a total of 2,528 outpatients with chronic HF between 2017 and 2019. Considering that



Diagnosis of PH was not associated with a differential risk of mortality during follow-up (HR 1.22; 95% CI 0.84-1.76)

Figure 1: Pulmonary hypertension in patients with heart failure in Colombia: an analysis of the Colombian Registry of Heart Failure (RECOLFACA). HFpEF = heart failure with preserved ejection fraction. LVEF = left ventricular ejection fraction. PH = pulmonary hypertension.

Table 1: Characteristics according to the diagnosis of pulmonary hypertension.

	Without PH N = 943, n (%)	With PH N = 890, n (%)	Total N = 1,833, n (%)	p
Male	549 (58.2)	507 (57.0)	1,056 (57.6)	0.588
Age [years]	69 (59.8)	71 (60.8)	70 (59.8)	**0.002**
Arterial hypertension	695 (73.7)	635 (71.3)	1,330 (72.6)	0.259
Alcoholism	33 (3.5)	28 (3.1)	61 (3.3)	0.673
Type 2 diabetes	231 (24.5)	212 (23.8)	443 (24.2)	0.735
Liver disease	1 (0.1)	5 (0.6)	6 (0.3)	0.088
Coronary heart disease	252 (26.7)	258 (29.0)	510 (27.8)	0.279
COPD	110 (11.7)	203 (22.8)	313 (17.1)	**< 0.001**
Atrial fibrillation	164 (17.4)	241 (27.1)	405 (22.1)	**< 0.001**
Thyroid disease	130 (13.8)	168 (18.9)	298 (16.3)	**0.003**
Chronic kidney disease	142 (15.1)	181 (20.3)	323 (17.6)	**0.003**
Valvulopathy	825 (87.5)	698 (78.4)	1,523 (83.1)	**< 0.001**
Coronary revascularization	77 (8.2)	55 (6.2)	132 (7.2)	0.100
Dyslipidemia	240 (25.5)	258 (29.0)	498 (27.2)	0.089
Smoking	150 (15.9)	175 (19.7)	325 (17.7)	**0.035**
Anemia	262 (29.0)	282 (33.4)	544 (31.1)	**0.049**
Chagas disease	29 (3.1)	30 (3.4)	59 (3.2)	0.720
NYHA functional class				**< 0.001**
I	140 (14.8)	87 (9.8)	227 (12.4)	–
II	521 (55.2)	462 (51.9)	983 (53.6)	–
III	253 (26.8)	284 (31.9)	537 (29.3)	–
IV	29 (3.1)	57 (6.4)	86 (4.7)	–
Use of medications				
ACEIs/ARBs-II	699 (74.1)	660 (74.2)	1,359 (74.1)	0.987
Beta-blockers	810 (85.9)	775 (87.1)	1,585 (86.5)	0.459
ARNI	91 (9.7)	88 (9.9)	179 (9.8)	0.864
MRA	534 (56.6)	513 (57.6)	1,047 (57.1)	0.662
Ivabradine	68 (7.2)	54 (6.1)	122 (6.7)	0.326
Diuretics	590 (62.6)	659 (74.0)	1,249 (68.1)	**< 0.001**
Nitrates	41 (4.3)	33 (3.7)	74 (4.0)	0.487
Anti-aggregants	463 (49.1)	394 (44.3)	857 (46.8)	**0.038**
Statins	531 (56.3)	504 (56.6)	1,035 (56.5)	0.890
Anticoagulants	199 (21.1)	268 (30.1)	467 (25.5)	**< 0.001**
SBP (mmHg)*	120 [110-135]	119 [104-131]	120 [107-134]	**0.011**
Heart rate (bpm)*	72 [65-80]	72 [65-84]	72 [65-81]	0.117
LVDD (mm)*	56 [48-65]	57 [48-65]	57 [48-65]	0.257
LVEF*	35 [25-42]	30 [24-42]	33 [25-42]	**0.002**
Hemoglobin (mg dL)*	13 [11.7-14.4]	13 [11.6-14.3]	13 [11.6-14.4]	0.549
NT-proBNP*	1,723.500 [571.3-4,911.5]	3,581 [1,428.3-8,692.3]	2,407.500 [954-6,043.3]	**< 0.001**
Prolonged QRS	171 (30.2)	218 (42.4)	389 (36.0)	**< 0.001**

ACEIs = Angiotensin-converting enzyme inhibitors. ARBs = angiotensin receptor antagonists. ARNI = angiotensin receptor neprilysin inhibitor. bpm = beats per minute. COPD = chronic obstructive pulmonary disease. LVDD = left ventricular diastolic diameter. LVEF= left ventricular ejection fraction. MRA = aldosterone receptor antagonists. NT-proBNP = N-terminal pro B-type natriuretic peptide. NYHA = New York Heart Association. PH = pulmonary hypertension. SBP = systolic blood pressure.
*Median and [interquartile range].

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Table 2: Characteristics in the presence of heart failure with preserved ejection fraction (HFpEF) according to the diagnosis of pulmonary hypertension.

	HFpEF		Total N = 605 n (%)	p
	Without PH N = 328 n (%)	With PH N = 277 n (%)		
Male	185 (56.4)	130 (46.9)	315 (52.1)	**0.020**
Age [years]	70 (60.79)	74 (65.82)	72 (62.81)	**< 0.001**
Arterial hypertension	253 (77.1)	220 (79.4)	473 (78.2)	0.497
Alcoholism	8 (2.4)	5 (1.8)	13 (2.1)	0.592
Type 2 diabetes	81 (24.7)	59 (21.3)	140 (23.1)	0.324
Liver disease	0 (0.0)	3 (1.1)	3 (0.5)	0.059
Coronary heart disease	92 (28.0)	73 (26.4)	165 (27.3)	0.641
COPD	40 (12.2)	90 (32.5)	130 (21.5)	**< 0.001**
Atrial fibrillation	52 (15.9)	94 (33.9)	146 (24.1)	**< 0.001**
Thyroid disease	52 (15.9)	66 (23.8)	118 (19.5)	**0.014**
Chronic kidney disease	49 (14.9)	53 (19.1)	102 (16.9)	0.170
Valvulopathy	50 (15.2)	74 (26.7)	124 (20.5)	**< 0.001**
Coronary revascularization	29 (8.8)	23 (8.3)	52 (8.6)	0.814
Dyslipidemia	118 (37.8)	92 (34.6)	210 (36.3)	0.421
Smoking	92 (28.0)	78 (28.2)	170 (28.1)	0.976
Anemia	8 (2.4)	6 (2.2)	14 (2.3)	0.824
Chagas disease	46 (14.0)	54 (19.5)	100 (16.5)	0.071
NYHA functional class				**< 0.001**
I	49 (14.9)	17 (6.1)	66 (10.9)	–
II	194 (59.1)	149 (53.8)	343 (56.7)	–
III	79 (24.1)	95 (34.3)	174 (28.8)	–
IV	6 (1.8)	16 (5.8)	22 (3.6)	–
Use of medications				
ACEIs/ARBs-II	243 (74.1)	225 (81.2)	468 (77.4)	**0.037**
Beta-blockers	255 (77.7)	228 (82.3)	483 (79.8)	0.163
ARNI	15 (4.6)	4 (1.4)	19 (3.1)	**0.028**
MRA	106 (32.3)	97 (35.0)	203 (33.6)	0.483
Ivabradine	171 (52.1)	197 (71.1)	368 (60.8)	**< 0.001**
Diuretics	9 (2.7)	5 (1.8)	14 (2.3)	0.444
Nitrates	11 (3.4)	11 (4.0)	22 (3.6)	0.686
Anti-aggregants	160 (48.8)	130 (46.9)	290 (47.9)	0.650
Statins	181 (55.2)	163 (58.8)	344 (56.9)	0.365
Anticoagulants	65 (19.8)	103 (37.2)	168 (27.8)	**< 0.001**
SBP (mmHg)*	122.5 [110-140]	123.5 [110-140]	123.0 [110-140]	0.683
Heart rate (bpm)*	71 [63-80]	70 [64-81]	70.5 [64-80]	0.299
LVEF*	47 [41.8-56]	50 [45-58]	49 [43-56]	**0.003**
Hemoglobin (mg dL)*	12.9 [11.3-14.0]	12.9 [11.3-14.1]	12.9 [11.3-14.1]	0.675
NT-proBNP*	1,153.5 [571.3-2,401.3]	3,131 [1,187.5-5,308.0]	1,719 [805.0-4,100.0]	**< 0.001**
Prolonged QRS	57 (25.5)	55 (31.9)	112 (28.3)	0.153

ACEIs = angiotensin-converting enzyme inhibitors. ARBs = angiotensin receptor antagonists. ARNI = angiotensin receptor neprilysin inhibitor. bpm = beats per minute. COPD = chronic obstructive pulmonary disease. LVDD = left ventricular diastolic diameter. LVEF = left ventricular ejection fraction. MRA = aldosterone receptor antagonists. NT-proBNP = N-terminal pro B-type natriuretic peptide. NYHA = New York Heart Association. PH = pulmonary hypertension. SBP = systolic blood pressure. *Median and [interquartile range].

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1,833 patients had sufficient echocardiographic information to confirm or rule out the diagnosis of PH, this was the population analyzed in the present study *(Figure 1)*.

Socio-demographic and clinical characteristics. The median age of the population was 70 years (Q1: 59; Q3: 78), being mainly male (57.6%). A total of 890 (48.6%) patients had a diagnosis of PH according to echocardiogram at the time of inclusion in the registry. *Table 1* summarizes the baseline characteristics of patients enrolled in the RECOLFACA according to their diagnosis of PH (PH versus Non-PH). Patients with PH had a significantly higher median age and reported a higher prevalence of COPD, atrial fibrillation, thyroid disease, chronic kidney disease, valvular heart disease, and anemia compared to those without this comorbidity. On the other hand, regarding clinical characteristics and pharmacological treatment, it was observed that patients in the HF and PH group had a significantly higher prevalence of patients in functional class NYHA III and IV and a more frequent prescription of diuretics and anticoagulants. In addition, patients diagnosed with PH had a lower median systolic blood pressure and a higher prevalence of QRS segment prolongation on the electrocardiogram. Finally, significantly lower LVEF was observed in those with PH, as well as a higher N-terminal brain natriuretic peptide (NT-proBNP) value *(Table 1)*.

PH in the patient with HFpEF. It was observed that patients with HFpEF and PH were more frequently female, with a median age significantly higher than that of patients with HFpEF without a diagnosis of PH *(Table 2)*. Similar to the results in the general population of RECOLFACA HF patients, individuals with HFpEF and PH had a higher prevalence of COPD, atrial fibrillation, thyroid disease, and valvulopathies compared to those without PH. On the other hand, although the prevalence of patients in functional class NYHA III and IV was similar, relevant differences were observed when analyzing the pharmacological prescription in the population of patients with HFpEF, highlighting a greater use of angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist, diuretics and anticoagulants, as well as a lower use of neprilysin inhibitor (ARNi) compared to those without PH *(Table 2)*.

Despite having a significantly higher median NT-proBNP, patients with HFpEF and PH had a significantly higher value of their LVEF compared to those with HFpEF without PH.

In addition, among the factors that could potentially differentiate those patients with HFpEF and PH from those with HFpEF alone, it was observed that the diagnosis of COPD, atrial fibrillation, valvulopathy, NYHA classification, use of diuretics, use of anticoagulants and LVEF were independently associated with a greater likelihood of presenting both conditions compared to presenting with HFpEF alone *(Table 3)*. Finally, in the logistic regression model including these independent variables, an area value under the ROC curve of 0.73 was obtained.

Table 3: Variables independently associated with PH and HFpEF versus isolated HFpEF.

Factor	Odds ratio	Confidence interval	
		Lower limit	Upper limit
COPD	3.14	2.02	4.87
Atrial fibrillation	1.73	1.05	2.84
Valvulopathy	1.93	1.24	2.98
NYHA II versus I	1.86	0.98	3.51
NYHA III versus I	2.54	1.28	5.01
NYHA IV versus I	6.86	2.16	21.77
Diuretic use	1.66	1.14	2.41
Anticoagulant use	1.60	1.01	2.56
LVEF	1.03	1.01	1.05

COPD = chronic obstructive pulmonary disease. HFpEF = heart failure preserved ejection fraction. LVEF = left ventricular ejection fraction. NYHA = New York Heart Association. PH = pulmonary hypertension.

Mortality. The median follow-up in the present cohort was 215 days (Q1: 188; Q3: 254). In the overall group, a total of 170 patients (6.76%) died during follow-up, for a mortality rate of 0.30 per 1,000 person-years (95% CI 0.26-0.35). On the other hand, patients diagnosed with HF and PH had a mortality rate of 0.32 per 1,000 person-years (95% CI 0.25-0.41), with no statistically significant differences observed with that observed in patients without this comorbidity (0.25 per 1,000 person-years; 95% CI 0.19-0.33). Consequently, the diagnosis of PH was not associated with a differential risk of mortality during follow-up (HR 1.22; 95% CI 0.84-1.76). No significant interactions were found between the diagnosis of PH and sex, age, or LVEF.

DISCUSSION

This study represents the first detailed analysis of the characteristics and outcomes of patients with HF and PH in Latin America. The relevant differences in comorbidities, drug use, echocardiographic parameters, laboratory analysis, and between those patients with HFpEF with and without PH are highlighted presenting a series of factors that allow differentiating both groups with modest performance.

The first studies that evaluated the prevalence of PH in HF were published in the late 1990's, highlighting the study by Butler et al.,[14] in which 320 patients with advanced HF were evaluated, noting that only 28% had normal pulmonary vascular resistance and the remaining 72% had elevated vascular tone, which negatively impacted

their maximum VO_2 value, as well as other ventilatory and hemodynamic parameters. On the other hand, Ghio et al.[6] observed a prevalence of PH of 60% in a cohort of 377 patients with chronic HF. The prevalence observed in the present study was 49%, this probably due to the relative better condition of the patients included compared to those evaluated in the aforementioned studies, since the median LVEF of the present study was 33%, while this value was 22% in the study by Ghio et al.[6] and 23% in that by Butler et al,[14] thus reflecting the close relationship between HF, ventricular function and PH prevalence.

The finding of a higher prevalence of atrial fibrillation and valvulopathies in patients with HF and PH has pathophysiological implications. In the case of mitral or aortic stenosis-type valvulopathies, it is well known that their presence is associated with increased pressures in the left heart chambers, subsequently reflected in increased pulmonary venous pressures.[15] On the other hand, atrial fibrillation may reflect an advanced state of PH, a product of the overload of the right atrium, which progresses into fibrosis and eventually leads to conduction disorders such as atrial fibrillation or atrial flutter.[16]

The finding of a higher prevalence of thyroid disease in patients with PH has been reported in other studies, mainly relating PH to the diagnosis of hyperthyroidism.[17] The mechanisms behind this association are not yet fully understood; however, it is believed that greater sensitivity to catecholamines may lead to greater vasoconstriction at the pulmonary level, in addition, a faster metabolism of vasodilator substances such as prostacyclin and nitric oxide, coupled with an alteration in the metabolism of vasoconstrictor molecules (serotonin, thromboxane and endothelin 1) may explain the higher prevalence of PH in this population.[18]

This study highlights the differences that can help in the clinical differentiation of patients with HFpEF with and without PH; taking into account the high prevalence found in the latter group in our study population and considering that complications and similar symptoms occur in both,[19] these results allow us to suspect early of those patients who, despite having a preserved LVEF, may present elevated pulmonary pressures and, therefore, to seek an optimized therapeutic treatment.[20] The model presented here consists of clinical variables (COPD, atrial fibrillation, valvulopathies and NYHA), treatment (use of diuretics and anticoagulants) and LVEF, obtained a modest performance to discriminate patients with HFpEF with PH from those without this condition (AUC-ROC 0.73). This fact potentially highlights the importance of other echocardiographic parameters in differentiating these two conditions, such as right ventricular pressures, aortic systolic pressure, and cardiac output.[21]

Finally, multiple studies have reported a wide variety of risk factors for adverse outcomes in the context of PH; however, the evidence evaluating these factors in patients with HF and PH is scarcer.[22-24] Among these factors, age, right ventricular function, functional class, LVEF, and kidney disease diagnosis have been highlighted.[25] Moreover, the finding of an increased risk of mortality in patients who are receiving nitrates may be due to the severity of PH rather than the effect of the medication. Unfortunately, no information was recorded in the RECOLFACA regarding PH severity markers such as PASP, among others.

Limitations. The present study has several limitations. One of them is participation in the registry, which was voluntary between the different centers, therefore, there may be a selection bias. On the one hand, there was no additional information regarding echocardiographic parameters relevant in the context of PH, such as end of diastole pressure of the aorta, right atrial pressure and pulmonary vascular resistances, among others. There was also no information available about the classification of PH in the patients evaluated, thus limiting the possibility of making additional adjustments by specific groups. On the other hand, it should be noted that RECOLFACA did not include information on pharmacological and non-pharmacological therapy of the evaluated comorbidities, limiting the possibility of including these relevant factors in the analyses of risk factors. Finally, no information was available on the severity and duration of the comorbidities evaluated, which limited a more detailed assessment of the impact of these conditions.

CONCLUSIONS

PH represents a condition frequently observed in patients with HF, regardless of their LVEF. There are important differences in the profiles of comorbidities when comparing patients with HF with and without PH, mainly related to the multiple pathophysiological mechanisms related to the development of the latter. This study highlights for the first time in a Latin American population the differential characteristics of patients with HF according to the diagnosis of PH, highlighting the subgroup of patients with HFpEF. Additional studies are required to evaluate other echocardiographic parameters as predictors of PH and adverse outcomes in this context.

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Ethical considerations: this study was reviewed and approved by the Biomedical Research Ethics Committee of the Valle del Lili Foundation, approval number 174-2017. Informed consent was not requested considering that no intervention was intended in the participants. In addition, the anonymity of participants' personal information was guaranteed.

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Clinical and functional independence differences in post-COVID-19 patients with and without stay in intensive care

Diferencias clínicas y de funcionalidad en pacientes pos-COVID-19 con y sin estancia en cuidados intensivos

Jhonatan Betancourt-Peña,* Valeria Perez-Hortua,‡,§ Jenifer Rodríguez-Castro,¶ Juan Carlos Ávila-Valencia,*,|| Vicente Benavides-Córdoba‡

*Facultad de Salud y Rehabilitación, Institución Universitaria Escuela Nacional del Deporte. Cali, Colombia; ‡Facultad de Salud, Universidad del Valle; §Grupo de Investigación Ejercicio y Salud Cardiopulmonar, Cali, Colombia; ¶Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia. Semillero de Investigación Cardiorrespiratorio, Cali, Colombia; ||Clínica de Occidente S.A., Cali, Colombia.

ABSTRACT. Introduction: people with COVID-19 can develop multisystemic complications that require hospitalization and sometimes admission to the intensive care unit, causing cognitive impairment, functional compromise, increased anxiety and depression. **Objective:** to describe the sociodemographic, clinical and functional differences, functional independence and anxiety/depression in post-COVID-19 patients with and without intensive care unit stay. **Material and methods:** observational study in patients with a diagnosis of COVID-19 confirmed by real-time polymerase chain reaction (RT-PCR) test who required hospital management in the year 2021. All participating patients signed the informed consent form. Sociodemographic and clinical variables, fatigue, dyspnea, functional independence and anxiety/depression were taken into account. Two groups were formed for the analysis, one group with ICU stay (stay longer than 72 hours) and another group without ICU stay. χ^2 test and t-test for independent samples were used and a statistically significant p-value < 0.05 was obtained. **Results:** there were 112 patients with an average age of 51 years old, mostly female (61.6%). The 71.4% required stay in ICU presenting greater comorbidities, number of days hospitalized and use of invasive mechanical ventilation value-p-value ≤ 0.05. Functional independence presented a mean difference in the constant care domain 0.525 ± 0.208 p-value $= 0.013$ and daily activities mean difference 0.575 ± 0.212 p-value $= 0.008$ presenting greater limitation in the group with ICU stay. **Conclusion:** post COVID-19 patients with ICU stay present greater comorbidities, use of invasive mechanical ventilation and require more days in hospital; in turn, these patients presented greater limitations in functional independence with the PCFS scale.

RESUMEN. Introducción: personas con COVID-19 pueden desarrollar complicaciones multisistémicas que requieren hospitalización y en ocasiones ingresar a la unidad de cuidados intensivos, ocasionando deterioro cognitivo, compromisos funcionales, mayor ansiedad y depresión. **Objetivo:** describir las diferencias clínicas y de funcionalidad en pacientes pos-COVID-19 con y sin estancia en la unidad de cuidados intensivos. **Material y métodos:** estudio observacional en pacientes con diagnóstico de COVID-19 confirmados por prueba de reacción en cadena de polimerasa en tiempo real (RT-PCR) que requirieron manejo hospitalario en el año 2021. Todos los pacientes participantes firmaron el consentimiento informado. Se tuvo en cuenta variables sociodemográficas, clínicas, fatiga, disnea, independencia funcional y ansiedad/depresión. Se conformaron dos grupos para el análisis, un grupo con estancia en la unidad de cuidados intensivos (estancia mayor a 72 horas) y otro grupo sin estancia en la unidad de cuidados intensivos. Se utilizó la prueba χ^2 y la prueba t para muestras independientes; se consideró un valor de $p < 0.05$ como estadísticamente significativo. **Resultados:** se vincularon 112 pacientes con edad promedio de 51 años, en su mayoría mujeres (61.6%). El 71.4% requirió estancia en la unidad de cuidados intensivos, presentando mayores comorbilidades, número de días hospitalizados y uso de ventilación mecánica invasiva ($p \leq 0.05$). La independencia funcional presentó una diferencia de medias en el dominio de cuidado constante 0.525 ± 0.208 ($p = 0.013$) y actividades diarias diferencia de medias 0.575 ± 0.212 ($p = 0.008$), presentando mayor limitación en el grupo con estancia en la unidad de cuidados intensivos. **Conclusión:** pacientes pos-COVID-19 en la unidad de cuidados intensivos presentan mayores comorbilidades, uso

Correspondence:
Valeria Perez-Hortua, MD
Facultad de Salud, Escuela de Rehabilitación Humana, Universidad del Valle. Cali, Colombia.
E-mail: valeriaperezhortua35@gmail.com

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de ventilación mecánica invasiva y requieren más días hospitalizados; estos pacientes presentaron mayores limitaciones en la independencia funcional de acuerdo con la Escala de Estado Funcional pos-COVID-19.

Keywords: COVID-19, post-COVID conditions, functional status, intensive care unit, symptoms.

Palabras clave: COVID-19, condiciones pos-COVID, estado funcional, unidad de cuidados intensivos, síntomas.

Abbreviations:

COVID-19 = Coronavirus disease 2019.
FAS = Fatigue Assessment Scale.
HADS = Hospital Anxiety and Depression Scale.
mMRC = Modified Medical Research Council scale.
PCFS = Post-COVID-19 Functional Status Scale.
ARDS = Acute Respiratory Distress Syndrome.
ICU = Intensive Care Unit.
IMV = Invasive Mechanical Ventilation.

INTRODUCTION

People with COVID-19 can develop major complications such as acute respiratory failure, acute respiratory distress syndrome (ARDS), acquired muscle weakness, delirium, neurological syndromes, and multi-organ dysfunction.[1,2] Between the year 2019 and 2020, Raymond et al. in their systematic review estimate that 12,437 patients with COVID-19 were admitted to the Intensive Care Unit (ICU); of these, 6,857 required invasive mechanical ventilation (IMV), with an average hospital stay of 7.78 days and 10.12 days for patients with IMV.[3]

60% of patients admitted to the ICU due to COVID-19 survive and experience post-ICU and post-COVID-19 complications.[4] Muscle weakness is considered to be present during the first six months after critical illness and can be resolved one year after the event; there are also limitations in the performance of activities of daily living due to compromises in walking speed, balance problems and the ability to exercise, in addition to a reduction in quality of life for two to five years after hospital discharge.[4,5]

In turn, there is evidence of a decrease in the functionality of patients who required mechanical ventilation; this is associated with greater presence of comorbidities, advanced age and a prolonged stay in the ICU compared to people who did not need an ICU presenting a higher Barthel index score.[6] However, this aspect has only been at the patient's discharge in the first stage and not in the long term.

In 2020,[7] the post-COVID-19 Functional Status Scale (PCFS) was designed as a tool to evaluate the functional limitations caused after COVID-19 infection, which was translated and adapted into Colombian Spanish in 2021[8] and validated in 2023,[9] allowing the patient to be evaluated and followed up in the medium and long term after discharge.

Consequently, knowing the functional, physical and mental status of these people in the medium and long term, allows identifying factors that influence the recovery processes and, in the same way, proposing treatment approaches that involve the person in different fields of action.[5] This study makes use of this scale and aims to describe the clinical and functional differences in post-COVID-19 patients with and without ICU stay.

MATERIAL AND METHODS

Observational study conducted under the recommendations of Strengthening the Reporting of Observational studies in Epidemiology (STROBE).[10] Participants were adults diagnosed with COVID-19 who required hospital treatment between March and December 2021 in Cali, Colombia. All participating patients understood and signed the informed consent form. This research is endorsed by the institutional ethics committee Act (#126.01.05.02). The inclusion criteria were: people over 18 years of age who have received a positive diagnosis of COVID-19 by means of the polymerase chain reaction (PCR) technique and who experience symptoms associated with the disease; additionally, for the ICU group, they had to present a stay of more than 72 hours. The exclusion criteria were: cognitive or mental difficulties that make it difficult to understand or answer the questionnaires, as well as presenting a new hospital admission due to COVID-19-related events after being discharged from the clinic.

Instruments. A sociodemographic and clinical questionnaire was designed and applied to post-COVID-19 patients that included the variables: gender, age, socioeconomic stratum (lower strata do not have the ability to pay and require subsidies), comorbidities, hospitalization for COVID-19, stay in the ICU for COVID-19, oxygen use, use of IMV, risk factors and symptoms.

The 10-question Fatigue Assessment Scale (FAS) was also administered. This scale allows for the selection of up to five categories of options, including: never, sometimes, regularly, often, and always;[11] the modified Medical Research Council (mMRC) scale, to assess dyspnea during activities of daily living;[12] the Hospital Anxiety and Depression Scale (HADS);[13] and the PCFS, which consists of five possible scores classified into: no functional limitations, minimal functional limitations, mild functional limitations, moderate functional limitations, and severe functional limitations.[8,14]

Procedure. After hospital discharge from the clinic in Cali, contact was established with patients, both those who were in the ICU due to COVID-19 and those who did not require intensive care. At eight weeks, an invitation to participate in the study was extended. A face-to-face

meeting was held in the clinic, explaining the purpose of the research, participants expressed their consent by signing the informed consent form. Then, a physiotherapist administered the different questionnaires and scales, starting with the sociodemographic and clinical questionnaire, followed by the FAS, mMRC, HADS questionnaires and finally the PFCS scale.

Statistic analysis. A database was established in Excel 2010 through the work of an external typist: it was subsequently exported for analysis in SPSS version 26 to perform information processing.

Two groups were formed for the analysis, one group with an ICU stay (stay longer than 72 hours) and another group without an ICU stay. The results obtained were analyzed descriptively, expressing the qualitative variables in frequency and percentages. Regarding the quantitative variables, the Kolmogorov-Smirnov statistical test was applied, and they were presented by means and standard deviation. Subsequently, the groups were divided into intensive care stays and no intensive care stays. In this way, we compared the variables between the groups using the χ^2 test for qualitative variables and the t test for independent samples in the quantitative ones, and considered a p value < 0.05 as statistically significant.

RESULTS

In the period between March and December 2021, 120 patients were diagnosed with COVID-19 and subsequently discharged. All patients were contacted by telephone and eight patients reported not being able to have time to answer the questionnaires, so in the end 112 patients with post-COVID-19 were linked to the study, of which 80 required a stay in the ICU and 32 without a stay in the ICU.

Regarding the sociodemographic characteristics, the average age of the patients was 51.43 years, being mostly female 69 (61.6%). The predominant socioeconomic stratum was the low average 50 (44.6%), followed by the low 31 (27.7%), high average 16 (14.3%), very low 11 (9.8%) and high four (3.6%).

Regarding comorbidities, 31 (27.7%) patients reported presenting some comorbidity; the group with the most patients with comorbidities was those who required an ICU stay with a total of 20 (12.5%) cases. High blood pressure was the comorbidity present in all patients 31 (100%), followed by cardiovascular disease and pulmonary disease with nine (29%) for each, and hypothyroidism with three (9.67%).

An average of 19.12 ± 10.02 days of hospitalization occurred. During hospitalization, 53 (47.3%) of the 80 patients admitted to the ICU required IMV and 72 (64.3%) of all patients required supplemental oxygen after hospital discharge, presenting statistically significant differences between the groups ($p < 0.05$).

After hospital discharge, persistent symptoms in all patients were: myalgia 51 (45.5%), headache 45 (40.2%), difficulty falling asleep 44 (39.8%), cough 39 (34.8%), fatigue 11 (9.8%) and odynophagia 10 (8.9%). Likewise, sedentary lifestyle 68 (60.7%) was the main risk factor, followed by overweight/obesity 47 (42%), cigarette consumption 13 (11.6%) and alcohol consumption 10 (8.6%), despite what was previously reported, there were no statistically significant differences between the groups ($p > 0.05$) *(Table 1)*.

The assessment of the FAS scale in the mental field presented an average of 12.28 ± 5.49, in the physical aspect 12.04 ± 5.46, for a total average score of 24.32 ± 10.67, being higher in the ICU stay group 25.14 ± 11.37; the mMRC scale presented an average in the entire population of 1.01 ± 1.19, and was higher in the ICU stay group 1.38 ± 1.173. The HADS scale in depression presented an average of 3.49 ± 4.01 and in the anxiety item 4.79 ± 4.38, with the ICU group having the highest scores. However, there were no statistically significant differences between the groups ($p < 0.05$) *(Table 2)*.

Regarding the application of the PCFS scale in the characteristics of functional independence, 34 (30.4%) of the patients presented slight functional limitations, followed by minimal functional limitations with 22 (19.6%) patients, without functional limitations 20 (17.9%), moderate functional limitations 18 (16.1%) and severe 18 (16.1%). In the ICU stay group, the most frequent rating was slight functional limitations (33.8%) and for the group without ICU stay it was minimal functional limitations (34.4%), $p < 0.005$ *(Table 2)*.

Patients who entered the ICU compared to those who did not, showed statistically significant differences in variables such as age, number of days hospitalized, constant care and activities of daily living (ADL), *(Table 3)*.

DISCUSSION

This study aimed to determine the clinical and functional differences in post-COVID-19 patients with and without ICU stay. Sociodemographic, clinical, fatigue, dyspnea, anxiety/depression, and functional independence characteristics were analyzed in post-COVID patients 19. It should be noted that these results have been previously explored in other research, which highlights a growing interest in delving into these aspects that have a significant impact on the quality of life and the ability to carry out activities of daily living in these patients.[15,16]

In relation to the sociodemographic characteristics of patients in the variables gender and socioeconomic stratum, similar results are presented regardless of the context or region.[6,17,18]

The average age in patients with post-COVID-19 was 51.46 years, very similar to that reported by other authors

Table 1: Socio-demographic and clinical characteristics.

Variables	Total N = 112 n (%)	With ICU stay N = 80 n (%)	Without ICU stay N = 32 n (%)	p
Age (years)*	51.46 ± 15.94	47.96 ± 15.38	60.22 ± 14.02	**0.000**
Gender				0.759
Male	43 (38.4)	30 (37.5)	13 (40.6)	
Female	69 (61.6)	50 (62.5)	19 (59.4)	
Socioeconomic stratum				0.371
Very low	11 (9.8)	10 (12.5)	1 (3.1)	
Low	31 (27.7)	24 (30.0)	7 (21.9)	
Lower middle	50 (44.6)	33 (41.3)	17 (53.1)	
Upper middle	16 (14.3)	11 (13.8)	5 (15.6)	
High	4 (3.6)	2 (2.5)	2 (6.3)	
Comorbidities				**0.019**
Yes	31 (27.7)	20 (12.5)	11 (34.4)	
No	81 (72.3)	60 (87.5)	21 (65.6)	
Diagnosed disease				
Arterial hypertension	31 (100.0)	20 (100.0)	11 (100.0)	0.316
Cardiovascular disease	9 (29.0)	8 (40.0)	1 (9.1)	0.227
Pulmonary disease	9 (29.0)	7 (35.0)	2 (18.1)	0.660
Hypothyroidism	3 (9.67)	2 (10.0)	1 (9.1)	0.853
Number of days hospitalized*	19.12 ± 10.02	21.11 ± 9.87	1,322 ± 8.05	**0.000**
ICU stay				**0.000**
Yes	80 (71.4)	80 (100.0)	–	
No	32 (28.6)	–	32 (100.0)	
Required IMV				**0.000**
Yes	53 (47.3)	52 (65.0)	–	
No	59 (52.7)	28 (35.0)	32 (100.0)	
Required supplemental oxygen after discharge from the hospital				0.280
Yes	72 (64.3)	61 (76.3)	11 (34.4)	
No	40 (35.7)	19 (23.7)	21 (65.6)	
Persistent symptoms				
Myalgias	51 (45.5)	39 (48.8)	12 (37.5)	0.223
Headache	45 (40.2)	35 (43.8)	10 (31.3)	0.126
Difficulty falling asleep	44 (39.3)	35 (43.8)	9 (28.1)	0.950
Cough	39 (34.8)	28 (35.0)	11 (34.4)	0.920
Fatigue	11 (9.8)	8 (10.0)	3 (9.4)	0.507
Odynophagia	10 (8.9)	8 (10.0)	2 (6.3)	0.272
Ageusia	9 (8.0)	5 (6.3)	4 (12.5)	0.111
Anosmia	5 (4.5)	2 (2.5)	3 (9.4)	0.872
Choking	4 (3.6)	3 (3.8)	1 (3.1)	**0.006**
Fever	3 (2.7)	–	3 (9.4)	0.853
Lumbar pain	3 (2.7)	2 (2.5)	1 (3.1)	0.525
Tinnitus	1 (0.9)	1 (1.3)	–	
Risk factors				
Overweight/obesity	47 (42.0)	34 (42.5)	13 (40.6)	0.856
Cigarette smoking	13 (11.6)	11 (13.8)	2 (6.3)	0.263
Alcohol consumption	10 (8.9)	9 (11.3)	1 (3.1)	0.173
Sedentary lifestyle	68 (60.7)	47 (58.8)	21 (65.6)	0.501

ICU = Intensive Care Unit. IMV = invasive mechanical ventilation.
* Values expressed as mean ± standard deviation.

Table 2: Characteristics of functional independence, dyspnea, fatigue, anxiety and depression.

Variables	Total N = 112 Mean ± SD	With ICU stay N = 80 Mean ± SD	Without ICU stay N = 32 Mean ± SD	p
Mental FAS	12.28 ± 5.49	12.75 ± 5.867	11.09 ± 4.306	0.151
Physical FAS	12.04 ± 5.46	12.39 ± 5.830	11.19 ± 4.395	0.240
Total FAS	24.32 ± 10.67	25.14 ± 11.370	22.28 ± 8.463	0.202
mMRC	1.01 ± 1.19	1.38 ± 1.173	1.03 ± 1.231	0.170
HADS depression	3.49 ± 4.01	3.93 ± 4.745	2.90 ± 2.749	0.255
HADS anxiety	4.79 ± 4.38	5.34 ± 4.933	4.06 ± 3.492	0.203
PCFS scale				
Survival	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.999
Constant care	0.50 ± 1.32	0.65 ± 1.485	0.13 ± 0.707	**0.013**
ADL	0.54 ± 1.36	0.70 ± 1.529	0.13 ± 0.707	**0.008**
IADL	0.94 ± 1.59	1.06 ± 1.679	0.63 ± 1.338	0.152
Role participation	1.17 ± 1.34	1.25 ± 1.383	0.97 ± 1.257	0.321
Symptoms	1.30 ± 0.85	1.38 ± 0.877	1.13 ± 0.793	0.165
Final score	1.93 ± 1.31	2.05 ± 1.330	1.63 ± 1.238	0.122
PCFS classification, n (%)				0.098
No functional limitations	20 (17.9)	14 (17.5)	6 (18.8)	
Minimal functional limitations	22 (19.6)	11 (13.8)	11 (34.4)	
Slight functional limitations	34 (30.4)	27 (33.8)	7 (21.9)	
Moderate functional limitations	18 (16.1)	13 (16.3)	5 (15.6)	
Severe functional limitations	18 (16.1)	15 (18.8)	3 (9.4)	

ADL = activities of daily living. FAS = fatigue assessment scale. HADS = hospital anxiety and depression scale. IADL = instrumental activities of daily living. mMRC = modified medical research council. PCFS = Post-COVID-19 functional status scale.

such as Muñoz et al.,[6] Rosa et al.,[19] Becerra et al.;[20] however, there are significant differences in the ICU group due to a lower age of patients not admitted to the ICU, it is believed that this is due to the fact that the ICU group presented greater diseases prior to COVID-19 infection compared to the group of No admission to the ICU. Fernández and his team[21] describe that there is a relationship between the underlying diseases, the risk factors of people and their admission to the ICU, in addition to being more likely to be infected by the virus and that the development of the disease is severe.

Within the clinical variables, it was observed that the majority of patients had admission to the ICU and also required IMV, which increases the possibility of presenting post-COVID-19 syndrome.[22]

Regarding the evaluation of the FAS, mMRC and HADS scales, low scores are reported, being a good indicator for the perception of the sensation of fatigue both physically and mentally, depression and anxiety; being contrary to what was demonstrated by Ostrowska and his group,[12] Carod[22] and Tabacof et al.,[11] who comment that persistent symptoms related to COVID-19 infection affect cognitive and physical function and the sensation of dyspnea in daily activities; the incidence of anxiety is described in 17.4% and depression in 13.7%.

Regarding the burden of comorbidities present in COVID-19 patients who traveled through the ICU, they are associated due to a faster and more aggressive progression of the disease, which implies much more exhaustive clinical decision-making with aggressive treatments, which prolongs the ICU stay, causing gradual physical deconditioning and implying greater functional dependence specifically on basic care due to prolonged immobility in this service, this is demonstrated in the study by Rodríguez M and associates and Salinas-Aguirre and colleagues, in 2022, with similar results where patients who required ICU had one or more comorbidities, presenting greater functional dependence and prolonged stays or deaths due to complications.[23-25]

This study shows that the majority of patients required admission to intensive care and even IMV, a circumstance that has been described by other authors.[26,27] This situation leads to muscle dysfunction, lethargy, pain and difficulty breathing, significantly deteriorating the patients' functionality in the short and medium term.[28]

Regarding functional status, significant differences were found in the domains of constant care and activities of daily living (ADL) with worse results in patients staying in the ICU, a situation already described by other authors who affirm that, although hospitalization in the ICU provides the

appropriate environment for the treatment and recovery of patients, the infectious process, prolonged immobility and risks related to physical deconditioning cause greater dependence on caregivers and family members in activities of daily living.[29] In addition, the loss of strength and functionality could also be related to high doses of sedatives, neromuscular blockers[6] and steroids[30] for the management of patients with COVID-19 in the ICU.

One limitation considered in this study was the lack of external validity criteria. In addition, the findings of this investigation require follow-up at 12 months to definitively determine the condition of functional independence. However, the use of various instruments that provide a more detailed view of the general condition of post-COVID-19 patients is highlighted. This study makes it possible to understand the differences between patients who were admitted to the ICU due to COVID-19 and those who were not, allowing the identification of their needs after hospital discharge. In addition, it orients towards patient-centered intervention strategies, proposing a medium- and long-term follow-up in a cost-effective manner.

CONCLUSION

Post-COVID-19 patients with ICU stay have greater comorbidities, use of IMV and require longer hospitalization days. In turn, these patients recorded higher scores in the domains of constant care and activities of daily living in functional independence with the PCFS scale. The need to implement the use of cost-effective measurement instruments, such as the PCFS scale, focused on the patient to know their evolution and follow-up objectively during their intervention and recovery process in the medium and long term is highlighted.

Table 3: Differences in means of the variables.

Variables	Differences in means	p
Age	–12.25 ± 3.140	**0.000**
Number of days hospitalized	7.890 ± 2.105	**0.000**
PCFS Scale		
Constant care	0.525 ± 0.208	**0.013**
ADL	0.575 ± 0.212	**0.008**
IADL	0.438 ± 0.302	0.152
Role participation	0.281 ± 0.282	0.321
Symptoms	0.250 ± 0.179	0.165
Final score	0.425 ± 0.273	0.122
Mental FAS	1.656 ± 1.145	0.151
Physical FAS	1.200 ± 1.014	0.240
Total FAS	2.856 ± 2.225	0.202
mMRC	0.344 ± 0.249	0.170
HADS depression	1.024 ± 0.891	0.255
HADS anxiety	1.277 ± 0.993	0.203

ADL = activities of daily living. FAS = fatigue assessment scale. HADS = hospital anxiety and depression scale. IADL = instrumental activities of daily living. mMRC = modified medical research council. PCFS = post-COVID-19 functional status scale.

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Historical considerations about tuberculosis treatment

Consideraciones históricas del tratamiento médico de la tuberculosis

Miguel Ángel Salazar-Lezama*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.

ABSTRACT. Although tuberculosis is as old as humanity, its medical treatment began in the 1940's with the discovery of streptomycin. This discovery caused great expectation; However, shortly after it was noticed that patients who received it died just as well as those who did not. This gave way to treatment with multiple drugs due to the growth nature of *M. Tuberculosis*. Multiple treatments have been given since then, with various organizations worldwide participating. Due to the changing nature of the mycobacteria due to ineffective treatments or insufficient doses, the fight against this bacteria has been long, due to the appearance of monoresistance, polyresistance, evolving until today to the so-called extended resistance. All current research is aimed at better diagnostic tests and treatments that shorten its duration. This article reviews the history of medical treatment of tuberculosis.

Keywords: tuberculosis, *Mycobacterium tuberculosis*, multidrug resistant, treatment.

RESUMEN. A pesar de que la tuberculosis es tan antigua como la humanidad, su tratamiento médico inició en los años 40 con el descubrimiento de la estreptomicina. Este descubrimiento causó gran expectativa; sin embargo, poco después se notó que los pacientes que la recibían morían igual que los que no. Lo anterior dio paso al tratamiento con múltiples fármacos debido a la naturaleza de crecimiento de *M. Tuberculosis*. Múltiples tratamientos se han dado desde entonces, participando varias organizaciones a nivel mundial. Debido a la naturaleza cambiante de la micobacteria a causa de tratamientos ineficaces o dosis insuficientes, la lucha contra esta bacteria ha sido larga por la aparición de la monorresistencia, la polirresistencia, evolucionando hasta hoy a la llamada resistencia extendida. Todas las investigaciones actuales se encaminan a mejores pruebas diagnósticas y de tratamientos que acorten la duración del mismo. En este artículo se hace una revisión de la historia del tratamiento médico de la tuberculosis.

Palabras clave: tuberculosis, *Mycobacterium tuberculosis*, multidrogorresistencia, tratamiento.

INTRODUCTION

Although the tuberculosis bacillus is as old as mankind, the treatment of the disease came much later; and this, for a long time, was based on trial and error, with the selection of strains resistant to multiple drugs, as it happens nowadays. This paper only mentions some of the schemes that have been used during the history of tuberculosis treatment.

THE TREATMENTS

Effective treatment began with the introduction of streptomycin in 1946, with the first trial by the British Medical Research Council (BMRC), and immediately a very significant improvement was found in the patients clinically, bacteriologically and radiologically.[1] This created great hopes and treatments were started with this drug alone. However, five years later, patients administered streptomycin died at the same rate as those who did not receive it, due to the frequent emergence of streptomycin resistance.[2] Subsequently, the Medical Research Council (MRC) demonstrated that the combination of streptomycin with para-aminosalicylic acid (PAS) significantly reduced the incidence of streptomycin resistance.[3]

In this context, in 1952 isoniazid[4] was discovered as a wonder drug that was compared alone with the

Correspondence:
Dr. Miguel Ángel Salazar-Lezama
Clínica de Tuberculosis, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.
E-mail: miguelsalazar02@gmail.com

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combination of streptomycin and PAS. The results were comparable, but the appearance of resistance to isoniazid was observed, so Crofton[5] initiated studies of combining isoniazid with streptomycin and PAS, reporting surprising results in England, Wales and Scotland; the duration of treatment lasted from one to two years. Treatment remained in-hospital. This work inspired the International Union for the Fight Against Tuberculosis to design a scheme based on streptomycin, PAS and isoniazid for three months, followed by nine months of PAS and isoniazid. The response was good, with no relapses or failures, but with many dropouts.[6] This scheme required one year of hospitalization and was very expensive, which meant that it could not be affordable in poor countries. This led to a modification of the treatment, replacing PAS with thiacetazone, which was much cheaper.[7] It was in 1960 that Wallace Fox published a study comparing outpatient versus inpatient treatment and showed that the former was much cheaper than the latter.[8] One obstacle was adherence to treatment, as one year of self-administration made it very difficult to achieve success. Thus, the World Health Organization (WHO) implemented the DOTS (Directly Observed Treatment Short course) strategy, to ensure that the patient ingested the drugs in the presence of health personnel. It was in Madras that a fully supervised intermittent regimen was established for the first time.

An important milestone in the treatment of tuberculosis during the 1950s and 1960s was the addition of pyrazinamide to isoniazid and streptomycin because of its action in killing persistent bacilli in organs after treatment with isoniazid and streptomycin.[9]

Subsequent research at the Pasteur Institute reported that rifampicin accelerated the death of bacilli in the mouse. In clinical practice, the addition of rifampicin or pyrazinamide to a six-month regimen was shown to significantly reduce the relapse rate.[10] Subsequently, several studies were conducted that adopted different conclusions to the medical treatment of tuberculosis such as: 1) the synergism of rifampicin with pyrazinamide for more rapid sterilization of lesions;[11-13] 2) the demonstration that rifampicin was an effective sterilizing agent throughout the entire treatment, while pyrazinamide was effective only during the initial phase of treatment;[14] and 3) the initial phase should last two months. The interesting thing was that, due to the cost of rifampicin at that time, in the continuation phase it was substituted by thiacetazone; however, with the appearance of the human immunodeficiency virus, there was a very significant number of toxic reactions, so it had to be substituted by ethambutol, which also made it possible to shorten the treatment time from eight to six months. The results of this treatment scheme were compelling, published by Professor Enarson of the Union for Tuberculosis and Respiratory Diseases.[15] The rifampicin regimen for the full six months proved to be much more effective than the eight months, particularly in those patients who initially had resistance to isoniazid. The WHO recommends this regimen to date.

Optimism about the treatment grew enormously and was associated with an immediate effect on fatality; patients who would have died of the disease remained alive. The trend in mortality after chemotherapy was illustrated in Norway; the greatest reduction occurred after the introduction, when multitherapy was used.[16] Subsequently, it was shown that patients did not relapse if they followed the prescribed multi treatment disciplined.[17] With the addition of rifampicin to the shortened treatment, it became possible.

After World War II, there was a major epidemic of tuberculosis and the need arose to search for the best strategies to deal with it. Styblo, from the Epidemiological Surveillance Research Unit in The Hague, The Netherlands, and the Scientific Committees of the International Union Against Tuberculosis in Paris,[18] laid the foundations for the modern epidemiology of tuberculosis, an essential element of current disease control programs. In addition, Styblo has the great merit of having been the first to demonstrate the feasibility of successfully applying modern tuberculosis control programs in some of the poorest countries in Africa. Crofton laid the foundations of modern treatment by establishing the principles universally accepted to this day.

Caneti, Rist and Grosset, from the Pasteur Institute in Paris, discovered the bacteriological principles on which the modern chemotherapy of the disease is based; and achieved the most widely used method in the world to measure the sensitivity of the bacillus to the different drugs.

Fox and Mitchinson laid the foundations of treatment by demonstrating, in their studies in Madras, that treatment within the sanatorium was not necessary, since it could be given intermittently on an outpatient basis, and the importance of directly observed treatment. This was later demonstrated in Singapore and Hong Kong.[19] The basic principles of tuberculosis treatment were tested and confirmed between 1948 and 1976.[20]

With the advent of rifampicin, initially synthesized in Italy in 1957 from *Streptomyces mediterranei*, the drug became a very important component of modern tuberculosis treatment. Rifampicin was initially introduced for drug-resistant cases. However, based on British Medical Research Council studies, it was shown that, together with isoniazid, the regimen substantially shortened treatment time, so it was included as a standard element in the late 1970s.[21]

In 1993, WHO declared tuberculosis a global emergency. In 1994, the agency launched the DOTS (Directly Observed Treatment Short course) program, or TAES (strictly observed treatment short course), with several points that made up this project; among them, supervised treatment, i.e., the

patient should take the medication in the presence of health personnel. This strategy continues to this day.[22] Directly observed treatment ensured adherence to treatment, but another important measure to prevent non-adherence was to incorporate medication in a single capsule to prevent «selective discontinuation» of treatment. Currently, a single tablet of four drugs is prescribed in an initial phase (isoniazid, rifampicin, ethambutol and pyrazinamide), followed by a continuation phase with two drugs (isoniazid and rifampicin).

DRUG RESISTANCE

Reports published by the WHO and various researchers since 1994 have warned about the increase in cases of resistance to antituberculosis drugs, especially to isoniazid and rifampicin, especially in regions of Eastern Europe, the former Soviet Union and China, as well as in Latin America, in the Dominican Republic and Argentina.[23-26] In Mexico, Granich et al.[27] published the results of surveillance of drug resistance to antituberculosis drugs, which were 2.4% for primary resistance to isoniazid and rifampicin, and 22.4% for previously treated cases. This led to the conclusion that resistance to antituberculosis drugs in Mexico was moderate to high.

Given the emergence of resistant cases, and that most of these were in low-resource countries, the International Union for Tuberculosis and Lung Disease Control[28] (UICTER) and the WHO[29] included in their guidelines standardized treatment in four categories. Category II with five drugs that included the four primary drugs plus streptomycin; and Category IV, «chronic» cases that already required expert management. Category II was indicated for failures, relapses or dropouts; it was recommended for those resource-poor countries that did not have cultures and susceptibility tests for these cases. These schemes were designed by expert opinions that did not have clinical trials to support them, which led the WHO not to recommend such schemes, as they needed to be designed based on susceptibility testing.[30] This was corroborated in a meta-analysis published by Cohen et al.[31] where treatment results varied between 11 and 85%, especially in resistance to isoniazid, rifampicin or both, in which the results were worse. The recommendation of this treatment scheme suggested by WHO was not adequate in regions where simultaneous resistance to isoniazid and rifampicin (MDR-TB) was high.

STANDARDIZED AND INDIVIDUALIZED RETREATMENTS

Due to the fact that resistant tuberculosis was prevalent in developing countries, where cultures and susceptibility tests for anti-tuberculosis drugs were difficult to access, in addition to long waiting periods for results and, added to the above, the lack of anti-tuberculosis drugs that, in addition to having been discarded previously, were toxic, expensive and difficult to acquire, and above all, the lack of experts in the field, standardized retreatment schemes were designed based on anti-tuberculosis drug profiles, In addition to this, the lack of anti-tuberculosis drugs that, in addition to having been discarded previously, were toxic, expensive and difficult to acquire, and above all the lack of experts in the field, standardized retreatment schemes were designed based on the resistance profiles in each region, and which were applicable in program conditions. Suarez et al.[32] published the results of a standardized retreatment of 18 months, based on kanamycin, three months, ciprofloxacin, ethionamide, pyrazinamide and ethambutol, with a cure success rate of 48%. As can be seen in the scheme, pyrazinamide and ethambutol were added, drugs already used previously and three never taken. In contrast, Goble et al. used an individualized regimen in 171 patients, who had a mean of six drugs taken previously, with a 56% cure rate, previously evaluated with susceptibility testing, and receiving six or more drugs for treatment.[33]

Faced with the alarming increase of resistant cases, already a global concern, with increases in cases in the so-called «red hot spots», such as some provinces in Russia, Latvia, Estonia, China, India, Argentina, attempts were made to provide treatment for resistant tuberculosis. However, this mainly affected countries with low economic resources, which did not have susceptibility tests or second-line drugs for this situation. This led organizations such as the Demian Foundation to initiate studies on standardized retreatment; Van Deun[34] published the results of a retreatment in Bangladesh in a cohort of 58 patients treated in three phases: Phase I consisted of three months with kanamycin, clofazimine, ofloxacin, prothionamide, isoniazid, pyrazinamide and ethambutol as an inpatient; Phase II consisted of the same drugs except kanamycin, this already on an outpatient basis; and a Phase III based on ethambutol and prothionamide for six months, with a cure rate of 69%. This study later gave rise to the STREAM Study (Standardized Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis) 1 and 2.[35-37] In STREAM 2,[37] they published the results in patients with multidrug-resistant tuberculosis in several countries; the patients were assigned to four treatment groups. The study resulted in important evidence that in 76 weeks two bedaquiline regimens, a nine-month oral regimen and a six-month regimen including a second-line injectable (kanamycin), were superior in efficacy in cases resistant to rifampicin and without evidence of resistance to quinolones or aminoglycosides.

It is worth mentioning that the research carried out with new drugs (bedaquiline,[38] delamanid,[39] pretomanid[40]) and

the repositioning of other antibiotics (such as linezolid and clofazimine[41]) have made a very important contribution to the treatment of patients with resistance to rifampicin, sensitive to quinolones. For the treatment of patients with highly resistant tuberculosis: preXDR (simultaneous resistance to isoniazid, rifampicin and a quinolone and/or aminoglycoside) and XDR (simultaneous resistance to isoniazid, rifampicin, quinolone and aminoglycoside), very important studies have been published, such as the Nix study,[42] which included 109 patients, 71 XDR and 38 MDR, treated with bedaquiline, pretomanid and linezolid for 26 weeks. In this study, linezolid doses of 1,200 mg were used. Treatment success was 92% in MDR patients and 89% for XDR patients, with an average of 90%. The drawback of this scheme was the large number of adverse reactions to linezolid, so in the ZeNix[43] study the dose of linezolid was reduced to reduce the side effects, without affecting the success of the treatment.

The WHO, in its 2022 treatment guidelines,[44] makes considerations about the different drug treatments and duration. In its new classification, it only recommends the use of amikacin or streptomycin when no other drugs are available. Quinolones, bedaquiline and linezolid are prioritized, and clofazimine is already taken into account as an antituberculosis drug.

The diagnosis and treatment of the disease has advanced significantly in the last ten years. Molecular tests that include sequencing of mycobacteria make it possible to know in a timely manner its susceptibility profile, which will allow prompt action and appropriate treatment.

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Review
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Benz[a]Anthracene exposure from e-cigarettes and its association with lung carcinogenesis. Descriptive review

Exposición al Benzo[a]Antraceno emitido de los cigarrillos electrónicos y su asociación con la carcinogénesis pulmonar. Revisión descriptiva

Jesús Valencia-Cervantes,*‡ Martha Patricia Sierra-Vargas*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City;
‡Consejo Nacional de Humanidades, Ciencias y Tecnologías, Mexico City.

ABSTRACT. Smoking is associated with a variety of adverse health effects, including cardiovascular and respiratory diseases, stroke, coronary heart disease, and cancer. Despite this, its use is widely prevalent throughout the world. In the past two decades, electronic cigarettes have emerged as an alternative to the use of conventional cigarettes. Nevertheless, the use of electronic cigarettes is not without adverse effects, particularly among adolescents and young adults, where respiratory, cardiovascular, and neurological damage has been demonstrated. However, further research is necessary to identify any potential association between electronic cigarette use and cancer incidence. Electronic cigarettes produce an aerosol upon heating e-liquids, which consist of mixtures of various compounds. These include particulate matter, nicotine, propylene glycol, glycerin, ethylene glycol, vitamin E, reactive oxygen species, heavy metals, volatile organic compounds, and polycyclic aromatic hydrocarbons, including Benz[a] Anthracene, which has the capacity to activate the aryl hydrocarbon receptor, that modulates the expression and activity of cytochrome P450 enzymes, thereby promoting the bioactivation of these compounds and the subsequent processes of mutagenesis and carcinogenesis. This review describes the potential risk of Benz[a]Anthracene content in electronic cigarettes, its activation-signaling pathway, and its association with lung carcinogenesis.

Keywords: electronic cigarettes, lung cancer, polycyclic aromatic hydrocarbons, cytochrome P450.

RESUMEN. El tabaquismo se asocia a varios efectos adversos para la salud, como enfermedades cardiovasculares y respiratorias, accidentes cerebrovasculares, cardiopatías coronarias y cáncer. A pesar de ello, su uso está muy extendido en todo el mundo. En las últimas dos décadas, los cigarrillos electrónicos han surgido como una alternativa para el uso de los cigarros convencionales. Sin embargo, el uso de cigarrillos electrónicos no está exento de efectos adversos, especialmente entre adolescentes y adultos jóvenes, donde se ha demostrado daño a nivel respiratorio, cardiovascular y neurológico. No obstante, se requiere mayor información sobre su posible asociación con la incidencia de cáncer. Los cigarrillos electrónicos producen un aerosol al calentar los e-líquidos, que consisten en mezclas de diversos compuestos, liberando material particulado, nicotina, propilenglicol, glicerina, etilenglicol, vitamina E, especies reactivas de oxígeno, metales pesados, compuestos orgánicos volátiles e hidrocarburos aromáticos policíclicos, donde se incluye al Benzo[a]Antraceno, capaz de activar el receptor de hidrocarburos de arilo, que a su vez modula la expresión y actividad de las enzimas del citocromo P450, favoreciendo la bioactivación de estos compuestos, promoviendo la mutagénesis y la carcinogénesis. Esta revisión describe el posible riesgo del contenido de Benzo[a]Antraceno en los cigarrillos electrónicos, su vía de activación-señalización y su asociación con la carcinogénesis pulmonar.

Palabras clave: cigarrillos electrónicos, cáncer de pulmón, hidrocarburos aromáticos policíclicos, citocromo P450.

Correspondence:
Martha Patricia Sierra-Vargas, MD
Departamento de Investigación en Toxicología y Medicina Ambiental, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas.
E-mail: mpsierra@iner.gob.mx
ORCID: 0000-0002-1894-745X

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INTRODUCTION

The global number of tobacco users is estimated to be 1.3 billion, representing a significant public health concern worldwide. The Global Burden of Disease report indicates that 7 million individuals use tobacco, while approximately 1.3 million non-smokers are exposed to second-hand smoke.[1] Smoking increases the risk of developing various health issues, including cardiovascular and respiratory diseases, stroke, coronary heart disease, and certain types of cancer.[2] Despite being marketed as a substitute for smoking, electronic cigarettes (e-cigs) can produce potentially harmful vapors. Several studies have demonstrated that both e-cigs aerosols and traditional tobacco products have detrimental effects.[3] The number of people who use e-cigs (vapers) reflects trends in nicotine consumption and is expected to reach 82 million in 2021, up from the previous estimate of 58 million in 2018. In the future, the displacement of smokers in low- and middle-income countries, where 80% of the total smoking population resides, is projected to have the most significant impact.[4,5] The prevalence of vapers has consistently increased among individuals aged 21-24 years. However, the health risks associated with the use of e-cigs at an early age are currently unknown.[6] As reported by Dahal *et al.,* the concurrent use of e-cigs and conventional smoking was the most prevalent among older individuals. The females (44.7%) were more likely than the males (39.8%) to have initiated e-cig use at an earlier age. The majority of the older population (> 45 years) used e-cigs for the cessation of smoking (74.1%), whereas the majority of the younger population used them for recreational (50.2%).[7] E-liquids (e-liqs) when are vaporized, they release compounds that may be equal to or different from the parent compound and may be more dangerous due to their physicochemical characteristics.[8-10] This review evaluates the potential impact of polycyclic aromatic hydrocarbons (PAH) compounds, particularly benz[a]anthracene (B[a]A) found in e-cigs, on the lung carcinogenic process. The information consulted was obtained using the keywords «electronic cigarettes», «polycyclic aromatic hydrocarbons», «aryl hydrocarbon receptor», and «lung cancer» in PubMed, Science Direct, Springer Link, and Science.gov. The works that employed in vitro and in vivo models were considered, regardless of the species used in the study.

Chemical composition of e-liqs and e-vapors

E-cigs consist of three primary components: an e-liq chamber, an atomizer, and a battery. The atomizer contains a heating coil activated by the battery, which heats the e-liq in the cartridge. This heating process produces an inhalable e-vapors (e-vaps) that resembles the smoke produced by traditional cigarettes. When the user inhales, a sensor is triggered, initiating the heating process of the e-liq in the cartridge. E-liqs are a crucial component of the vaping system.[9,11] When burned, cigarettes generate more than 7,000 chemicals, including at least 69 known to cause cancer or toxicity, from approximately 600 ingredients.[2] In contrast, e-cigs do not contain tobacco, but the temperature at which e-vaps is produced contributes to the formation of several compounds.[11] Kuehl *et al.*, demonstrated that flavoring compounds undergo thermal degradation at both low (250 °C) and high (750 °C) temperatures. This process results in the formation of e-vaps containing ~300 compounds, including volatile organic compounds (VOCs), carbonyls (aldehydes and ketones), PAH, particulate matter, nicotine, propylene glycol, glycerol, ethylene glycol, vitamin E, flavors, reactive oxygen species (ROS), and heavy metals (Pb, Ni, and Cr).[8-10,12] E-liqs flavors used to simulate or enhance the taste of e-cigs include compounds such as piperidine, butanoic acid, ethyl maltol, vanillin, 1-butanol 3-methyl acetate, and ethyl acetate. These compounds are classified as Generally Recognized as Safe due to their longstanding use in food production, but are limited to ingestion and do not extend to inhalation.[13] Nawi *et al.*, analyzed seventy-two e-liqs from over 60 brands to determine the principal presence of VOC, flavors, nicotine, propylene glycol, and glycerin in 75%, in addition, the analysis of e-liqs identified 116 compounds while e-vaps contained 275 compounds. Forty-two compounds were found in both e-liqs and e-vaps, seven were found only in e-liqs and thirty-eight were found only in e-vaps.[11] Also, Czoli *et al.*, identified a total of 119 flavoring chemicals, including benzaldehyde (21.7%), vanillin (21.7%), and benzyl alcohol (19.9%). Other chemicals, such as 2-acetyl pyrazine, acrolein, cinnamaldehyde, diacetyl, toluene, diacetin, acetone, and isopropyl alcohol, were also detected but at lower frequencies. It also found that tobacco-specific nitrosamines were present, which are potential carcinogens such as N-nitrosonornicotine at 69.8% and nicotine-derived nitrosamine ketone at 42.1%.[14] Beauval *et al.*, identified trace elements (Cd, Cr, and Sb) in six e-liqs and their corresponding e-vaps. Some e-liqs samples contained pesticides such as chlorpyrifos ethyl and trifluralin, but they were not detected in the e-vaps. The major PAH found in e-liqs and e-vaps were naphthalene, phenanthrene, formaldehyde, and acetaldehyde.[15]

Kosarac *et al.*, analyzed 825 e-liqs and identified 1,507 compounds, with the total chemicals detected exceeding 14,000, including nicotine, propylene glycol, glycerol, β-Nicotyrine, and nicotine oxidation products.[16] Finally, Larcombe *et al*, found in sixty-five samples of e-liqs and e-vaps containing excipients, solvents, flavorings, nicotine, and PAH such as B[a]P, B[a]A, acenaphthylene, acenaphthene, anthracene (ANT), chrysene, fluorene, fluoranthene, phenanthrene, naphthalene (NAP), and

pyrene. It is important to note that B[a]P and B[a]A have mutagenic and carcinogenic properties. Although low levels of PAH in e-cigs and e-vaps products may not individually pose a risk of causing disease, their presence as a mixture may potentiate their effects and lead to adverse health outcomes.[17] Compounds such as B[a]A, found in e-cigs and belong to the PAH group, are of great concern due to their ability to cause mutagenesis and carcinogenesis.[18] The processes are initiated by activating the aryl hydrocarbon receptor (AHR) and cytochrome P450 (CYP) enzymes, which play a significant role in the bioactivation and metabolism of carcinogenic agents.[19] *Figure 1A and 1B* illustrates the classification of compounds and the PAH identified in e-cigs and e-vaps.

Activation of the AHR

PAH are a group of chemicals that contain two or more fused aromatic rings. Sixteen are priority pollutants due to their high occurrence and toxicity. Among them, B[a]P, B[a]A, benzo[b]fluoranthene, benzo[j]fluoranthene, and benzo[k]fluoranthene have been found to have genotoxic, mutagenic, and carcinogenic effects.[18] The toxicity of PAH is associated with reactive electrophilic metabolite formation and the activation of cellular receptors, such as the AHR. The AHR is a transcription factor that belongs to the basic helix-loop-helix-PER-ARNT-SIM (bHLH-PAS) subgroup of the bHLH superfamily and is exclusively activated by ligands. Activation of the AHR pathway leads to the transcription of several CYP genes, which play a significant role in the bioactivation and metabolism of carcinogenic agents.[19] *Figure 2* shows how PAH, such as B[a]A, activate the AHR pathway by regulating the expression of CYP involved in their metabolism. Many compounds bind to the AHR with high affinity, causing ligand-dependent changes in its activity. The AHR is an attractive target for small molecule manipulation due to its potential for strong agonist activity. Examples of compounds that fall under this category include persistent planar halogenated polycyclic hydrocarbons (2,3,7,8-tetrachlorodibenzo-p-dioxin, 2,3,7,8-tetrachlorodibenzofuran, B[a]A, B[a]P, 3-methylcholanthrene, and β-naphthoflavone), flavonoids (quercetin, apigenin, and kaempferol) and cruciferous vegetables (curcumin, indole-3-carbinol), are considered ligands.[19] Certain ligands, including resveratrol and galangin, can display agonist and antagonist activities.[20]

Formation of a 3,4-diol-1,2-epoxide metabolite of B[a]A

B[a]A is mainly produced by burning fossil fuels and is found in tobacco smoke. It can bind to suspended particulate matter and accumulate in aquatic organisms. It can also adsorb solid particles in soil, which extends its half-life to 261 days. Its atmospheric half-life is about 7.7 hours due to photochemical degradation.[21] *Figure 3* shows the principal metabolic pathway for the carcinogenic mechanisms of B[a]A by CYP1A1. The stereoisomeric diol epoxides found in the bay-region exhibit significant tumor-initiating activity. It is widely acknowledged that diol epoxides formed from the oxidative metabolism of PAH compounds in the bay-region are more mutagenic than their non-bay counterparts. Furthermore, the resulting adduct structures impede DNA replication and repair, leading to increased mutations. Mutagenicity was observed in bay-region B[a]A adducts when tested in a repair-deficient prokaryotic *in vivo* replication system. However, the corresponding non-bay region adducts of B[a]A were easily bypassed by *Escherichia coli* replication complexes and were not mutagenic.[22] Song *et al.*, discovered that exposing hepatoblastoma HepG2 cells to B[a]A led to an increase in gene and protein expression for CYP1A1 and CYP1B1. Furthermore, it was found that B[a]A-3,4-diol-1,2-epoxide has more potent cytotoxic and

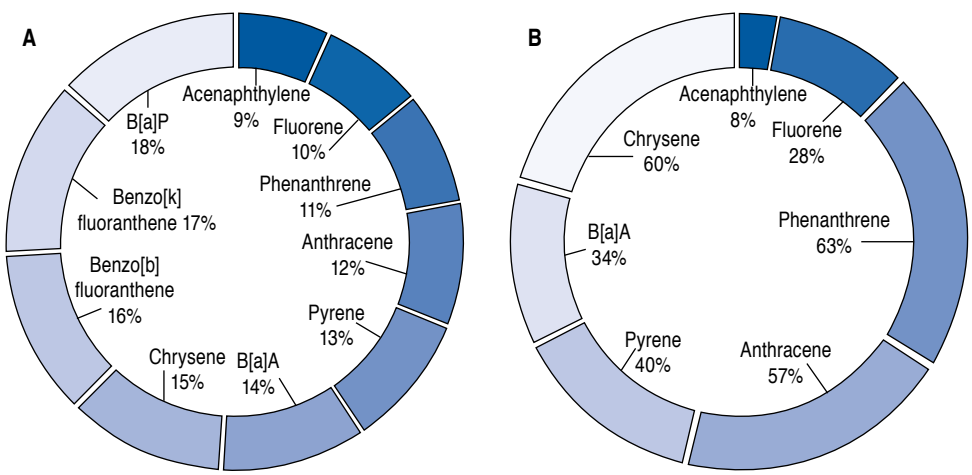

Figure 1:

A) Identification of PAH in e-liqs and e-vaps. **B)** of e-cigs. Benz[a]Anthracene (B[a]A), Benzo[a]Pyrene (B[a]P). The chemical composition of 65 e-liqs before and after an accelerated aging process.

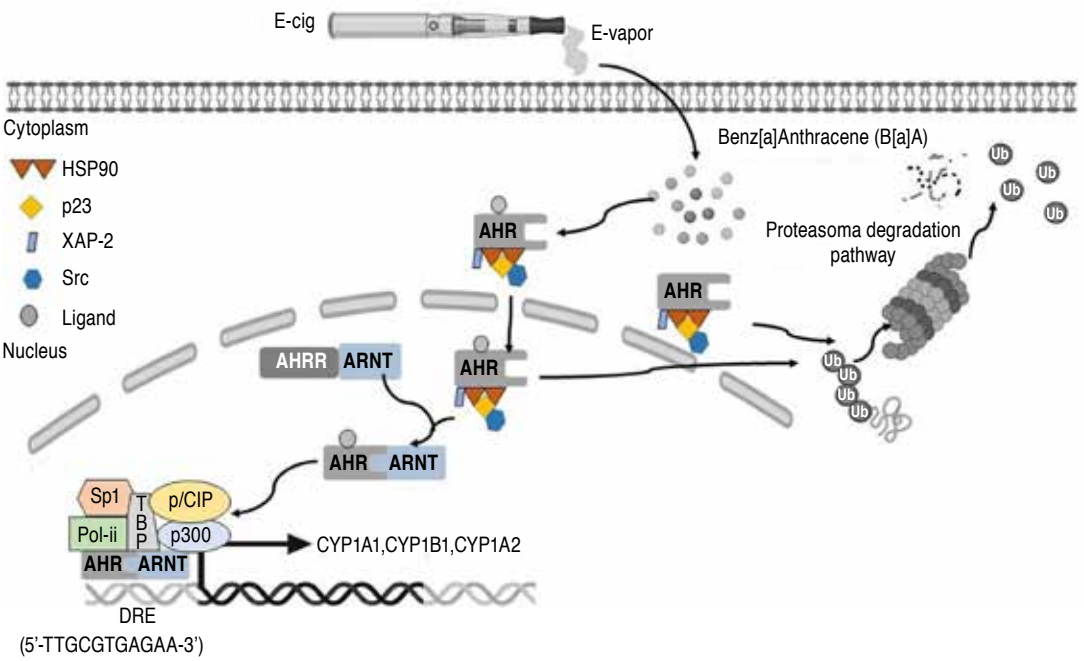

Figure 2: The activation of the AHR pathway by B[a]A. E-liqs are heated and produce e-vaps that contains chemical compounds, including PAH like B[a]A. These compounds activate the AHR pathway by regulating the expression of CYP involved in their metabolism. Certain genes regulate enzymes involved in phase I xenobiotic metabolism, including CYP isoforms 1A1, 1A2, and 1B1. Heat Shock Protein 90 (HSP90); Hepatitis B virus X-associated protein 2 (XAP2); p23; Src kinase; Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT); Dioxin Response Element (DRE); Aryl Hydrocarbon Receptor Repressor (AHRR).

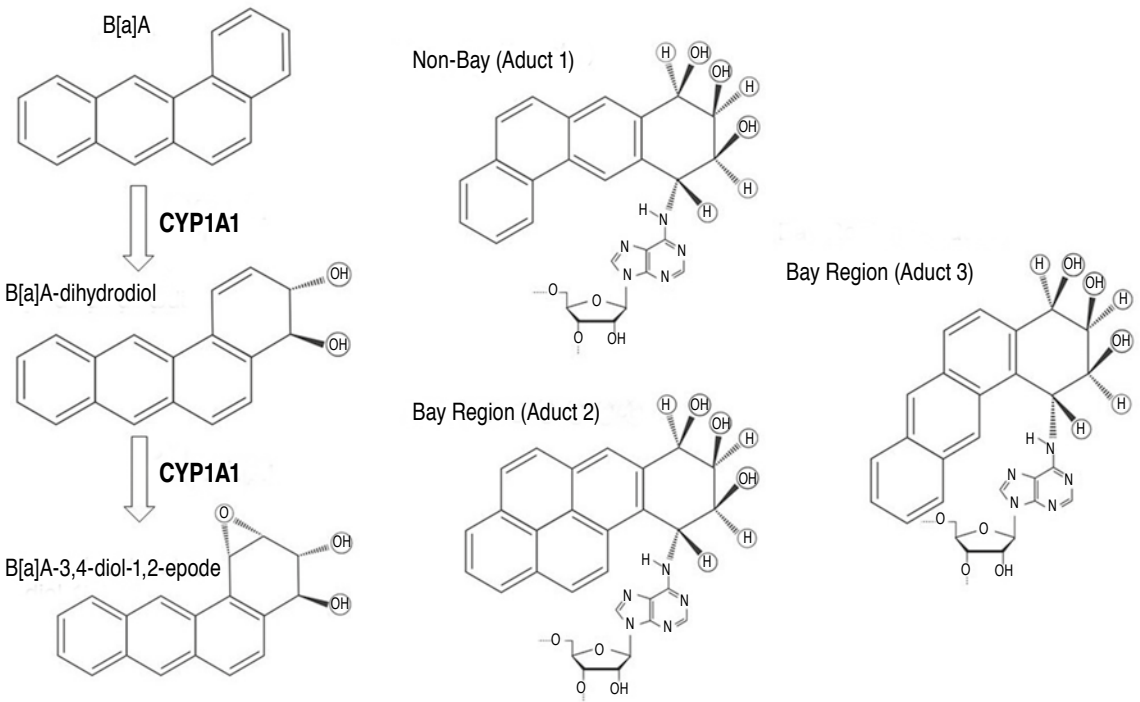

Figure 3: Formation of metabolites of B[a]A by CYP1A1. CYP1A1 metabolically activates B[a]A, forming the carcinogenic compound B[a]A-3,4-diol-,2-epoxide. This compound is classified as a non-bay-region B[a]A adduct 1 ((8S,9R,10S,11R)-N6-[11-(8,9,10,11-Tetrahydro-8,9,10-trihydroxybenz[a]anthracenyl)]-2'-deoxyadenosyl) and a bay-region adduct 2 (-)-(7S,8R,9S). 10R)-N6-[10-(7,8,9,10-Tetrahydro-7,8,9-trihydroxybenzo[a]pyrenyl)]-2'-deoxyadenosyl and bay-region adduct 3 ((1R,2S,3R,4S)-N6-[1-(1,2,3,4-Tetrahydro-2,3,4- trihydroxybenz[a]anthracenyl)]-2'-deoxyadenosyl.

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genotoxic effects than higher doses of B[a]A.[23] The results also suggest that treatment with trans-3,4-dihydroxy-3,4-dihydro-B[a]A in mice resulted in a 24% incidence of malignant lymphoma, while only 4% of the subjects treated with B[a]A developed the same condition. Moreover, it was found that trans-3,4-dihydroxy-3,4-dihydro-B[a]A induced about 35 times more lung adenomas than B[a]A.[24] Additionally, Wood *et al*, reported that B[a]A-3,4-dihydrodiol was 10 times more mutagenic than B[a]A in *Salmonella typhimurium*. Furthermore, it was discovered that trans-dihydrodiol-B[a]A can cause skin tumors in female CD-1 mice. The mutagenic activity of the two diastereomeric 1,2-epoxides of trans-3,4-dihydrodiol-B[a]A is significantly higher in *Salmonella typhimurium* and strain V79-6 of Chinese hamster lung cells than the diastereomeric pairs of B[a]A-8,9-diol-10,11-epoxides or B[a]A-10,11-diol-8,9-epoxides.[25,26] Additionally, male mice exposed to the (+)-diol-epoxide-2 isomer showed a significant incidence of hepatic tumors. The results indicate that bay-region epoxides of unsubstituted PAH are reactive forms of these carcinogenic compounds.[25-27] According Levin *et al*, reported a significant occurrence of tumors caused by two isomers of bay-region diol-epoxides. The (+)-diol-epoxide-2 isomer induced a 100% incidence of lung tumors in mouse models, whereas the (+)-diol-epoxide-1 isomer produced a 31% incidence.[28]

Regulation of cellular functions by the AHR and CYP1 family in the lung

PAH are lipophilic compounds that can passively diffuse across cell membranes when inhaled. Enzymes, including CYP, metabolize PAH to form phenols, catechols, and quinones. These compounds can react with DNA, forming adducts, such as diol-epoxides, radical cations, or reactive and redox-active quinones.[29] The activation of AHR increased in human bronchial epithelial cells, associated with pulmonary diseases, such as asthma and chronic obstructive pulmonary disease.[30] Matsumoto *et al*, demonstrated that AHR plays a significant role in carcinogenesis induced by airborne particulate extract in mice, as well as in the activation of carcinogenic PAH by CYP1A1.[31] Additionally, Lin *et al*., found that the protein expressions of AHR were higher in two out of four adenocarcinoma A549 cells compared to bronchial epithelial BEAS-2B cells and squamous carcinoma cells.[32] The metabolism of PAH involves three functional genes in two subfamilies of the CYP1 family. The catalytic activities of CYP1 enzymes overlap and include hydroxylation and other oxidative transformations of B[a]P, B[a]A, and other aromatic substances.[33] CYP are responsible for processing 75% of the xenobiotics in humans.[34] Shimada *et al*., found that tumor formation rates were lower in CYP1B1 gene-knockout mice treated with 7,12-dimethyl-B[a]A and dibenzo[a,l]pyrene compared to wild-type mice.[35] Additionally, PAH and polyhalogenated hydrocarbons, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin, induce gene expression of CYP1A1 and CYP1B1 via the AHR. Addition the effects of three PAH (5-methylchrysene, B[a]P) and B[a]A) inhibited the metabolic activation of 5-methylchrysene-1,2-diol, B[a]P-7,8-diol, dibenzo[a,l]pyrene-11,12-diol, and 2-amino-3,5-dimethylimidazo[4,5-f]quinolone to genotoxic metabolites catalyzed by CYP isoforms 1A1, 1B1, and 1A2 in *Salmonella typhimurium*.[36] The distribution of CYP1 enzymes was detected in bronchial and bronchiolar epithelium, Clara cells, alveolar lining cells, and alveolar macrophages. CYP1A1 expression is limited to the epithelium of the peripheral airways in the lungs of smokers and does not extend to bronchial epithelium larger than > 1 mm in diameter. Furthermore, alveolar macrophages do not express CYP1A1.[37]

Diseases of the respiratory tract associated with B[a]A

PAH mixtures have short-term (acute) effects that cause skin irritation and inflammation; ANT, B[a]P, and NAP are direct skin irritants. Additionally, ANT and B[a]P have been reported to be skin sensitizers, causing an allergic reaction in animal models and humans. Long-term (chronic) effects include decreased immune function, cataracts, and damage to the kidneys, liver, and lungs, resulting in breathing problems, asthma-like symptoms, immunotoxicity, neurodevelopmental abnormalities, thyroid dysfunction, and disruption of steroid hormones and reproductive functions.[38,39] The American Cancer Society is closely monitoring research on the health effects and symptoms of newly introduced tobacco products with PAH, such as coughing, shortness of breath, chest pain, nausea, vomiting, or other related.[40]

Analysis of epithelial cells from biopsy samples revealed approximately 300 differentially expressed proteins in the airways of smokers and vapers. Among these, seventy-eight proteins showed alterations in both groups, while 113 were unique to vapers. The study found that vapers exhibited increased levels of CYP1B1. Additionally, the research showed that e-liqs rapidly enter the cells. The study also observed that propylene glycol and vegetable glycerin decrease membrane fluidity and hinder protein diffusion, suggests that long-term vaping may have significant biological effects on the lungs, which could lead to the development of chronic lung disease.[41] E-vaps on human bronchial epithelial HBEC cells resulted in 546 differentially expressed genes among the e-cigs, tobacco cigarettes, and air-exposed groups. Moreover, the exposure to e-cigs activated genes associated with oxidative and xenobiotic stress pathways and increased the production of ROS.[42]

E-cigs or vaping use-associated lung injury (EVALI) can cause severe lung damage and inflammation. The vitamin E acetate is the most recognized agent associated with e-cig use with EVALI, as evidenced by the presence of vitamin E acetate in bronchoalveolar lavage fluid samples of 48/51 patients with EVALI, in contrast to the absence of vitamin E acetate in the samples obtained from the healthy control.[43] Among hospitalized patients with EVALI, several chronic conditions were prevalent, including asthma, chronic obstructive pulmonary disease, cardiac disease, and any mental health condition.[44] Nicotinic acetylcholine receptors regulate the cystic fibrosis transmembrane conductance (CFTR) in the airways. Inhaling nicotine can adversely affect these receptors, leading to impaired CFTR function. This decrease in CFTR function has been associated with the progression of asthma, hypertension, and chronic obstructive pulmonary disease.[9,45-47]

Lung cancer

Genetic susceptibility and multiple factors contribute to the activation and elimination of PAH, which can lead to lung cancer development. Exposure to PAH for extended periods was associated with tumor formation in various organs, such as the lungs, prostate, bladder, colon, stomach, breast, and oral cavity.[48] Staudt *et al*., discovered that after inhaling e-cigs containing nicotine, ten non-smokers experienced alterations in the transcriptomes of small airway epithelium and alveolar macrophages and elevated levels of plasma endothelial microparticles, disrupt normal human lung homeostasis.[49] Cioroiu *et al*., assessed the levels of PAH in the lungs of thirty-one Romanian patients with lung cancer, identified fifteen PAH, including B[a]P, B[a]A, fluoranthene, benzo[b]fluoranthrene, and benzo[k]fluoranthrene.[50] This compelling evidence that PAH are etiological factors in human lung cancer. Tang *et al*., demonstrated that exposure to e-cigs for fifty-four weeks in FVB/N mice resulted in the development of lung adenocarcinomas (22.5%) and bladder urothelial hyperplasia (57.5%). This indicates that e-cigs damage DNA in both lung and bladder tissues and inhibit DNA repair in the lungs.[51] Canistro *et al*., found that e-vaps have co-mutagenic and cancer-initiating effects on male Sprague Dawley rats, discovered that e-cigs enhance the activity of phase-I carcinogen-bioactivation enzymes, leading to increased production of ROS and DNA oxidation, resulting in 8-hydroxy-2′-deoxyguanosine.[47] Lee *et al*., investigated the impact of nitrosamines from e-cigs on DNA damage in multiple organs of FVBN mice and discovered the presence of mutagenic O6-methyldeoxyguanosines and γ-hydroxy-1,N2-propano-deoxyguanosines in the lung, bladder, and heart and found a significant reduction in DNA-repair activity and repair proteins in the lung.[52] Zahedi *et al*, showed that exposure of human adenocarcinoma A549 cells to menthol or tobacco-flavored e-liqs or e-vaps induced an Epithelial-to-Mesenchymal Transition (EMT). This transition was characterized by the acquisition of a fibroblast-like morphology, loss of cell-to-cell junctions, internalization of E-cadherin, increased motility, and upregulation of other EMT markers in the oral epithelium of both vapers and smokers. Molecular pathway showed that cancer was the primary disease associated with the deregulated genes in both vapers and smokers, with a prevalence of ~62% and ~79%, respectively.[53] According to Tommasi *et al*., the Wnt/Ca^{2+} pathway was the most affected in vapers, while the integrin signaling pathway was in smokers. The GTPases signaling pathway was identified as the top disrupted pathway.[54] It has been demonstrated that menthol has direct toxic effects on the lung and other tissues and potential oncogenic effects.[55] Other substances found in e-cigarettes include formaldehyde, toluene, acetaldehyde, and acrolein, as well as heavy metals that are associated with the incidence of cancer of the head, neck, bladder, and breast. However, further research is required to substantiate the direct relationship between these compounds and the incidence of a specific type of cancer.[56]

CONCLUSION

E-cigs, as an alternative to conventional cigarettes, do not prevent the occurrence of adverse effects. The e-vaps contain several chemical compounds, including PAH such as B[a]A, which is a potential carcinogen. When the e-vaps are generated, they release other compounds that are equally or more toxic than the parent compounds. The evidence indicates that B[a]A regulates the AHR signaling pathway, which in turn induces the expression of CYP genes that participate in the metabolism of this PAH, favoring the formation of active metabolites with carcinogenic capacity. This suggests that B[a]A may be an etiological factor in human lung cancer. Furthermore, the presence of low levels of PAH in e-cigs and e-vaps products may not individually pose a risk of causing disease. However, their combined presence may potentiate their effects and lead to adverse health outcomes. Currently, there is no official regulation of the chemical composition of e-liqs, making their control and sales difficult. Although e-cigs have gained popularity among young people since their appearance two decades ago, recent information warns about potential health risks associated with their use. Therefore, it is necessary to identify molecular targets and signaling pathways that can prevent the emergence of any disease.

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Procedures and recommendations

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Diffusing capacity of the lung for carbon monoxide: updates on recommendations and procedure

Difusión pulmonar de monóxido de carbono: actualizaciones en las recomendaciones y procedimiento

Gustavo I. Centeno-Sáenz,* Irlanda Alvarado-Amador,* Florisel Almonte-Mora,* Atzimba E. Castillo-Ayala,* Alan U. Camacho-Jiménez,* Paulina Guinto-Ramírez,* Karla M. Pérez-Kawabe,* Rogelio Pérez-Padilla,* Laura Gochicoa-Rangel,*‡ Luis Torre-Bouscoulet,‡ Ireri Thirión-Romero*

*Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas;
‡Instituto de Desarrollo e Innovación en Fisiología Respiratoria. Mexico City, Mexico.

ABSTRACT. The pulmonary diffusing capacity for carbon monoxide is a test that allows quantitative evaluation of the transfer of oxygen from the alveolar air to its union with hemoglobin through the alveolo-capillary membrane. Since its original description in 1957, the pulmonary diffusing capacity for carbon monoxide test has evolved thanks to the advent of rapid response gas analyzers, as well as standardization efforts and vast improvements in the software and reference values. Currently, the single-breath measurement method is strongly standardized and recommended for clinical purposes. The pulmonary carbon monoxide diffusing capacity with the single breath technique has implications for both the diagnosis and the follow-up and prognosis of patients with chronic diseases not limited to the respiratory system. This document is based on the 2005, 2017 and 2021 European Respiratory Society and American Thoracic Society standards to describe technical recommendations for rapid response gas analyzers-based with the single breath systems. The pulmonary carbon monoxide diffusing capacity is underutilized despite its clinically proven value, which ranks second only to spirometry testing. However, it holds particular relevance for patients with interstitial lung diseases, emphysema, and pulmonary vascular diseases.

Keywords: respiratory function tests, pulmonary diffusing capacity, carbon monoxide, alveolar volume.

RESUMEN. La capacidad de difusión pulmonar de monóxido de carbono es una prueba que permite evaluar cuantitativamente la transferencia de oxígeno del aire alveolar a la hemoglobina sanguínea a través de la membrana alveolocapilar. Desde su descripción original en 1957, la prueba de difusión pulmonar de monóxido de carbono ha evolucionado gracias al advenimiento de los analizadores de gases de respuesta rápida. Actualmente, el método de medición de respiración única está sólidamente estandarizado y es el recomendado con fines clínicos. La prueba de difusión pulmonar de monóxido de carbono de respiración única tiene implicaciones tanto para el diagnóstico como para el seguimiento y el pronóstico de pacientes con enfermedades crónicas no sólo del sistema respiratorio. Este documento se actualiza con información propuesta por la *European Respiratory Society* y de la *American Thoracic Society* en los estándares de los años 2005, 2017 y 2021 e incluye las recomendaciones técnicas para sistemas de respiración única basados en los analizadores de gases de respuesta rápida aceptadas internacionalmente. A pesar de su valor clínicamente comprobado, la difusión pulmonar de monóxido de carbono es subutilizada, aunque se posiciona como la segunda prueba más importante después de la espirometría. Sin embargo, su relevancia es especialmente destacada en pacientes con enfermedades pulmonares intersticiales, enfisema y enfermedades vasculares pulmonares.

Palabras clave: pruebas de función pulmonar, capacidad de difusión pulmonar, monóxido de carbono, volumen alveolar.

Correspondence:
Ireri Thirión-Romero, MD
Department of Respiratory Physiology, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas. Mexico City, Mexico.
E-mail: ireri.thirion@iner.gob.mx

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Contents

Abbreviations:

ATPD = ambient temperature, atmospheric pressure, dry conditions.
ATPS = ambient temperature, atmospheric pressure, saturated with water vapor conditions.
ATS = American Thoracic Society.
BHT = breath holding time.
BTPS = body temperature, ambient pressure, saturated with water vapour conditions.
CH3 = methane.
COHb = carboxyhemoglobin.
DLCO = pulmonary diffusion of carbon monoxide.
$DLCO_{sb}$ = single-breathing carbon monoxide lung diffusion.
ILD = Interstitial lung disease.
COPD = chronic obstructive pulmonary disease.
ERS = European Respiratory Society.
ERV = expiratory reserve volume.
FRC = functional residual capacity.
FVC = forced vital capacity.
He = helium.
IVC = inspiratory vital capacity.
KCO = pulmonary transfer coefficient for carbon monoxide.
LIN = lower limit of normal.
Ne = neon.
PiO2 = inspired oxygen pressure.
RGA = rapid response gas analyzers.
RV = residual volume.
TI = inspiratory time.
TLC = total lung capacity.
TLCO = pulmonary transfer of carbon monoxide.
VA = alveolar volume.
VIN = inspiratory volume.
V/Q = ventilation to perfusion ratio.

INTRODUCTION

The measurement of pulmonary diffusion of carbon monoxide (DLCO) has undergone significant evolution since its standardization in 1957 by Ogilvie et al.[1] The classical method used small samples of exhaled gas and required several minutes to measure the carbon monoxide concentration. In recent years, rapid response gas analyzers (RGA) have been developed that perform the measurement in less than 150 milliseconds. These advances coupled with rapid microprocessor calculations, and better and more numerous reference values, have led to a revolution in DLCO measurement.[2]

DLCO is a fundamental test for assessing gas exchange at the alveolocapillary membrane, playing a crucial role in the diagnosis, management and prognosis of various diseases not limited to the respiratory system.[3,4] Several techniques have been used to assess carbon monoxide transfer across the alveolocapillary membrane.[5] These include: the multiple-breath (multibreath) method; the intrabreath method, which is performed when maximal inspiration is followed by a slow and uniform maximal exhalation, without a period of apnea in the maneuver;[6] and the «one-breath» method developed by Krogh in 1910.[7] The latter method is widely used and the most standardized.[8,9] In the «one-breath» or «single-breath» ($DLCO_{sb}$) method, a 10-second apnea period is performed during maximal inspiration.[10] In addition to the measurement of $DLCO_{sb}$, simultaneous inhalation of inert gasses, such as helium (He), methane (CH3) or neon (Ne), allow calculation of alveolar volume (VA), total lung capacity (TLC) and residual volume (RV).

This review references the 2005 and 2017 update of the European Respiratory Society (ERS) and American Thoracic Society (ATS) standards,[2,8] as well as the ERS/ATS-2021[11] standard for pulmonary function test interpretation strategies. These standards seek to provide a technical update for DLCO systems based on RGA development and to describe new calculation standards that incorporate continuous gas analysis of the entire exhaled sample, as well as clinical and functional interpretation of test results.

DLCO measurement, performed under standardized conditions and under strict quality control, is a sensitive tool to detect changes in lung function, even less than 10%.[12] Its decrease may indicate chronic lung diseases such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD), showing a direct correlation with the degree of emphysema, inflammation or fibrosis.[3,13,14] $DLCO_{sb}$ also reflects abnormalities in pulmonary vascular diseases such as pulmonary hypertension,[15] embolism and vasculitis, as well as extrapulmonary diseases such as hemoglobinopathies,[16] obesity,[17] musculoskeletal abnormalities and elevated carboxyhemoglobin (COHb) levels.[18] This broad spectrum of clinical applications highlights the versatility of $DLCO_{sb}$ as a sensitive indicator of multiple conditions affecting lung function and the overall health of the individual.

PHYSIOLOGICAL BASIS

DLCO is a test that measures the properties of the alveolocapillary membrane for oxygen exchange from alveolar air to erythrocytes in the alveolar capillaries, thus involving not only the physiological mechanism of pulmonary diffusion *(Figure 1)*, but also ventilation, perfusion and the ventilation to perfusion ratio (V/Q). For this reason, especially in Europe, it is more appropriately called pulmonary transfer of CO (TLCO). If you would like to learn more about the physiological basis of pulmonary carbon monoxide diffusion, please refer to the supplementary material.

INDICATIONS AND CONTRAINDICATIONS OF THE TEST

In general, the main indication for $DLCO_{sb}$ testing is the diagnostic evaluation and follow-up of lung parenchymal

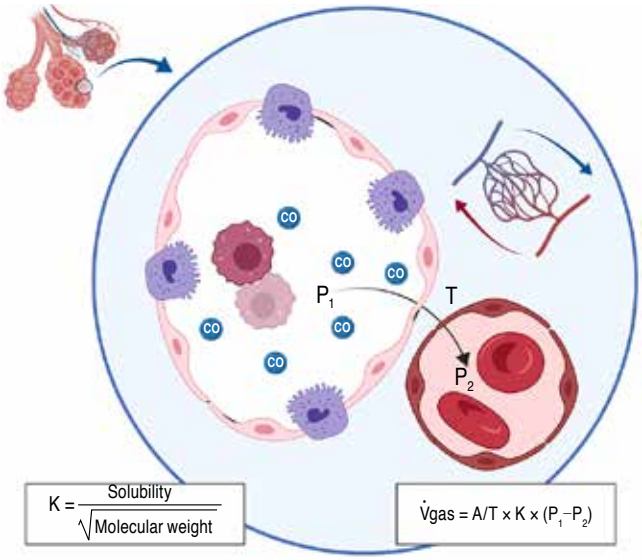

Figure 1: Fick's Law. Fick's law describes the factors that determine the diffusion of a gas through a given surface (A), the thickness of the tissue (T), and the diffusion constant of the gas (K), which corresponds to the solubility and the molecular weight of the test gas, as well as the partial pressure difference across the tissue (P1-P2). The diffusion constant is proportional to the solubility of a gas and is inversely proportional to the square root of the molecular weight of the gas.
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diseases *(Table 1)*. The updated contraindications for the $DLCO_{sb}$ test are listed in *Table 2*.[2,3,19]

DLCO EQUIPMENT AND SUPPLIES

DLCO equipment should meet the international technical recommendations issued by ATS/ERS 2017,[2] with the following recommended minimum requirements for volume measurements and rapid gas analyzer, which can be found in the equipment user manual and supplementary material.

PRE-TEST PREPARATION

Preparation of technical personnel prior to testing

During the COVID-19 pandemic, disease transmission became more prominent in order to mitigate risks. Rigorous implementation of safety and disinfection measures are required *(Table 3)*.[20]

Quality control and equipment calibration[2,21]

1. Daily calibration check: start with zero flow before each maneuver. Verify volume calibration with a 3 L syringe, performing at least three different flows (low, medium and high) between 0.5 and 12 L/s, meeting an accuracy requirement ≤ 2.5%.
2. Weekly procedures or in case of problems: should be performed with a calibrated 3 L syringe, ensuring that the VA calculation is within ± 300 mL of the expected value and DLCO is < 0.166 mmol/min/kPa or < 0.5 mL/min/mmHg. The biological control test should not have deviations > 12% or > 3 mL/min/mmHg, because it could indicate quality control problems.
3. Monthly testing: leak testing of the 3 L calibration syringe is recommended. If it does not return within 10 mL of full fill, it should be sent for repair. Also, a linearity evaluation of the gas analyzer should be performed using known dilutions of the test gas or using a high precision test gas. However, automation of linearity by manufacturers is preferred.
4. General recommendations: In the absence of a high accuracy DLCO and gas simulator, system checks

Table 1: Indications for the $DLCO_{sb}$ test.

1. Obstructive diseases: a. COPD (decreased proportionally to the degree of emphysema) b. Asthma (usually normal or increased) c. Cystic fibrosis (decreased in advanced stage) d. Chronic bronchitis (usually normal or slightly decreased)
2. Evaluation and follow-up of restrictive diseases: a. Interstitial diseases (frequently decreased) b. Extrapulmonary restrictive diseases (usually normal)
3. Pulmonary vascular diseases (frequently decreased): a. Chronic pulmonary thromboembolism b. Pulmonary hypertension c. Pulmonary vasculitis
4. Preoperative evaluation: a. Resection for lung cancer b. Volume reduction surgery c. Lung transplantation
5. Impairment and disability evaluation: a. COPD, interstitial diseases, others b. Prediction of arterial desaturation during exercise in some patients with lung disease c. Assessment of pulmonary effects of chemotherapeutic agents and other drugs known to cause lung damage, as well as radiotherapy
6. Other useful clinical applications of DLCO measurement: a. Evaluation of pulmonary hemorrhage (usually elevated) b. Evaluation of some diffuse pulmonary infectious diseases (e.g., *Pneumocystis pneumonia*) c. Timely diagnosis and follow-up in respiratory surveillance programs in occupational medicine, especially in subjects exposed to inorganic dust

DLCO = pulmonary diffusion of carbon monoxide. COPD = chronic obstructive pulmonary disease.

Table 2: Contraindications to the $DLCO_{sb}$ test.

Absolute
1. Severe hypoxemia (SpO_2 < 75%) In this case its performance can be evaluated according to the altitude where the test is being performed, and always under medical supervision 2. Elevated carboxyhemoglobin levels (COHb > 10 to 15%)
Relative
1. Confusion or poor muscle coordination that prevents the proper maneuver from being performed 2. Acute or decompensated cardiovascular disease (infarction, heart failure, cerebrovascular disease) 3. Pneumothorax in the last three months 4. Risk of bleeding due to hemoptysis or aneurysms 5. Surgery (thorax, abdomen, eye, ear) in the last month 6. Acute respiratory infections in the last two weeks (influenza, common cold) 7. Active pulmonary tuberculosis 8. Advanced or complicated pregnancy 9. Patients with tracheostomy or pleural probes 10. Patients who cannot withhold supplemental oxygen for at least 10 minutes 11. Patients with VC or FVC less than the minimum volumes required by the equipment

COHb = carboxyhemoglobin. $DLCO_{sb}$ = single-breath carbon monoxide lung diffusion. FVC = forced vital capacity. SpO_2 = pulse oximetry oxygen saturation. VC = vital capacity.

Table 3: Preparation of technical personnel before performing the $DLCO_{sb}$ test.

1. Barrier devices and cleaning procedures: – Use of barrier devices, such as filters, should be made to prevent cross transmission of diseases – Despite the use of in-line filters, the ATS and ALAT standards stress the continuous need for regular cleaning and decontamination of equipment
2. Personal hygiene: – Health personnel should follow the recommended standards of hand washing, either by hand washing (40-60 seconds) or by rubbing with alcohol gel (20-30 seconds) – The 5 moments of hand washing/hand hygiene, according to World Health Organization (WHO) guidelines, should be followed
3. Personal Protective Equipment (PPE): – PPE includes gown for activities that may generate splashes or sprayable liquids from blood, organic fluids, secretions or excretions – Use of disposable gloves in procedures with potential contact with infectious material, changing them between tasks and procedures, and washing gloves with alcohol gel before removing them – Use of surgical mask or N95 during patient care, and eye protection to prevent splashes, in case of contagious diseases
4. Disinfection and sterilization: – Before caring for each patient, disinfection and/or sterilization of equipment, instruments and surfaces must be carried out

These measures, based on ALAT (Latin American Thorax Association) recommendations, are essential to ensure a safe testing environment and minimize the risk of disease transmission.[20]
ATS = American Thoracic Society. $DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide.

should be performed using a 3 L calibration syringe in ambient temperature, atmospheric pressure, saturated with water vapour (ATPS) conditions, with VA reporting in ambient temperature, atmospheric pressure, dry (ATPD) conditions instead of body temperature, ambient pressure, saturated with water vapour (BTPS) conditions. A digital calibration option should be available to verify the computational algorithms of the system. This option should use simulated flow data, CO concentration and tracer gas concentration from standardized maneuvers with a known DLCO.

Instructions for the patient

To minimize variability, the following pre-test specifications, pre-test patient instructions *(Table 4)* and patient preparation for the test *(Table 5)* should be considered.

PROCEDURE[2,8,22,23]

1. In the diffusing equipment system the patient data will be placed, for the interpretation of $DLCO_{sb}$ values an adjustment for equipment dead space and barometric

pressure (altitude) is required, which should be done by the equipment software before calculating the predicted values.
2. Perform spirometry to obtain a forced vital capacity (FVC) maneuver according to the latest international standards.
3. The individual is positioned correctly, holding the mouthpiece and positioning the nose clip appropriately. A new mouthpiece with a filter should always be used on each patient and check that there are no leaks through the mouthpiece or nose.
4. As illustrated in *Figure 2*, start with two to three breaths at tidal volume, maintaining a stable functional residual capacity (FRC).[24]
5. From FRC, the patient is asked to exhale in a relaxed manner until RV (expiratory reserve volume maneuver, ERV), where a plateau (< 25 mL) of at least one second should be achieved, and then the valve is activated.
   a. In obstructive patients, where exhalation to RV may require more time, it is recommended that

Table 4: Instructions for the patient before the $DLCO_{sb}$ test.

1. Avoid smoking or vaping on the day of the test, write down the time of last consumption
2. Avoid using chest-restrictive garments (vests, corsets or very tight clothing)
3. It is not necessary to suspend basic medication
4. Fasting is not required for the test, light eating is recommended
5. Avoid intense exercise, at least four hours before (if the patient has exercised, it is necessary to specify it)
6. Do not use supplemental oxygen for ≥ 10 minutes, if the patient's clinical status allows it
7. Avoid consuming alcohol on the day of the test
8. If a nitrogen flushing test must also be performed, it is recommended that the carbon monoxide diffusion test be performed first; If carried out later, wait twice as long as the duration of the nitrogen flushing test[2]
9. In case of suspicion of high COHb levels (smokers, firefighters, etc.), it is recommended to measure them[18,24]
10. It is recommended to apply a brief medical history questionnaire, which includes:
    a. History of current or past smoking and vaping, total number of years of smoking, and average daily number of cigarettes per day
    b. History of occupational exposure to fumes or dusts, total number of years of exposure and average hours per day
    c. History of respiratory symptoms: dyspnea, wheezing, cough, and expectoration
    d. Contraindications of the test: acute cardiovascular disease, acute or active respiratory infections (influenza, common cold, tuberculosis, etc.), advanced or complicated pregnancy

COHb = carboxyhemoglobin. $DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide.

Table 5: Patient preparation to perform the $DLCO_{sb}$ test.

1. Reception and confirmation of identity:
   – The technician or doctor in charge receives the patient and confirms his or her full name and date of birth, ensuring that they match the medical request and the file or registration number, if applicable
   – Contraindications are reviewed, and if any are present, the test is not performed unless authorized in writing by the treating physician or approved by the laboratory medical director
2. Anthropometric measurements of weight and height will be carried out in accordance with what is established in other pulmonary function tests
3. Demographics:
   – The patient's age in years on the day of the test and other demographic data such as ethnicity are recorded
   – The altitude of the region where the test is performed should be recorded for adjustments, if necessary
   – These data are entered into the equipment data program
4. Additional information:
   – Tobacco or vaping consumption, previous intense physical exercise and the use of inhaled bronchodilators are recorded
   – The patient rests sitting for at least 10 minutes before the test
5. Instructions for the maneuver:
   – The maneuver is explained in clear and easy language for the patient, ensuring that they understand each step
   – The use of the nose clip is explained and the patient is instructed on the proper use of the mouthpiece
   – Instructions include holding the mouthpiece with your teeth, without biting, sealing it with your lips around it, and avoiding inserting your tongue into the hole
   – Place the patient in the correct position: sitting, with both feet resting on the floor, trunk upright and head slightly elevated (maintain this position throughout the maneuver)

$DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide.

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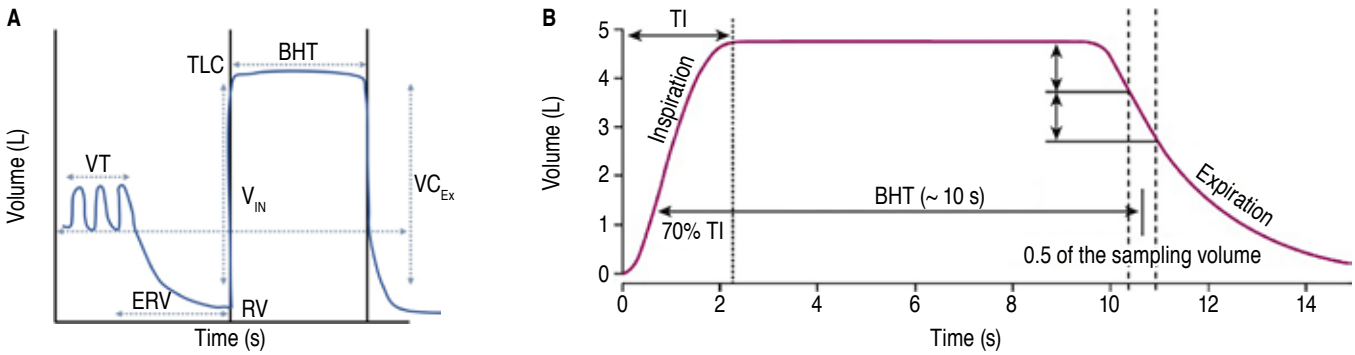

Figure 2: $DLCO_{sb}$ maneuver, single breath. **A)** The maneuver begins with stable breathing at tidal volume (VT) followed by a relaxed expiratory reserve volume (ERV) maneuver. Upon reaching residual volume (RV), the subject must complete the inspiratory vital capacity that determines the inspiratory volume (VIN) of the maneuver in less than four seconds, until reaching total lung capacity (TLC). After this, an apnea of 10 ± 2 seconds is performed followed by unforced expiration (VCEx) for at least four seconds. **B)** breath holding time (BHT) is calculated by the Jones-Mead method, which includes 70% of the inspiratory time (TI) up to half of the alveolar sampling time.
$DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide.
Modified from: DeCato TW.[23]

this part of the maneuver be limited to < 12 s, allowing this group of patients to exhale enough to achieve maximum vital capacity on the subsequent inhalation.

6. In VR, the subject is asked to inhale rapidly to TLC (where the mouthpiece is connected to the gas source).
7. The maximum inspiratory vital capacity (IVC) maneuver should be performed in less than four seconds, reaching a volume ≥ 90% of the FVC measured by spirometry previously (with a minimum tolerance of 85% for a B quality and 80% for a C quality).
8. The patient is asked to maintain a period of apnea for 10 ± 2 s, avoiding leaks and Valsalva or Müller maneuvers (expiratory or inspiratory effort against a closed glottis, respectively).
9. The subject is instructed to perform an unforced exhalation, without interruptions or hesitations.
10. In rapid systems (RGA), exhalation should be continued to RV, which improves VA measurement.
11. In case of a failed maneuver, instructions and demonstration should be repeated if necessary.
12. The time between maneuvers should be at least four minutes, to allow adequate tracer gas removal, in cases of severe airflow obstruction up to 10 minutes of waiting time is recommended.
13. A minimum of two maneuvers that meet acceptability and repeatability criteria must be completed, with a maximum of five attempts, in order to avoid increasing COHb in the blood (five $DLCO_{sb}$ maneuvers increases 3-3.5% of COHb in the blood).[24]

A submaximal inspiratory volume of the sample gas less than the known vital capacity may affect carbon monoxide inhalation, depending on whether it was from a suboptimal exhalation to RV (performed at TLC) or was from a suboptimal inhalation from RV (maneuver achieved below TLC). In the first case, VA and calculated $DLCO_{sb}$ reliably reflect lung volume and lung properties at TLC. In the second case, VA is reduced and DLCO measurement is affected.

Inspiration must be rapid, as the $DLCO_{sb}$ calculation assumes instantaneous lung filling, this explained because when the lungs fill more slowly, they decrease the amount of time the lung is in full inspiration, with a consequent reduction in carbon monoxide entry.

Valsalva or Müller maneuvers can affect the calculation of $DLCO_{sb}$ by decreasing or increasing intrathoracic blood volume, resulting in an increase or decrease in $DLCO_{sb}$, respectively for each maneuver. *Figure 3* shows some artifacts that may be observed during the maneuver.

RESULTS REVIEW

Acceptability criteria[2]

1. Obtain an inspiratory volume (VIN) ≥ 90% of the largest FVC in the same test session; if this is not achieved, we can obtain an A quality with a VIN ≥ 85% of the largest FVC in the same test session along with a VA within 200 mL or 5% (whichever is greater) of the largest VA from other acceptable maneuvers.
2. Inspiratory time (IT) less than 4 seconds (obtain 85% of the test gas inhaled in < 4 seconds).
3. Stable breath holding time (BHT) for 10 ± 2 seconds with no evidence of leaks or Valsalva/Müller maneuvers during this time.

4. On classical analyzers the exhalation time must be greater than 4 seconds (i.e., sample collection is completed within 4 seconds of the onset of exhalation). In rapid response analyzers the exhalation should continue up to the residual volume, with a maximum exhalation time of 12 seconds, which provides a better measurement of VA.

Repeatability evaluation

The variability of $DLCO_{sb}$ depends more on technical than biological factors. The $DLCO_{sb}$ test should have at least two repeatable maneuvers in two units of $DLCO_{sb}$ in mL/min/mmHg (equivalent to 0.67 unit in mmol/min/kPa). It is considered that more than 95.5% of patients can achieve this repeatability criterion.[2,9]

Quality control of $DLCO_{sb}$ maneuvers

A grade A maneuver is one that meets all acceptability criteria, therefore, the average $DLCO_{sb}$ of two repeatable grade A maneuvers should be reported. If after repeating the test, the operator cannot obtain two repeatable grade A maneuvers, then the values are reported with the warning to the interpreter that the test session was not optimal *(Table 6)*.[2]

$DLCO_{SB}$ REPORT

Special considerations and limitations for $DLCO_{sb}$

1. For interpretation of $DLCO_{sb}$ results, equipment dead space adjustment should be performed.[11] The dead space adjustment should include the respiratory circuit proximal to the sampling point, the filter, and the gas analyzer mouthpiece, which should be < 200 mL. Smaller dead space volumes are recommended for pediatric-aged patients and adults with a vital capacity of less than 2 L.[25]
2. $DLCO_{sb}$ increases at higher altitudes because of lower oxygen competition due to lower PiO2.[26]
3. Hemoglobin, COHb and backpressure concentrations or increased carbon monoxide outflow resistances may affect the $DLCO_{sb}$ test, and should be considered when interpreting.[11,16]
4. Diurnal variation in the DLCO result has been reported (1.2%/hour drop from 9:30 a.m. to 5:50 p.m.).[27]
5. There is a change of up to 13% during menstrual cycles. The highest value of $DLCO_{sb}$ is just before menstruation and the lowest value on the third day of menstruation.[28]
6. There may be a reduction of up to 15% of the $DLCO_{sb}$ value within 90 minutes of ingesting alcohol.[29,30]
7. Smoking affects test results; a prevalence of a $DLCO_{sb}$ below the lower limit of normal (LLN) in patients without airway obstruction has been observed in 26.7% when they are active smokers, and 14.4% in those who have quit smoking.[31]
8. An increase in $DLCO_{sb}$ during pregnancy (first trimester) has been described but not consistently found in other studies.[32,33]
9. The Valsalva maneuver can decrease $DLCO_{sb}$ because it decreases the amount of blood in the pulmonary capillaries.[12]
10. In subjects with obstructive disease, bronchodilator use increases $DLCO_{sb}$ by up to 6%, so the use of these drugs should be recorded by the technician.[34] However, recent studies have found no significant effects on DLCO with doses lower than 1,000 μg of salbutamol, so the use of bronchodilators before DLCO testing is not inadvisable.[2]

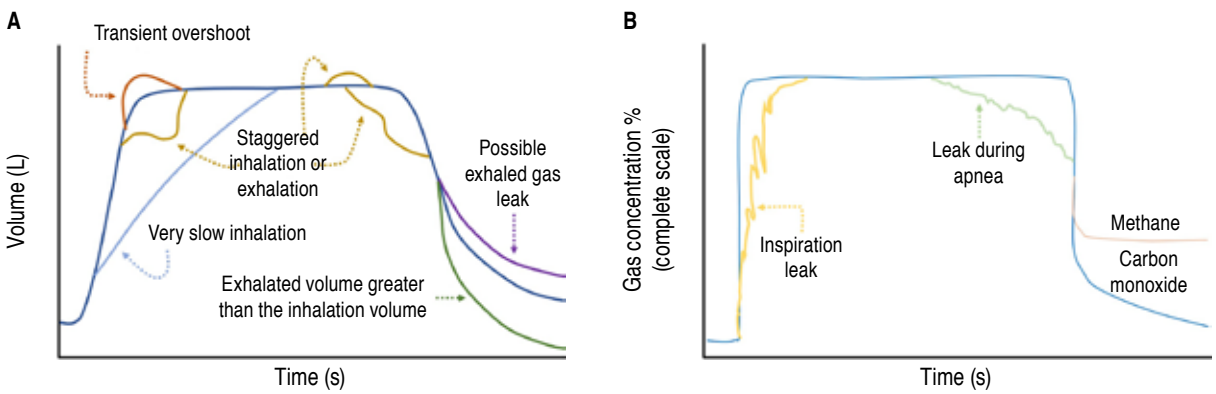

Figure 3: DLCO artifacts. **A** and **B)** Problems that can occur during the maneuver for $DLCO_{sb}$ that can lead to measurement errors are shown. DLCO = pulmonary diffusion of carbon monoxide. $DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide.
Modified from: Graham BL, et al.[2]

Table 6: Classification of quality control.

Quality	V_{IN}/FVC (%)	T_A	Sample collection time* (seconds)
A	≥ 90‡	8-12 s	≤ 4
B	≥ 85	8-12 s	≤ 4
C	≥ 80	8-12 s	≤ 5
D	≤ 80	< 8 o > 12 s	≤ 5
F	≤ 80	< 8 o > 12 s	> 5
Quality A: meets all acceptability criteria. Report the average $DLCO_{sb}$ of two repeatable quality A maneuvers.			
Unsuccessful repetition (if two repeatable quality A maneuvers are not obtained):			
1. Two or more maneuvers A not repeatable, but acceptable: Report the average $DLCO_{sb}$ of those acceptable maneuvers 2. Only one maneuver A is obtained: Report the $DLCO_{sb}$ value of that maneuver 3. Maneuvers A are not obtained: report the average $DLCO_{sb}$ of the maneuvers with grades B, C or D 4. Only F maneuvers are obtained: Do not report any $DLCO_{sb}$ value			

Note: In each of these situations, these deviations from the acceptability criteria should be noted to alert the interpreter of the test results.
$DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide. FVC = forced vital capacity. T_A = apnea time. VA = alveolar volume. V_{IN} = inspired volume.
* Only in classic analyzers, in fast response analyzers it is necessary to reach the residual volume with a maximum of 12 seconds.
‡ V_{IN}/FVC ≥ 85% and alveolar volume within 200 mL or 5% (whichever is greater) of the largest VA of another acceptable maneuver.

ADJUSTMENTS IN THE $DLCO_{SB}$ VALUE

There are physiological factors that can affect the $DLCO_{sb}$ measurement, inducing changes in opposite directions, therefore, current standards recommend four adjustments: Hb, COHb, the inspired pressure of oxygen (PiO_2) or altitude adjustment and VA adjustment. It is suggested to adjust for these factors in the predicted value of $DLCO_{sb}$ rather than the measured value. This predicted value is calculated from measurements in healthy individuals without disease, with normal Hb and COHb levels, performed at rest and breathing at room air. If any of these conditions are not met, corresponding adjustments to the predicted value are advised and can be found in the supplementary material.[2,11]

BASIC INTERPRETATION PROCESS

1. The primary measurements are the pulmonary transfer coefficient for carbon monoxide (KCO) (carbon monoxide concentration change measured over time per unit volume and pressure) and VA, its product (DLCO = KCO × VA) is the key index interpreted for gas transfer.
2. Define the alveolocapillary membrane diffusion pattern according to the $DLCO_{sb}$ concentrations proposed by the 2022 ATS/ERS interpretation strategies technical standard,[11] algorithm in *Figure 4*.
3. For severity grading it is recommended to use the $DLCO_{sb}$ Z-score, i.e., the DLCO measurement expressed in standard deviations outside that predicted by reference values for individuals of the same height, age and sex generating the following categories:

   a. Normal DLCO: ± 1.645 SD.
   b. Mild decrease: from –1.645 to –2.5 SD.
   c. Moderate decrease: from –2.51 to –4.0 SD.
   d. Severe decrease: < –4.1 SD.

4. It is also useful to compare VA with TLC measured by body plethysmography to analyze whether maldistribution of the test gas that may contribute to lower $DLCO_{sb}$ (i.e., carbon monoxide uptake can only be analyzed for regions where the test gasses are distributed). The normal value for the VA/TLC ratio in adults is approximately 0.85-0.90.[35] Values significantly below this suggest that deficiencies in the gas mixture are likely to contribute to a low measured $DLCO_{sb}$. In the absence of lung volume data by plethysmography, the presence of a steep downward slope in the inert gas tracing during exhalation suggests the possibility of gas maldistribution; however, there are no ideal ways to adjust for these conditions.[11]
5. Quality grading according to *Table 6*.
6. The choice of reference equation may affect the final interpretation. Each laboratory must select the most appropriate equation for the methods and population selected. This is essential since large differences between reference equations have been described.[11,26,36]
   In Mexico we have two reference equations, which were mostly performed in Mexico City (2,240 m above sea

level), in a pediatric population (4 to 20 years of age) by Gochicoa et al.[37] and in an adult population (22 to 83 years of age) by Vázquez et al. the latter includes adjustment for altitude.[38]

7. For interpretation, the relevant adjusted values for altitude (PiO2), Hb value and COHb should be considered.

CONCLUSIONS

DLCO is a pulmonary function test that assesses gas exchange and plays a crucial role in the diagnosis, monitoring and prognosis of multiple diseases. It is crucial to note that DLCO cannot be assessed in isolation; its constituent components, such as VA and KCO, need to be considered. Ignoring these variables may result in the loss of relevant clinical information. Furthermore, the importance of performing an integrated analysis of DLCO in conjunction with other pulmonary functional tests and available clinical data is emphasized.

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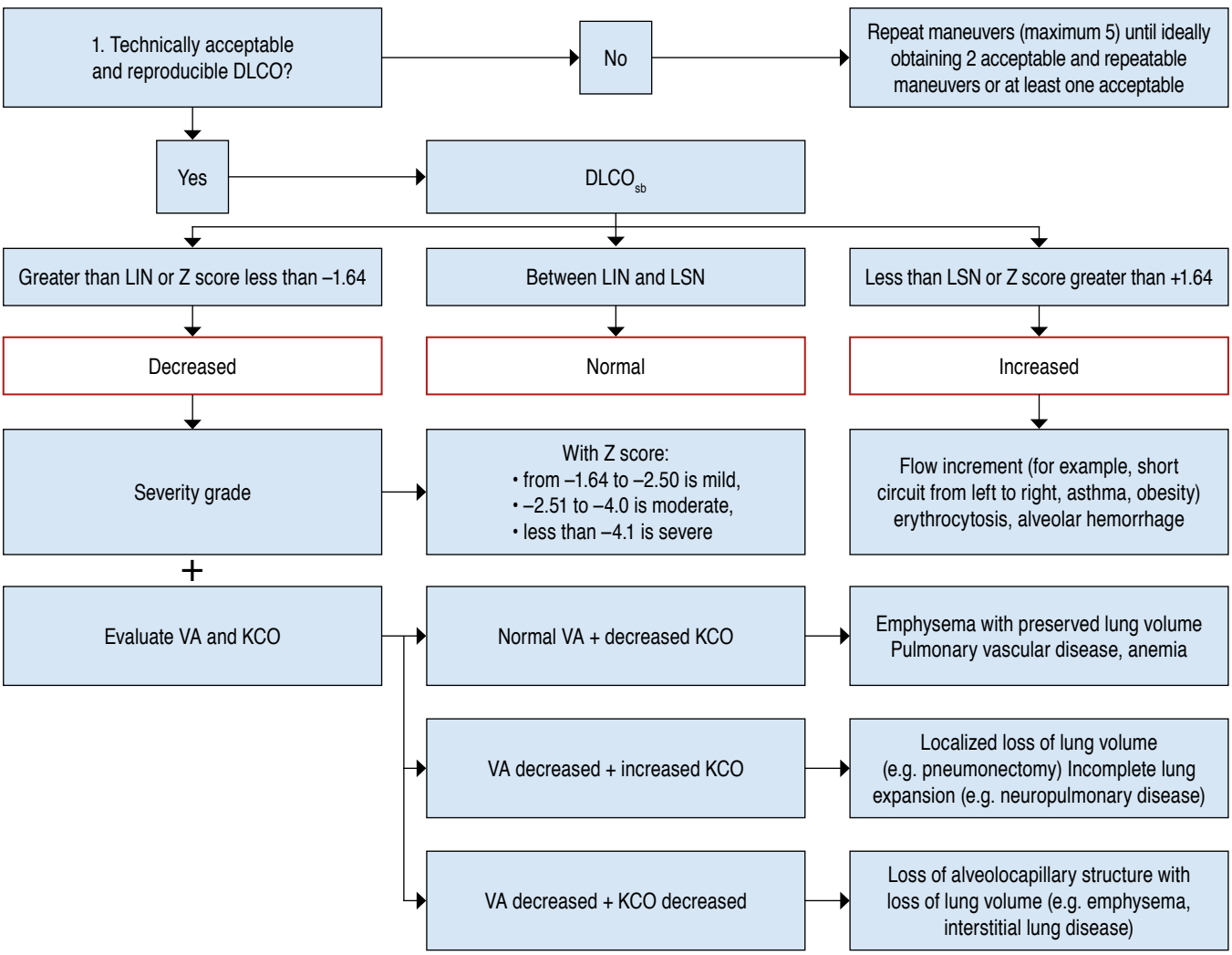

Figure 4: Algorithm for interpreting abnormal $DLCO_{sb}$ patterns. The interpretation of $DLCO_{sb}$ involves, first, determining whether it is low or high in relation to the 5th and 95th percentiles of the reference values. An elevated $DLCO_{sb}$ generally indicates increased pulmonary blood volume, erythrocytosis, or free hemoglobin in the airways. To understand a low $DLCO_{sb}$, the components are examined: alveolar volume (VA) and CO transfer coefficient (KCO). Normal VA suggests pulmonary vascular involvement, emphysema with preserved volume, or anemia. A low VA with low or normal KCO indicates loss of alveolocapillary structure, as in emphysema or interstitial lung disease (ILD). With low VA and high KCO, a state of low lung volume is suggested.
Note: the interpretation of this algorithm refers to presumptive clinical diagnoses, they should not be considered definitive diagnoses.
DLCO = pulmonary diffusion of carbon monoxide. $DLCO_{sb}$ = single-breath pulmonary diffusion of carbon monoxide.

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SUPPLEMENTARY MATERIALS

Pulmonary diffusion of carbon monoxide: updates in recommendations and procedure

PHYSIOLOGICAL BASES

The extraordinary affinity of carbon monoxide (CO) for hemoglobin allows this gas to be useful for evaluating gas exchange in the alveolocapillary membrane. This measurement reflects both the diffusion of CO and the rate of absorption by hemoglobin (Hb). There are several processes by which the transfer or uptake of CO from the outside to the Hb is interfered with, these processes are determined by Fick's diffusion law, which describes the flow of a gas through a semipermeable barrier, formula 1:

$$\text{Gas flow } (\dot{V}) = (A/T) \times (P1 - P2) \times K$$
(Formula 1)

The amount of gas transferred per unit of time ($\dot{V}$) is directly proportional to the diffusion area or surface (A), the gas diffusion constant (K) and the partial pressure gradient of the gasses across the membrane (P1 – P2); and inversely proportional to the thickness of the membrane (T). Applying this equation to pulmonary gas transfer, P1 and P2 are the gas concentrations in the alveolus and pulmonary capillary, respectively. Since it is not possible to specify the alveolar area (A), the membrane thickness (T) and the diffusion constant (K) of the alveolocapillary membrane for the entire lung, these variables are replaced by a single constant (DL), which represents the diffusion capacity for the lung as a whole[1] *(Figure 1S)*.

Measurement of CO transfer capacity is preferred over oxygen (O_2) for several reasons. Although both gases diffuse easily through the alveolocapillary membrane and combine with Hb, CO has a higher affinity than O_2; that is, about 210 times more related by Hb. The measurement of CO, being easily detectable, provides a more precise evaluation of pulmonary diffusion properties. When CO is measured, the P2 in the equation is assumed to be zero due to the high affinity of CO for Hb,[2,3] in contrast, the partial pressure of oxygen (PO_2) in the capillary increases as the erythrocyte It travels along the pulmonary capillary, so that, under normal conditions of rest and cardiac output, the oxygen pressure in the alveolus and capillary comes to a near equilibrium when the erythrocyte is only one-third the length of the capillary. At this point, no more O_2 can be transferred. However, if more blood flows through the capillary, more O_2 can be taken up, making O_2 uptake both «diffusion-limited» and «perfusion-limited».[4]

Although there are situations in which O_2 transfer may be diffusion limited, ventilation-perfusion imbalance and shunt are much more important causes of resting hypoxemia than changes in membrane thickness. alveolocapillary.[5,6] On the other hand, diffusion can more easily reach its maximum and limit oxygen transfer during exercise and at altitude.

The initial partial pressure of CO in the alveolus (PACO) can be analyzed assuming that CO is diluted to the same extent as the inhaled inert gas (such as helium), which is used to calculate the instantaneous dilution of inhaled CO by volume residual. DLCO is expressed as the volume of CO (in milliliters) transferred per minute per millimeter of mercury of alveolar partial pressure of CO (mL/min/mmHg).

As illustrated in *Figure 1S*, the CO diffusion pathway requires passing through the alveolocapillary membrane. Roughton and Forster[2] simplified this process into two steps: 1) diffusion of CO, described as the membrane component (Dm), and 2) binding of CO to Hb, described as the chemical reaction rate of COHb (θ) multiplied by pulmonary capillary blood volume (Vc), formula 2:

$$DLCO = Dm + \theta Vc$$
(Formula 2)

This basic equation for DLCO is a conductance, flow divided by pressure change ($\dot{V}/\Delta P$). The uptake of CO can be simplified to two properties of gas conductance. First, the CO conductance across the alveolocapillary membrane (Dm), which reflects the diffusion capacity of the membrane; and second, the binding capacity of CO to Hb (θVC). These two conductances are in series and are summarized in formula 3:

$$1/DLCO = (1/Dm) + (1/\theta Vc)$$
(Formula 3)

Starting from formula 3, the conductances through which the molecules of a gas in the alveolocapillary membrane have to pass are represented as the reciprocals of the resistances, so that they can be added in series.

The Dm depends on: 1) surface area and thickness of the alveolocapillary membrane, 2) the thickness and surface area of the erythrocyte membrane contained in the alveolar capillaries and 3) the thickness of the plasma barrier, including all its components. The product of θVC is also called reactive conductance. Theta (θ) is the product of the ratio of the chemical reaction between CO and Hb, expressed as a ratio of 1 mL of blood (with a standard hemoglobin concentration); and Vc is the volume of Hb in the alveolar capillary blood.

Understanding this formula is important for interpretation purposes. Alveolar recruitment due to lung hyperinflation affects Dm, while capillary recruitment, as occurs in changes in body position, for example, supine position or during the Müller maneuver (deep inspiration with closed glottis), increases θVc.

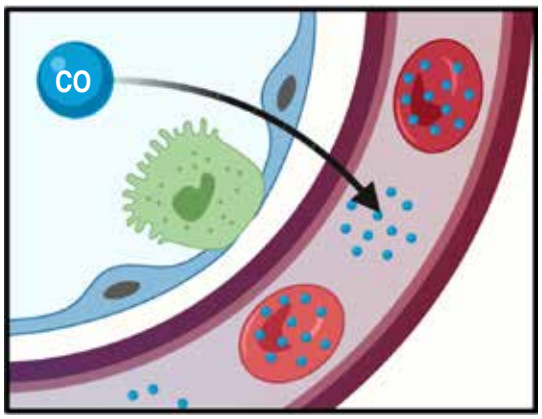

Figure 1S: Representation of carbon monoxide diffusion from the alveolus to hemoglobin; it must pass through the alveolocapillary membrane (consisting of the alveolar epithelium, basement membrane, a potential interstitial space and capillary endothelium), a thin plasma layer and the erythrocyte membrane, until it binds with hemoglobin.
«Created with BioRender.com»

DLCO EQUIPMENT AND CONSUMABLES

DLCO equipment should meet the international technical recommendations issued by the American Thoracic Society and the European Respiratory Society (ATS/ERS 2017),[7] with the following recommended minimum requirements for volume measurements and rapid gas analyzer, which can be found in the equipment user manual:

1. The equipment must meet the flow and volume measurement requirements established by ATS/ERS 2019 for spirometry.[8] Flow measurement accuracy should be in the range of –10 to +10 L/s, which should be within ± 2%.
2. Calibration with 3 L syringe, with specified maximum error of ± 0.5% (i.e., 2.985 to 3.015 L), the calibration volume should be within ± 2.5%, which is equivalent to an error tolerance ≤ 75 mL. This volume measurement accuracy must be maintained over the entire range of gas composition and concentration.
3. The response time from 0 to 90% should be ≤ 150 ms.
4. The CO and tracer gas analyzer should have a linear response from zero concentration to full concentration of the test gas. The error in the linear response of the analyzer should not exceed more than 0.5% on the full scale.
5. The gas analyzer output should be accurate to within ± 1% of full scale.
6. The gas analyzer should be stable throughout the test, maintaining a minimum zero offset (measured in ppm and percent) and minimum gain offset. The gas analyzer offset should be ≤ 10 ppm in 30 seconds for carbon monoxide and ≤ 0.5% of full scale in 30 seconds for tracer gas.
7. The presence of carbon dioxide (CO_2) and water vapor should not interfere with the gas analyzer. If so, the equipment should remove these gasses before the sample passes through the analyzer or the equipment makes adjustments to the gas measurement according to the concentration of CO_2 and H_2O vapor present.
8. Circuit resistance should be < 1.5 $cmH_2O/L/s$ at a flow rate of 6 L/s, if the test gas tank uses a flow demand regulator, the maximum inspiratory pressure across the circuit and valve should be < 10 cmH_2O.
9. The device timer should be accurate to 1% (100 ms over 10 seconds).
10. Monitor and report tracer gas and CO concentrations at end-expiration (alert operator if flushing is incomplete).
11. Ensure correct alignment of gas concentration signals and flow signal.
12. The equipment should measure the anatomical dead space using the Fowler method; failure to do so may result in an estimate of the anatomical dead space, but with the risk of inaccurate results.[9]
13. Display a graph of gas concentration versus exhaled volume to confirm the dead space washout point and report the amount of manual adjustment if performed.
14. Report DLCO adjusted for the change in PAO2 due to barometric pressure.
15. Ability to enter simulated digital test data and calculate DLCO, VA, TLC, VD.
16. Compensate for end-expiratory gas concentrations prior to test gas inhalation in the calculation of VA and DLCO.
17. The equipment dead space volume (DV) for both the inspired test gas and the alveolar sample should be known, its role in all data computation algorithms should be identified and documented. For adults, the VD should be < 200 mL, including the breathing circuit proximal to the gas analyzer sampling point, filter, and mouthpiece. Smaller dead space volumes are recommended for pediatric population and persons with a vital capacity (VC) < 2 L.
18. The system should be free of leaks.
19. For the digitized signal to accurately follow the gas concentration signal and provide adequate opportunity for signal processing for data alignment, the minimum signal sampling rate should be ≥ 100 Hz per channel with > 14 bits of resolution; however, a rate of 1,000 Hz is recommended.
20. The accuracy of the barometric pressure sensor should be within ± 2.5%.
21. Must have the capability to perform a quality check (with a 3 L syringe, under ATPS conditions and inhalation of ~2 L of test gas), the equipment must calculate total volume (VA) of 3 ± 0.3 L and DLCO of < 0.5 mL/min/mmHg or < 0.166 mmol/min/kPa.

Other equipment and consumables

1. Gas mixture tank for medical use; example: 0.27-0.33% CO, 9-11% helium, 18-25% oxygen and the rest nitrogen.
2. Computer and printer, according to device requirements.
3. Scales for weight and height measurement and tape measure for arm extension measurement, when required.
4. Environmental thermometers with an accuracy of 1 °C.
5. Disposable in-line filter nozzle with > 99% efficiency for filtration of viruses, bacteria and mycobacteria; dead space < 100 mL and resistance less than 1.5 cmH_2O at a flow rate of 6 L/s.
6. Infection control attachments:
7. Access to hand washing and disinfectant gel.
8. Surgical mask for general protection, and when N95 mask is required it must have a leakage of less than 10% and a filtration efficiency of > 95% at a flow of 50 L/min.

Adjustment for hemoglobin

Because Hb is the binding site for CO, $DLCO_{sb}$ can change significantly depending on the Hb concentration in the blood. Better results are obtained with Hb measured on the same day, particularly in suspected polyglobulia, anemia or long-term measurements. Using these relationships and expressing Hb in g/dL, the predicted DLCO in adolescents and adult men can be adjusted using the following equation:

$$DLCO\ [predicted\ for\ Hb] = DLCO\ [predicted] \times (1.7 \times Hb/(10.22 + Hb))$$

While that of children under 15 years of age and women is adjusted using the following equation:[7]

$$DLCO\ [predicted\ for\ Hb] = DLCO\ [predicted] \times (1.7Hb/(9.38 + Hb))$$

Adjustment for carboxyhemoglobin

CO binds to Hb, and DLCO depends on the amount of Hb, therefore, DLCO is reduced if COHb increases. Adjustment for COHb is not routinely required, but is recommended, if COHb levels are suspected to be high, usually in smokers. Smokers have COHb of 5-10%, while nonsmokers < 3%. If COHb is < 2% no adjustment is required. Adjustment of DLCO for COHb is performed following the following equation.[7,10,11]

$$DLCO\ [predicted\ for\ COHb] = DLCO\ [predicted] \times (102\text{-}COHb\%)$$

It should be remembered that CO inhalation in the single-breath maneuver causes COHb to increase by 0.6 to 0.7% for each maneuver.[7,12]

Alveolar Oxygen Pressure Adjustment (P_AO_2)

Oxygen and CO compete for the same binding sites with Hb, so P_AO_2 affects DLCO. If P_AO_2 is high, DLCO decreases and vice versa. The first adjustment to this level is a concentration of 21% oxygen in the test gas. The DLCO value will change by approximately 0.35% for every 1 mmHg change in P_AO_2 or approximately 2.6% for every 1 kPa change in P_AO_2.[8]

Altitude adjustment

Altitude also affects P_AO_2. The higher the altitude, the higher the DLCO because P_AO2 decreases. Adjustment for altitude could be made in two ways:

1. DLCO [adjusted PB] = DLCO (0.505 + 0.00065 PB)
2. Altitude-adjusted DLCO = measured DLCO × [1 + 0.0031 (PiO_2-150)].

Where estimated IOP_2 = 0.21 (barometric pressure –47), or predicted values can be adjusted.

$$The\ P_AO_2 = 0.21\ (PB\text{-}47)$$

Example: BP in Mexico City averages 585 mmHg, therefore:

$$IOP_2 = 113\ mmHg$$

The adjustment in Mexico City would correspond to:

$$DLCO\ CDMX = DLCO\ (0.885)$$

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Clinical case

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Severe tracheo-esophageal fistula induced by stent: repair by membranous tracheoplasty with double esophagus flap

Fístula traqueoesofágica severa inducida por *stent*: reparación por traqueoplastía membranosa con doble *flap* de esófago

Rogelio Sancho-Hernández,* Nadia Nohemí Mata-Favela,*
Pedro Azuara-Galdeano,* José Goben-Arredondo*

*Instituto Nacional de Pediatría. Mexico City, Mexico.

ABSTRACT. Introduction: acquired tracheoesophageal fistula (ATEF) in children is caused by aspiration of foreign bodies and caustic ingestion, iatrogenic causes induced by an intraesophageal stent are unusual but are always severe defects with high mortality and morbidity, due to their severity resection of large tracheal extensions in children are not surgically feasible. **Case description:** 11-year-old male adolescent with placement of an intraesophageal stent due to caustic stenosis with dysphagia and bronchopulmonary suppuration. Esophagography and tomography confirmed large-scale ATEF and bronchoscopy showed destruction of the membranous trachea with impossibility of extracting it, systemic and local conditions improved and by right thoracotomy, the stent is removed by esophagotomy and the esophageal wall is used to form a membranous tracheoplasty with a double esophageal patch without tracheal resection, the integrity of the tracheoplasty is corroborated by bronchoscopy and the aerodigestive tract is restored with a subsequent method esophageal replacement. **Conclusion:** the reconstruction technique by membranous tracheoplasty with a double esophageal patch is a safe and effective surgical method in the multidisciplinary management of severe ATEF.

Keywords: acquired tracheoesophageal fistula, esophageal flap, stent, tracheoplasty.

RESUMEN. Introducción: la fístula traqueoesofágica adquirida en niños es originada por aspiración de cuerpos extraños e ingestión cáustica, las causas iatrogénicas inducidas por un *stent* intraesofágico son inusuales, pero son siempre defectos severos con alta mortalidad y morbilidad. Debido a su severidad, la resección de grandes extensiones traqueales en niños no es quirúrgicamente factible, no hay reportes nacionales de esta técnica. **Descripción del caso:** adolescente masculino de 11 años con colocación de *stent* intraesofágico por estenosis cáustica con disfagia y supuración broncopulmonar. En esofagografía y tomografía se corrobora fístula traqueoesofágica adquirida de gran extensión; y en broncoscopia se muestra destrucción de tráquea membranosa con imposibilidad para su extracción. Se mejoran condiciones sistémicas y locales y por toracotomía derecha se realiza la extracción del *stent* por esofagotomía y se utiliza la pared esofágica para conformar una traqueoplastía membranosa con doble parche esofágico sin resección traqueal. Fue corroborada la integridad de la traqueoplastía por broncoscopia y la restitución de la vía aerodigestiva con posterior método de sustitución esofágica. **Conclusión:** la técnica de reconstrucción por traqueoplastía membranosa con doble parche esofágico resulta un método quirúrgico seguro y efectivo en el manejo multidisciplinario de la fístula traqueoesofágica adquirida severa.

Palabras clave: fístula traqueoesofágica adquirida, *flap* esofágico, *stent*, traqueoplastía.

Correspondence:
Rogelio Sancho-Hernández, MD
Pediatric Endoscopist and Thoracic Surgeon, Instituto Nacional de Pediatría, Mexico City, Mexico.
E-mail: saherog@yahoo.com.mx

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INTRODUCTION

Acquired tracheoesophageal fistula (TAEF) is an abnormal communication between the tracheal airway and the esophageal tract with destruction of the adjacent walls, originating from trauma, malignancy, endotracheal tube and mechanical ventilation-related injury, foreign body aspiration and caustic ingestion.[1] Iatrogenic causes induced by an intraesophageal stent are unusual, but they are always severe defects of high mortality and morbidity where because of their severity resection of large tracheal extensions in children is not surgically feasible.

The present report describes the usefulness of a novel surgical procedure with reconstruction of severe stent-induced TAEF by membranous tracheoplasty with double esophageal patch without tracheal resection. There are no national reports describing multidisciplinary treatment of TAEF in children.

CASE PRESENTATION

An 11-year-old male with a history of caustic ingestion underwent seven unsuccessful esophageal dilatations and endoscopic percutaneous gastrostomy; however, he persisted with stricture, so a 13 and 2 cm metal stent esophageal prosthesis was placed. He was referred to the National Institute of Pediatrics (INP) nine months later due to the difficulty in endoscopic extraction, he presented dysphagia, sialorrhea and productive cough, febrile for six months of evolution, 18 months after the ingestion of caustics.

Radiology shows bronchial pattern and presence of intrathoracic radio-opaque esophageal prosthesis, esophagogram shows termination in blind end of the proximal esophagus, gastrogram shows distal esophagus with total stenosis and the distance between both ends of approximately 17 cm; digestive endoscopy shows total esophageal stenosis of the upper third, and the lower esophagus by gastrostomy view with critical and fibrous stenosis > 90% with total esophageal exclusion. The CT scan showed irreversible atelectasis of the left lower lobe due to bronchiectasis; bronchoscopy showed abundant bronchopulmonary suppuration originating in the left bronchus and a foreign body (metallic stent) was observed in the posterior wall of the proximal and middle third of the trachea with radical destruction of the membranous trachea adjacent to the stent, so a diagnosis of TAEF was made. Clinical and nutritional conditions improved with mixed parenteral nutrition and by gastrostomy bronchoscopic drainage of purulent secretions was performed weekly on three occasions and antibiotics were administered *(Figure 1A-1D)*.

Surgical technique

With initial endotracheal intubation guided by bronchoscopy 1 cm below the subglottis, right lateral posterior thoracotomy is performed and esophagus with intense inflammatory reaction is identified, longitudinal esophagotomy is performed, intraesophageal stent is observed, which is removed by fragments with difficulty due to the presence of firm adhesions to the posterior part of the trachea. Once the stent is completely removed, the endotracheal tube is advanced up to 1 cm above the carina, the patient is ventilated with an insufflated balloon and a tracheoesophageal fistula is observed in the membranous portion of the trachea, 10 cm long, the insufflated balloon of the endotracheal cannula allows occluding the air leak and allows distal mechanical ventilation. The edges of the residual esophagus and the excluded membranous trachea are revitalized, the anterior cartilaginous trachea is preserved, esophageal mucosa is removed and the membranous tracheoplasty is performed with two esophageal flaps, A short flap with mucosectomy as the first plane of membranous tracheoplasty anastomosed to the cartilaginous edge of the trachea and a subsequent long esophageal flap covering in a second plane the totality of the neotrachea with simple stitches with 3-0 vicryl. Hemostatic tissue adhesive is placed on the surface of the tracheoplasty and distal esophageal closure is performed in blind end and proximal esophageal derivation as cervical esophagostomy; adequate air tightness of the tracheoplasty is corroborated without air leak and with adequate ventilation by endotracheal cannula in transanastomotic position at 1 cm from the carina *(Figure 2A-2F)*.

In the Critical Care Unit he was kept sedated and with endotracheal intubation for 72 hours and six days after surgery an early revision bronchoscopy was performed where a membranous neotrachea was observed with no data of anastomotic leakage and without complications; a new control bronchoscopy was performed 20 days after surgery where there was again permeability of the neotrachea. Due to persistence of bronchopulmonary suppuration, left lower lobectomy was performed two months after surgery and six months later esophageal substitution method by retrosternal reverse gastric tube, clinical, radiological and endoscopic evolution was favorable at five years of follow-up.

DISCUSSION

TAEF is a severe complication whose etiology in children is divided into malignant acquired causes, which are rare, and benign acquired causes where caustic ingestion, foreign bodies and trauma are the main ones; iatrogenic causes are unusual as in the case presented, which originated from

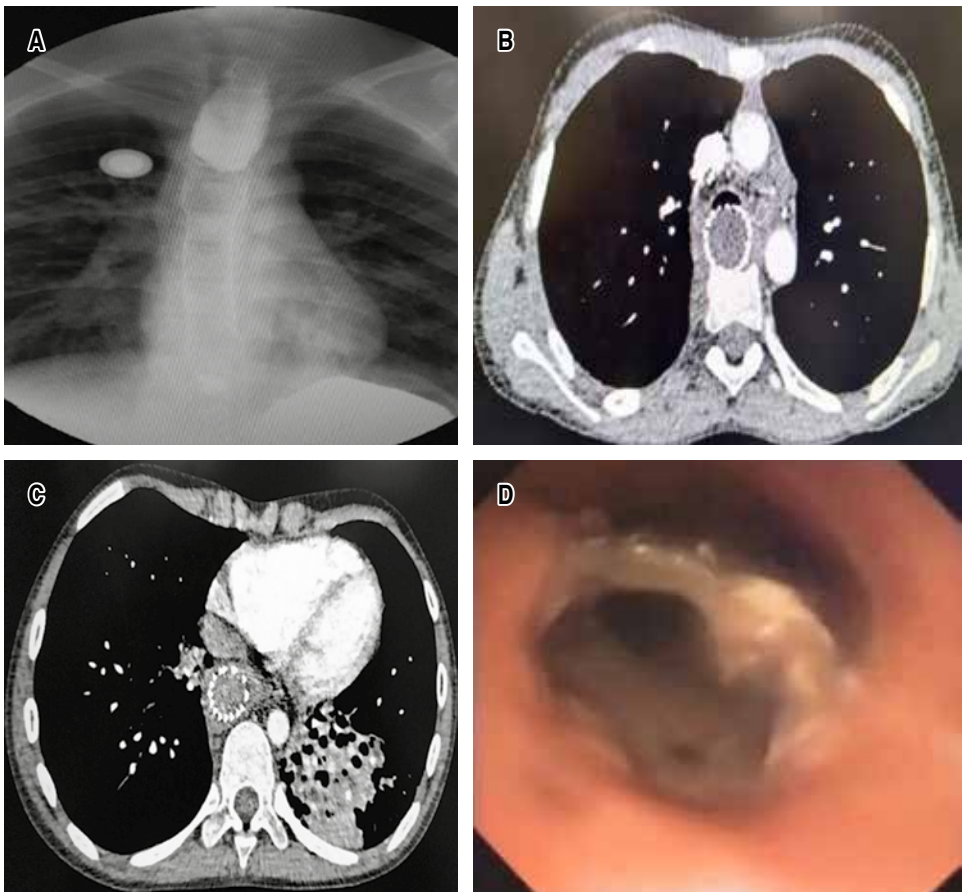

Figure 1:

A) Thoracic radiology with presence of intrathoracic stent and esophagogram with blind proximal esophageal end. **B)** Upper level CT scan with acquired tracheoesophageal fistula due to the presence of intraesophageal stent and total exclusion of the membranous trachea due to migration of the stent towards the cartilaginous trachea. **C)** CT scan at lower level with total exclusion of the esophagus and presence of bronchiectasis in the left lower lobe. **D)** Bronchoscopy with exposure of the intraesophageal metallic stent inside the trachea, radical destruction of the membranous trachea and bronchopulmonary suppuration.

the endoscopic insertion of an intraesophageal stent that is required for the management of refractory esophageal strictures. The prolonged stay of this stent (more than 90 days) caused high pressures on the common wall in the membranous tracheal portion with necrosis that predispose to its development. The incidence of TAEF related to esophageal stents is 4% with a latency of five months after placement.[2] The clinical manifestations depend on the size and location of the TAEF, as well as the patient's comorbidities; chronic aspiration pneumopathy, recurrent pneumonias, fever with bronchopulmonary suppuration and chronic malnutrition being the most frequent clinical scenarios, which requires a multidisciplinary evaluation.

Thus, in the preoperative evaluation, esophagogram diagnosis shows TAEF in 70% and in those who cannot swallow or are ventilated, CT scan shows the extension of TAEF or, as in our case, the involvement of adjacent organs and the presence of bronchiectasis; endoscopic evaluation is crucial because it visualizes the location, measurement and characterization of TAEF, facilitates the drainage of purulent material and aspirated gastric contents. Placement of intraesophageal pneumatic balloons and advancing an endotracheal cannula with balloon distal to the fistula to inhibit aspiration of gastric and purulent contents, as well as taking biopsies to orient the etiology, have been reported to be elementary in clinical stability to eliminate the risk of pulmonary sepsis. Suppressing aspiration and associated acute lung damage and allowing an enteral nutrition pathway by means of percutaneous endoscopic gastrostomy and during the transoperative period allowed positioning the endotracheal tube proximal to the fistula to initiate ventilation and subsequently the advancement of the same endotracheal cannula with distal balloon to the TAEF once the stent had been removed and the airway secured, as well as support the reconstruction of the neotrachea and its integrity following membranous tracheoplasty in the immediate postoperative period.[2,3]

The techniques of esophageal and stricture-involved tracheal ring resection with subsequent primary anastomosis are described for defects greater than 1 cm and up to less than five involved tracheal rings of pediatric tracheal length; in these extensive and complex TAEFs, such combined resections are not surgically feasible;[2,4,5] the use of autologous tissue (cartilage, flap or vascularized muscle and/or pericardial flap) or use of other biological covering prosthetic materials have the disadvantage of insufficient

blood supply, limited availability, allograft rejection, need to separate and devascularize the surrounding tissue and consequently high recurrence of TAEF, in addition, they may not withstand the high pressures of the compromised airway.[6] Endoscopic intervention has been shown to be of pediatric utility for small TAEF < 5 mm with reepithelialization intervention techniques in combination with the application of chemical sealants and/or tissue adhesives that are beyond the scope of this review.[7]

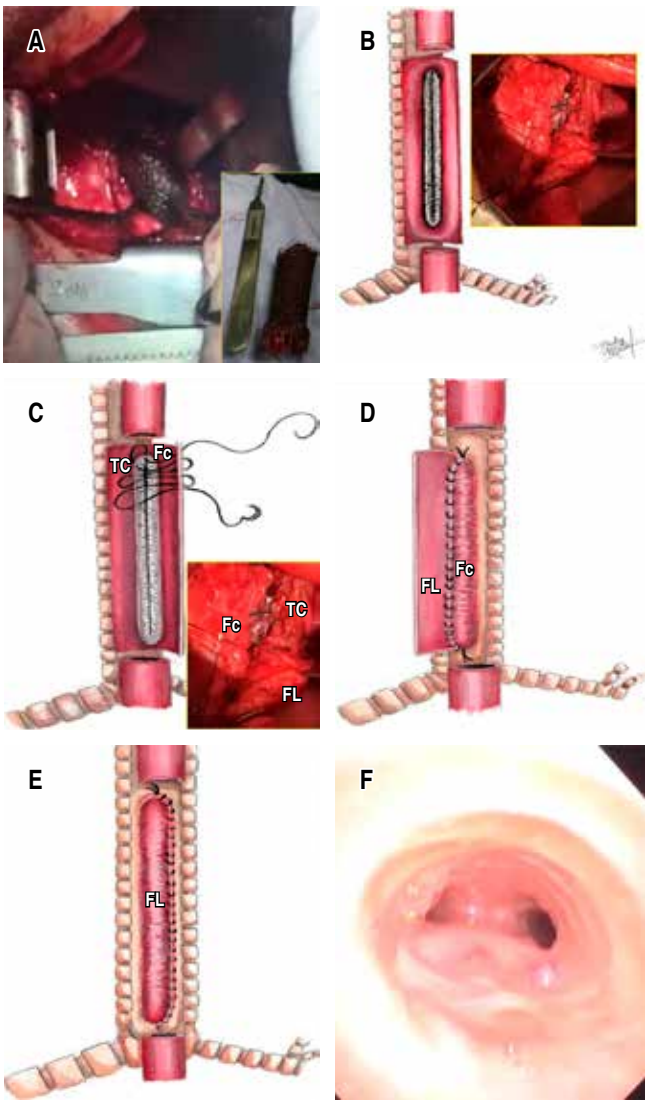

Figure 2: A) Stent exposure posterior to esophagus, longitudinal myotomy. **B)** Severe acquired tracheoesophageal fistula following intraesophageal stent removal, graphic extension of the defect from the thoracic trachea to the carina. **C)** Close-up plasty anastomosing the esophageal short flap (Fc) with mucosectomy to the cartilaginous trachea (CT). **D)** Close-up of the completed membranous tracheoplasty. **E)** Long flap (LF) covering the second plane of the membranous tracheoplasty. **F)** Membranous tracheoplasty under final endoscopic view.

The use of esophageal and airway metal self-expandable stents, single for distal TAEF or in combination for medial and proximal TAEF placed endoscopically is described in the adult population as temporary bridging measures until a definitive surgical option is reached.[2,8] In our patient the stent causing the TAEF could only be removed transoperatively to secure the aeroesophageal pathway, which necessitated definitive surgical correction. Jouraud et al. described the use of the esophageal wall as a biological patch to reconstruct large, inseparable and unsuturable tracheal defects.[9] The technique of membranous tracheoplasty reconstruction with double esophageal patch results in a safe and effective surgical method by exhibiting the following qualities: a) it does not require separation of the TAEF avoiding injury to the recurrent laryngeal nerve; b) the esophageal portion of the defect could be used for definitive repair; c) the tracheal portion of the defect could be repaired with the esophageal segment without mucosa to provide stability and rapid recovery of the neotrachea; d) the double patch technique has excellent blood supply and provides support and stability against high airway pressures; e) post-reconstruction recurrence is very low and would allow subsequent success with endoscopic methods; and f) a reconstruction method is needed in the aerodigestive continuity, as in our case, an esophageal substitution method and post-bronchiectasis lung resection.[6,10]

CONCLUSIONS

Intraesophageal stent-induced TAEF is a severe defect with high mortality and morbidity, multidisciplinary management and bronchoscopic evaluation of the pediatric aerodigestive model are crucial in clinical stability to eliminate pulmonary sepsis, suppress aspiration and associated acute lung damage, and allow a nutritional pathway. The use of adjacent esophageal wall with membranous tracheoplasty with double esophageal patch is a safe and effective method in aerodigestive reconstruction and is an opportune option where due to its severity resection of large tracheal extensions in children is not surgically feasible and endoscopic treatment is not a conservative option.

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Delayed diagnosis of tuberculosis in a patient with coccidioidomycosis

Retraso en el diagnóstico de tuberculosis en un paciente con coccidioidomicosis

Eva Alejandra Rojas-Rojas,* Wendy Rosario Cinencio-Chávez,* Rafael Laniado-Laborín*,‡

*Autonomous University of Baja California. Tijuana General Hospital, Mexico; ‡Sistema Nacional de Investigadores, CONAHCYT.

ABSTRACT. We present the case of a 24-year-old man from Sonora, residing in Tijuana, Mexico, who referred symptoms of cough and hemoptysis for a year. A chest CT scan showed fibrocavitary lesions, initially suspected to be tuberculosis. Rapid molecular tests did not detect *Mycobacterium tuberculosis*, while coccidioidomycosis serology was positive and cultures identified *Coccidioides spp.*; treatment with itraconazole was initiated, but subsequently, the mycobacterial culture was reported as positive for *M. tuberculosis*, confirming coinfection and antituberculosis treatment was added. The Xpert MTB/RIF test is recommended by the World Health Organization as an initial diagnostic method for tuberculosis due to its high sensitivity and specificity. However, its sensitivity can be low in cases of very low bacillary load, justifying the need for complementary mycobacterial cultures for a thorough diagnosis. In this case, the culture allowed for the detection of tuberculosis despite negative sputum smears and rapid molecular tests, highlighting the importance of phenotypic methods in the diagnosis of tuberculosis. The coinfection of tuberculosis and coccidioidomycosis is a significant diagnostic challenge. The combination of molecular tests and cultures remains essential for an accurate diagnosis and effective treatment, especially in endemic areas for both diseases.

Keywords: tuberculosis, coccidioidomycosis, coinfection, Xpert MTB/RIF, mycobacterial culture.

RESUMEN. Presentamos el caso de un hombre sonorense de 24 años, residente en Tijuana, México, que presentó cuadro de tos y hemoptisis de un año de evolución. Una tomografía torácica mostró lesiones fibrocavitarias, inicialmente sugestivas de tuberculosis. Las pruebas moleculares rápidas no detectaron *Mycobacterium tuberculosis*, mientras que la serología para coccidioidomicosis fue positiva y los cultivos identificaron *Coccidioides spp.*; se inició tratamiento con itraconazol, pero posteriormente el cultivo micobacteriano se reportó positivo para *M. tuberculosis*, confirmándose la coinfección, por lo que se agregó tratamiento antituberculosis. El Xpert MTB/RIF está recomendado por la Organización Mundial de la Salud como método de diagnóstico inicial de tuberculosis debido a su alta sensibilidad y especificidad. Sin embargo, su sensibilidad puede ser baja en casos de baja carga bacilar, justificando la necesidad de cultivos micobacterianos complementarios para un diagnóstico exhaustivo. En este caso, el cultivo permitió la detección de tuberculosis a pesar de baciloscopias y prueba molecular rápida negativas, destacando la importancia de los métodos fenotípicos en el diagnóstico de tuberculosis. La coinfección de tuberculosis y coccidioidomicosis representa un importante desafío diagnóstico. La combinación de pruebas moleculares y cultivos es esencial para un diagnóstico preciso y un tratamiento eficaz, especialmente en zonas endémicas de ambos padecimientos.

Palabras clave: tuberculosis, coccidioidomicosis, coinfección, Xpert MTB/RIF, cultivo de micobacterias.

INTRODUCTION

Coccidioidomycosis is an endemic mycosis of the southwestern United States, northern Mexico, and the rest of Latin America.[1] Tuberculosis and coccidioidomycosis share epidemiological, clinical, radiographic, and even histopathological characteristics, making diagnosis difficult when they present simultaneously.[2] Additionally, they share some common risk factors, including areas of endemicity and various conditions that cause immunosuppression, such as diabetes and HIV, among others.

Clinical presentation can be similar, with prolonged constitutional symptoms, various respiratory syndromes, and chronic meningitis, years or decades after the initial

Correspondence:
Eva Alejandra Rojas-Rojas, MD
Faculty of Medicine and Psychology, Autonomous University of Baja California, Mexico.
E-mail: rojas.eva@uabc.edu.mx

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exposure. Radiographic findings in the chest of patients with chronic pulmonary coccidioidomycosis are virtually identical to those of pulmonary tuberculosis, with the presence of cavitations and fibrous tracts.[1]

We present a case of pulmonary coinfection in which the rapid molecular test was reported negative for *Mycobacterium tuberculosis* complex, while coccidioidomycosis was diagnosed through smear, culture, and positive serology. Since all samples from patients suspected of tuberculosis should routinely be cultured, it was also possible to detect, although late, the presence of pulmonary tuberculosis.

PRESENTATION OF THE CASE

A 24-year-old male, originally from Sonora and residing in the city of Tijuana sought medical attention for his chronic respiratory symptoms. His clinical history was negative for substance abuse, and he did not report any significant illnesses in the past. Symptoms began a year earlier with cough and hemoptysis. He received private medical care, without a definitive diagnosis, and no information is available on the prescribed treatment. A chest CT showed fibrocavitary lesions in both upper pulmonary lobes, with an intracavitary mass suggestive of mycetoma *(Figure 1)*. Given the suspicion of tuberculosis, a series of sputum smears were requested and later reported as negative, as well as an Xpert MTB/RIF (*Mycobacterium tuberculosis* complex not detected); as routinely done, a culture for mycobacteria was also processed. Sputum smears reported abundant spherules of *Coccidioides spp.*; later, a positive culture for *Coccidioides spp.* was reported, in addition to a positive coccidioidomycosis serology with an IgG titer of 1:64. No evidence of extrapulmonary involvement was detected during the clinical evaluation. Treatment with itraconazole 400 mg daily was started; after two months of treatment, the patient was asymptomatic and had gained 2.7 kg.

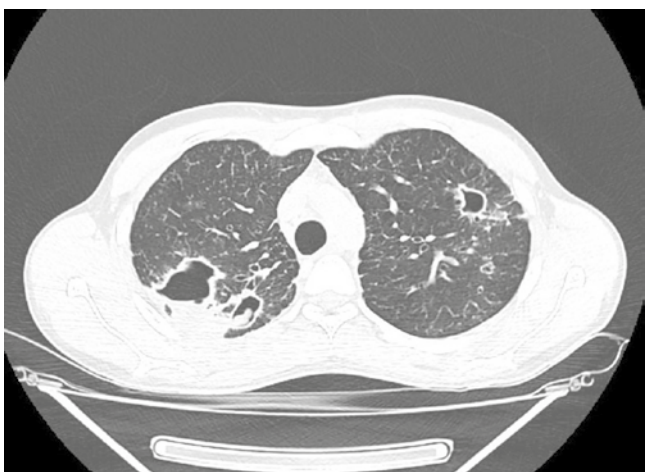

Figure 1: Axial tomographic section showing fibrocavitary lesions in both upper lung lobes.

Two months later, the culture was reported positive for mycobacteria with a positive rapid chromatographic test for the MTB complex. After dilution, the culture material was examined with the Xpert MTB/RIF Ultra test, confirming the presence of the MTB complex with medium load and without detection of mutations in the *rpoB* gene associated with rifampicin resistance (susceptible to rifampicin). Treatment with the primary regimen (rifampicin, isoniazid, ethambutol, and pyrazinamide) was initiated and the antifungal regimen was continued.

The patient has currently been discharged as cured from antituberculosis treatment and will continue with antifungal treatment for at least one year according to the initial serology of 1:64, which is considered a marker of disseminated disease.

DISCUSSION

The Xpert MTB/RIF polymerase chain reaction (PCR) test is an automated real-time molecular test for the diagnosis of tuberculosis.[3] The World Health Organization (WHO) recommends that this rapid molecular test be used as an initial diagnostic test, replacing sputum smear microscopy due to its higher sensitivity and specificity and that it also offers the advantage of simultaneously providing rifampicin susceptibility.[4] However, since there are no genotypic commercial tests for all the drugs used in tuberculosis, phenotypic testing remains necessary at this time as a complement to molecular tests. Additionally, during treatment follow-up, molecular tests are not useful because they require the extraction of mycobacterial DNA with the consequent death of the bacilli; cultures remain the only method available to determine mycobacterial viability.[5]

While the diagnostic performance of the Xpert MTB/RIF Ultra is far superior to microscopy, false negatives do occur since the sensitivity of the assay varies between 83 and 96%, depending on the bacillary load, and sensitivity under 80% has been reported in patients with negative smears.[5] This issue has been partially addressed with the new Ultra cartridges, which have greater sensitivity than the older G4 cartridges. The Xpert MTB/RIF Ultra incorporates two amplification targets for the identification of *M. tuberculosis* (IS6110 and IS1081) and requires only about 15 colony-forming units (CFUs) for detection versus 116 CFUs for the G4 cartridge. This is partly due to a larger sample volume processed by the Ultra method, which has a reaction chamber with a capacity of 50 vs 25 µL for the G4 cartridge.[5,6]

Our patient had active tuberculosis and coccidioidomycosis simultaneously at the time of his first consultation at the Tuberculosis Clinic, but his initial sputum smears and Xpert MTB/RIF test were negative. As all samples processed for microscopy and molecular testing are routinely cultured, after eight weeks of observation, the sputum culture was reported as positive for *M. tuberculosis*.

CONCLUSIONS

This case demonstrates the need to include mycobacterial cultures as a backup for molecular tests, as their sensitivity is affected when the bacillary load is very low, and, as mentioned, there are no commercial molecular drug susceptibility tests for all antimycobacterial drugs.

Conflict of interests: the authors do not have any conflict of interests to declare.

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Utility of intraoperative electrophysiology in intrathoracic resection of schwannoma

Utilidad de la electrofisiología intraoperatoria en resección intratorácica de schwannoma

Rogelio Sancho-Hernández,* Alfonso Marhx-Bracho,*
Lizbeth Solorio-Rodríguez,* Nadia Nohemí Mata-Favela*

*Instituto Nacional de Pediatría, Mexico City, Mexico.

ABSTRACT. Introduction: primary tumors of the brachial plexus are rare and correspond to schwannomas and neurofibromas. These are treated as cervical-mediastinal masses with apical intrathoracic extension. They may debut with symptoms of neural compression. **Case description:** 14-year-old woman with neurofibromatosis type I, pain in the left upper limb, paresis and paresthesia, atrophy and decreased muscle strength with generalized dermatosis and increased volume in the left side of the neck; in the MRI with extradural lesion originating at the level of left C7-T1 and displacement of the trachea and esophagus and invasion towards the mediastinal region; electromyography with decreased sensory and motor amplitude of the left ulnar nerve. Tumor excision was performed through anterior thoracic cervical approach with neurophysiological monitoring, finding: encapsulated mass resected by central enucleation dependent on nerve roots C5, C6 and C7, extrapleural. Pathology report with cervicothoracic schwannoma; gradual recovery of mobility at seven years of follow-up with rehabilitation support. **Conclusion:** approaching masses located in the brachial plexus with mediastinal extension and to the cervicothoracic junction is a surgical challenge. Intraoperative neurophysiological monitoring increases safety and prognostic benefit.

Keywords: schwannoma, brachial plexopathy, case report, neurophysiological monitoring.

RESUMEN. Introducción: los tumores primarios del plexo braquial son infrecuentes y corresponden con schwannomas y neurofibromas, éstos son abordados como masas cervicomediastinales con extensión intratorácica apical, pueden debutar con síntomas de compresión neural. **Descripción del caso:** femenino de 14 años con neurofibromatosis tipo I, dolor en miembro superior izquierdo, paresia y parestesia, atrofia y disminución de la fuerza muscular con dermatosis generalizada y aumento de volumen en hemicuello izquierdo. En la resonancia se muestra lesión extradural que se origina a nivel de C7-T1 izquierdo y desplazamiento de tráquea y esófago e invasión hacia región mediastinal; electromiografía con disminución de amplitud sensorial y motora del nervio cubital izquierdo. Se realiza exéresis tumoral a través de abordaje cervicotorácico anterior con monitoreo neurofisiológico, encontrando: masa encapsulada resecada por enucleación central dependiente de raíces nerviosas C5, C6 y C7, extrapleural. El reporte de patología es diagnóstico de schwannoma cervicotorácico; recuperación gradual de movilidad a siete años de seguimiento con apoyo de rehabilitación. **Conclusión:** el abordaje de las masas localizadas en el plexo braquial con extensión mediastinal y a la unión cervicotorácica representa un desafío quirúrgico. La monitorización neurofisiológica transoperatoria aumenta la seguridad y el beneficio pronóstico.

Palabras clave: schwannoma, plexopatía braquial, reporte de caso, monitorización neurofisiológica.

INTRODUCTION

Primary tumors of the brachial plexus are infrequent entities and correspond to schwannomas and neurofibromas, these are approached as cervicomediastinal masses with apical intrathoracic extension, and may debut with symptoms of vascular and neural compression.[1]

The clinical presentation of an adolescent girl with brachial plexus schwannoma is described with the technical-surgical details of its resection assisted by

Correspondence:
Dr. Rogelio Sancho-Hernández
Pediatric Endoscopist and Thoracic Surgeon, Instituto Nacional de Pediatría, Mexico City, Mexico.
E-mail: saherog@yahoo.com.mx

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neurophysiological evaluation. There are no national reports of this novel intervention in the pediatric population.

CASE PRESENTATION

14-year-old female diagnosed with neurofibromatosis type I, since the age of 10 years with ascending pain throughout the left upper limb to the neck, with paresis and paresthesia, atrophy and decreased muscle strength, weight loss of 7 kg; with generalized «coffee with milk» dermatosis, enlargement with left hemicollar base, painful, asymmetry of the left thoracic limb at the expense of atrophy of interosseous, tenar and hypothenar muscles, functional limitation, generalized hyperreflexia, preserved proprioceptive and exteroceptive sensitivity.

Magnetic resonance imaging shows extradural lesion originating at the level of the left C7-T1 conjunctival foramen, widening and rostral extension towards the neck and displacement of the trachea and esophagus and in contact with the carotid sheath and invasion towards the ipsilateral mediastinal region. Electromyography was performed, showing a decrease in the amplitude of sensory and motor latencies of the left ulnar nerve *(Figure 1A-D)*.

Tumor excision was performed through anterior cervicothoracic approach with neurophysiological monitoring, finding: spherical mass of 9 × 7 × 5 cm and encapsulated, resected by central and intracapsular enucleation dependent on C5, C6 and C7 nerve roots, extrapleural corroborated by a left thoracoscopic approach, without drains.

The pathology report is a diagnosis of cervicothoracic schwannoma. At two weeks' post-surgery, the patient had recovered mobility but continued with significant atrophy; however, he presented gradual recovery of muscle tone and strength and movement in the affected limb at seven years of follow-up with rehabilitation support *(Figure 2A-H)*.

DISCUSSION

Schwannomas are usually benign extrathoracic and supraclavicular masses, intrathoracic and mediastinal growth are rare and, even more so, in the pediatric population, with few reports in the literature; but they are the most common intrathoracic neurogenic tumors.[2,3] In

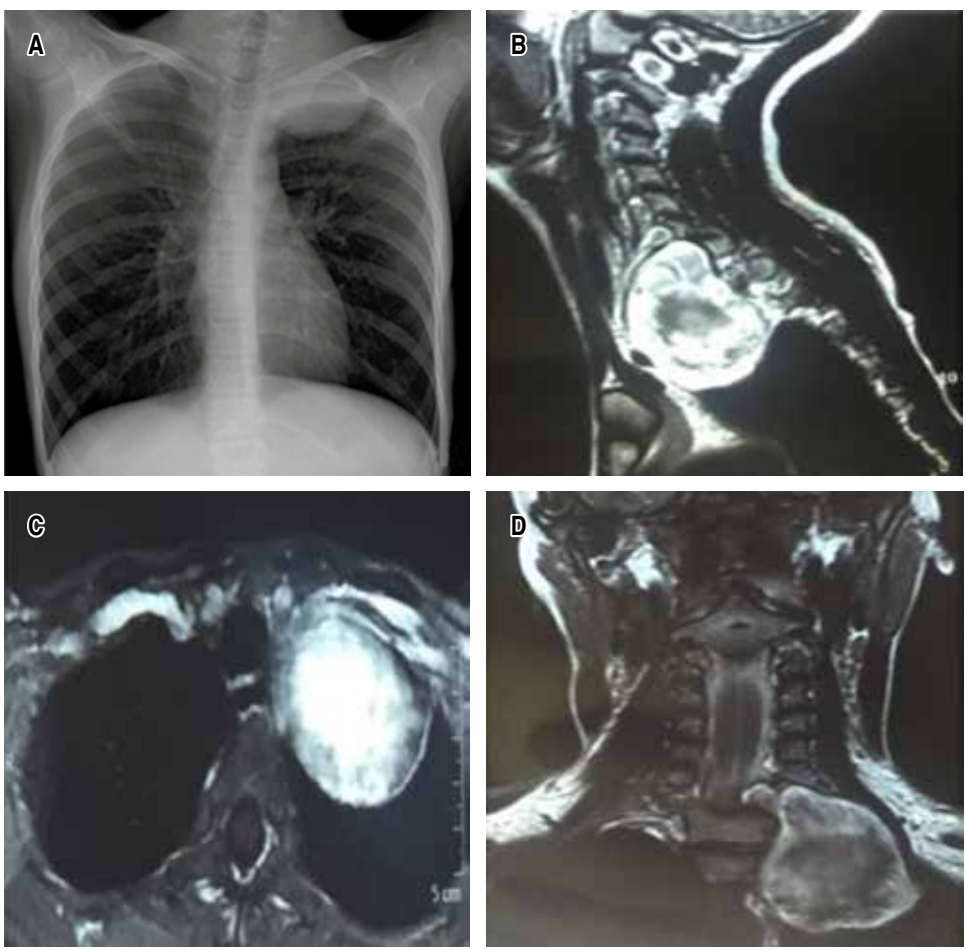

Figure 1:

A) Radiology with left cervicothoracic sign and apical mass effect. **B)** Magnetic resonance imaging with mass showing T2 hyperintensity with mediastinal and intrathoracic extension. **C)** With displacement in mediastinal structures, but without invasion by contiguity. **D)** T1-weighted MRI with posterior extension mass originating in the anterior cervicothoracic region of the brachial plexus.

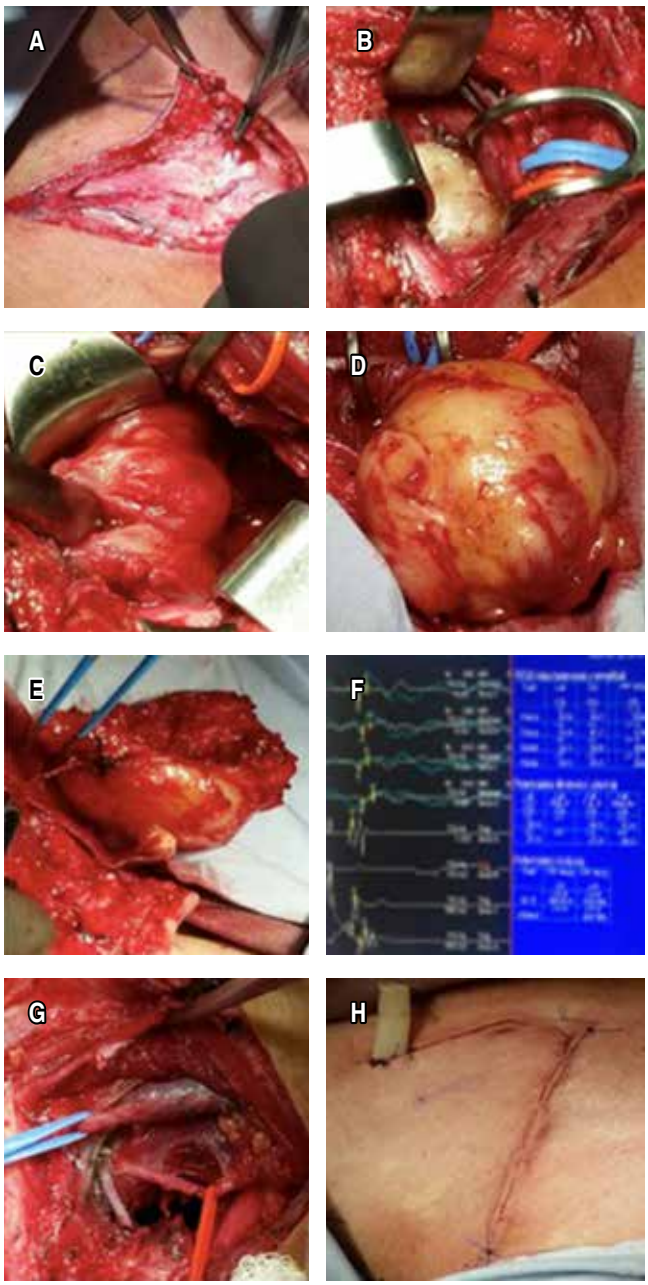

Figure 2: A) Anterior cervicothoracic and supraclavicular L-shaped approach. **B)** Exposure of schwannoma with its capsule and reference of the nerve roots of the brachial plexus for electrostimulation. **C)** Longitudinal incision over the capsule of the mass parallel to the nerve fibers to initiate enucleation. **D)** Total exposure of the proximal and distal poles of the schwannoma. **E)** Electrostimulation by NAP to determine potential lesion by continuity of the nerve fibers of the brachial plexus. **F)** Transoperative neurophysiological monitoring recording by NAP and SEP of preserved and functional C5-C7 roots. **G)** Total resection of the mass with intact brachial plexus with baseline recording and final functional prognosis. **H)** Final closure of the approach with preserved pleura under thoracoscopic vision and without air leak, a drain is left.
NAP = nerve action potentials. SEP = somatosensory evoked potentials.

our case, this encapsulated and peripheral tumor contrary to neurofibromas originated from the nerve sheath around the brachial plexus receiving irrigation from the axillary subclavian trunk. They may present with symptoms of nerve compression with neurological deficit, distal pain, sensory loss and weakness, with a palpable cervicothoracic mass being the most common initial presentation.[4]

Color Doppler ultrasonography and tomography could show that the nerves enter eccentrically to the schwannoma, which in turn is not observed in neurofibroma (main differential diagnosis and prognosis); however, schwannomas are iso to hypointense in T1 and hyperintense in T2 of gadolinium magnetic resonance imaging, defining the preoperative anatomical relationships as a study protocol of the brachial plexus and thoracic sulcus.[5,6] However, the hard and invasive consistency of the lesion associated with systemic symptoms with adenopathies could propose fine needle aspiration biopsy as an alternative to predict a final diagnosis. In our case, the diagnostic association with neurofibromatosis type I was suggestive of brachial plexopathy due to schwannoma.[2]

The use of S100 protein in the pathologic diagnosis of neural crest tumors is very popularized and associated with microscopic findings of spindle cells with areas of myxoid stroma with striated bundles of dense collagen, as occurred in our report. SOX10 protein is a more sensitive and specific marker than S100 for schwannoma and melanocytic tumors, especially in those diagnostic situations where sarcoma-like morphologic changes can be demonstrated. Calretinin is detected in almost all schwannomas and only in a small percentage of neurofibromas, which adds an important differential diagnostic marker.[2]

Surgery is indicated for tumors that cause neurological deficits, progressive lesions with suspected malignancy and to prevent or minimize neural damage, with complete surgical excision by enucleation of the schwannoma and dissection and preservation of the nerve fascicles being the most recommended surgical approach.[4,7] In our case, an anterior supraclavicular cervicothoracic approach combined with a left thoracoscopic approach was initially considered to safely manipulate the vascular and nerve structures of the thoracic outlet and to rule out potential intrapleural involvement of the lesion. However, series have found that a neurological deficit of 5% preoperatively increases to 11.5% after resection of schwannoma and brachial plexus neurofibromas, so nerve sparing as possible is important to maintain the patient's motor function.[3,4]

The causes of postoperative neurological deficits are related to preoperative nerve compression, mechanical injury or transoperative ischemia, reoperations associated with incomplete enucleation. Therefore, several perioperative neurological monitoring methods have been developed, such as spontaneous electromyography (EMG), somatosensory

evoked potentials (SEP) and nerve action potentials (NAP).[8] With EMG, nerve stimulation is performed and muscle activity is recorded to identify or avoid nerve damage; with SEP, it is useful for recording brachial plexus lesions and evaluates whether there is continuity with the central nervous system; with NAP, the nerve trunk proximal to the lesion area is directly stimulated and a recording is obtained in the area distal to the lesion; it is useful in nerve lesions due to continuity and determines the need for other reconstruction procedures with sural nerve grafts. The critical steps in surgical resection of brachial plexus schwannoma with electrophysiological monitoring in our case were: a) exposure of the nerve proximal and distal to the tumor by neurolysis; b) capsular exposure and electrostimulation of the tumor to localize and map the functional nerve distribution; c) longitudinal incision of the capsule in the direction of adjacent nerves with no recordable functional activity; d) enucleation and electrostimulation to avoid damage to functional nerve fibers; e) final exposure of the proximal and distal poles of the tumor where the nerves run and evaluation by NAP to determine a potential continuity injury requiring reconstruction with sural graft; and f) postoperative monitoring of basal and functional deficits for future rehabilitation and prognosis.

The schwannoma, in our case, facilitated surgical separation of healthy and functional nerve fibers; neurorrhaphy or sural grafting was not necessary as described for neurofibromas and primary malignancies; the anterior cervicothoracic approach with an L-shaped incision was sufficient. However, the cervico transsternal trap-door approach should be considered for invasive masses with a large intrathoracic and mediastinal component.[9,10]

CONCLUSIONS

The approach to masses located at the cervicothoracic junction represents a surgical challenge, both because of their location in contact with vascular and nervous structures, and because of the adequate control and management that must be carried out to avoid complications such as chronic pain and alterations in limb mobility, transoperative neurophysiological monitoring increases safety and perioperative prognostic benefit.

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Dr. Gastón S. Madrid Sánchez, icon of Mexican pulmonology (1908-1996)

Dr. Gastón S. Madrid Sánchez, ícono de la neumología mexicana (1908-1996)

Rafael Laniado-Laborín*

*Universidad Autónoma de Baja California, Mexico, SNI III Conahcyt.

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I met Dr. Gastón Madrid *(Figure 1)* at the beginning of my undergraduate rotating internship year in the summer of 1975, when he was already a legend in the local medical community and already had an enormous prestige as a pulmonologist and expert in coccidioidomycosis at a national and international level.

Originally from Mexico City, he studied at the Faculty of Medicine of the *Universidad Nacional Autónoma de México* and later trained in the care of tuberculosis patients under the tutelage of Dr. Ismael Cosío Villegas at the Tuberculosis Service of the General Hospital of Mexico City in the early 1930's. After receiving a job offer, he decided to emigrate to the city of Hermosillo in the state of Sonora, taking charge of the tuberculosis clinic of the Department of Health and Assistance.

In April 1942, Casa San Vicente, a sanatorium for the care of patients affected by tuberculosis, opened its doors in Hermosillo, and shortly thereafter Dr. Madrid was appointed medical director, a position he held until shortly before his death. This sanatorium, with its 80 beds, became a reference center for tuberculosis patients, not only for other regions of the state, but also for neighboring states. In addition to hospital care for periods of up to one year, as was recommended until the beginning of the 1960's, the sanatorium had the necessary infrastructure to carry out surgical treatment of the disease, which was an integral part of the treatment at the time.

Don Gaston, like all pulmonologists trained in the first half of the 20th century, in addition to clinical care, practiced thoracic surgery throughout his professional career, initially almost exclusively on patients with tuberculosis and later on patients with other pulmonary pathologies. As the only treatment available for tuberculosis before the advent of effective chemotherapy in the 1950's, multiple techniques were developed including collapse therapy (thoracoplasty, extrapleural pneumothorax), phrenisectomy, pneumonolysis, pneumoperitoneum and later, as an adjunct to chemotherapy in some cases, resectional surgery (lobectomies and pneumonectomies). I had the opportunity to review the operating room books in which surgical procedures were recorded at the sanatorium and I found more than three thousand records, with excellent results in spite of the rudimentary anesthetic techniques and the non-existence of postoperative advanced care units during that period.

Since the 1940's Dr. Madrid held the position of Chief of the Pneumology Service of the General Hospital of the State of Sonora, serving as its director during the period 1943-1950. Being a pioneer of medicine in the state, he participated in the creation of the Hermosillo Medical Association and later of the Medical Federation of Sonora, being president of both shortly after.

I had the privilege of working with him on a daily basis for over seven years, and I have not met a better clinician in my nearly 50 years of practice. He possessed a masterful physical examination technique (today we cannot diagnose even a pleural effusion without ultrasound), which he combined with his enormous experience in fluoroscopic examination of the thorax, which he performed with an old upright fluoroscope that still required a darkroom. As a clinical practitioner, he possessed an inexhaustible curiosity; every case had some interesting aspect for him and he argued that each case was unique and should be evaluated in this way. He always demonstrated an impeccable ethical sense, dedicating himself for more than forty years, with great empathy, to the care of the most helpless patients suffering from a disease, which, to this day, is a cause of stigma in our society. In spite of being a legend in the institution, he treated with the same simplicity and respect a chief of service as the most novice undergraduate intern. On his 50th anniversary as a physician, this icon of Hermosillo received a tribute from the city by naming the street in front of Casa San Vicente as Dr. Gastón Madrid Street.

The state of Sonora is an endemic area for coccidioidomycosis and being a disease that shares epidemiological, clinical, radiographic and even histopathological characteristics with tuberculosis, it is not surprising that cases of this mycosis were referred to Casa San Vicente when there was clinical suspicion of tuberculosis.

Figure 1: Dr. Gastón Madrid.

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Over the years, Dr. Madrid became the leading national expert in the diagnosis and treatment of coccidioidomycosis. He reported in a publication the first case of coccidioidomycosis in Mexico, and also the first isolation of the fungus from soil in the country. In 1974, he published a book on coccidioidomycosis, the only monograph in Spanish to date on this disease.

Don Gaston passed away at his lifelong home on January 12, 1996 at the age of 87, surrounded by his family and friends. The state of Sonora will be eternally grateful for his dedication and devotion to the health of its citizens. We will always remember him with admiration and affection, dear master.

Correspondence:
MSP. Rafael Laniado-Laborín
Facultad de Medicina y Psicología, Universidad Autónoma de Baja California, Mexico.
E-mail: rlaniado@uabc.edu.mx

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Letter to the editor

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Let's make Medicine great again

Hagamos a la Medicina grande otra vez

Luis Torre-Bouscoulet*

*Instituto de Desarrollo e Innovación en Fisiología Respiratoria INFIRE. Mexico City, Mexico.

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The decade of the 1990s and the first years of the current century was my time as a medical student and resident; first at the *Universidad Autónoma de San Luis Potosí* and later at the *Universidad Nacional Autónoma de México*. The medical training of those years would be considered today as completely inappropriate, retrograde and against human rights. In those training programs, what mattered the least was the student's opinion; it was an authoritarian, monotonous, repressive, unidirectional, jealous and, frequently, humiliating training. In spite of these adjectives, that training was very successful because most of the graduates were not only intellectually competent physicians, but also people with a strong sense of identity and a very particular philosophy about life and medical work. A philosophy that we could call «medical mysticism», which at first is the opposite of the earthly or rational. The physician was surrounded by a mysterious halo that made him different from any other professional and that formed and lived, with other physicians, in a fraternity based on respect for professional dignity that was born of having lived through a formative stage with the common denominator of being hostile, adverse, enormously demanding, but that generated a deep shared satisfaction. The institutional and trade union mystique –perhaps tribal– is due to the difficulties overcome during the training period. Physicians of many generations made the mystique their own because of difficult times; not comfortable times. The more effort it took to solve a problem, the more work it cost, the greater the identification and cohesion with the group. Completing medical training was almost like reaching the promised land and that made us heirs to the manna that dignified the physician.

Today we have, amazingly, all of humanity's knowledge at our smartphone's reach.[1] Now machines learn and generate intelligent algorithms, but a few decades ago, knowledge was earned, conquered. Complex searches had to be made in the index medicus and, if lucky, the journal might be available in the library.[2] Vertical transmission of knowledge from colleagues or residents of higher generations was also gained. We had to show interest, dedication, perseverance, in order to be allowed to explore a patient or perform a medical procedure. It is often said that the current training should not be compared with the previous one because the current world is different from the one that we lived in; I believe that this statement is partially true; however, there are constitutive elements that prevail in spite of generational modifications. The end does not justify the means; that is a truth from then and now, but I believe that the training of the physician, especially the resident, has not been understood. Now there are more and more theories of education and any form of pressure on the student is censured. What has not been understood is that the resident is not trained or educated; the resident is selected. Or, rather, they are made to experience circumstances in which they self-select; circumstances in which the student questions whether they have the talent and fortitude to be a physician or specialist. The training of a physician is like that of a soldier or a firefighter; if they are not taken out of their comfort zone, there is no training. If there is no demand and discipline, there is no training. The physician, the resident, should be trained as far away as possible from their comfortable, controlled area. Do not confuse training with knowledge. The sailor may know perfectly the operation of his ship, the wind direction and the sailing route; but if he has not experienced a storm, it is of no use. No passenger would feel safe with a captain who lacks experience in a storm; what better example of a storm than the COVID-19 pandemic? We didn't know what we were capable of until the pandemic tested us. Now we are better prepared for new storms.

The lives of many people depend on the firefighter, the soldier, the doctor, and on many occasions, their work will have to be carried out in circumstances of crisis, urgency, extreme fatigue, adversity. The resident's training period must be full of obstacles of different kinds, intellectual, ethical, integrative, adaptive obstacles, etc., and only when his determination leads him to overcome them, will they be worthy of being called physicians. It may be an arrogant stance, but the training of the physician or specialist should not be undervalued. We need leading physicians who are strong in action, thought and decision. Physicians who carry out a fast, efficient, correct analysis of consequences, with the least probability of error. An overprotected mind is weak and complains about everything, everything seems negative and victimizes itself. On the contrary, a strong mind accepts, analyzes and resolves. The physician must be, by definition, resilient. This characteristic dignifies our work.

The social image of the physician has deteriorated, there is less and less respect for the physician and we want to be seen as if we were another profession... no, we are not another profession. Whoever sees medicine from the myopic vision of a profession is underestimating the scope of the meaning of being a physician. Medicine is a philosophy of life. The best engine for development is adversity. Adversity generates frustration and the physician must learn to tolerate, manage and sublimate it. A physician with low frustration tolerance should not dissect a pulmonary hilum or perform a pulmonary thromboendarterectomy. A physician who lacks determination and strength in their thinking and decisions should not affect a patient's life.

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It is now common that there is no tolerance for frustration and difficult tasks are abandoned; now, more than ever, the law of minimum effort prevails. Now we want success and money immediately, without effort, without understanding that medicine and life are a slow and random process. We want social networks to give us the success we deserve and we want it to be quick. Less restrictive training has been confused with training without limits.

This is the way things are now, the strategy in the training of physicians cannot be the same as that of other professionals for the simple fact that physicians deal with the most valuable thing we have, which is health. Although the work of other professionals is also related to life, the physician's work is special –if not superior– because they try to help the suffering subject. An engineer's mistake, for example, can cost the lives of many people if a building collapses; true, but the engineer works with equations, materials, calculations, projections, all of them «modeled», meditated, even simulated over and over again. Medicine is not like that.

I believe that, if we do not return to the path of discipline and intellectual demand, physicians in training will have progressively fewer limits. The consequence will be intolerance, licentiousness, weak thinking, lack of recognition of authority, absence of leaders, immediacy, victimization. These are characteristics that do not add up in the complex process of restoring individual or collective health. Let us set the limits we need in medical training; I am sure that with discipline, intellectual demand and passion we will make medicine great again.

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Correspondence:
Dr. Luis Torre-Bouscoulet
Dirección Médica, Instituto de Desarrollo e Innovación en Fisiología Respiratoria INFIRE, Mexico City, Mexico.
E-mail: luistorreb@gmail.com

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