*Rev. Inst. Med. trop. São Paulo*
**25**(2):73-78, *março-abril*, 1983

*UDC* 616.992.282

# PULMONARY LOCALIZATION OF PARACOCCIDIOIDOMYCOSIS: LUNG FUNCTION STUDIES BEFORE AND AFTER TREATMENT

Alfred LEMLE (1), Bodo WANKE (2) and Moyses Bernardo MANDEL

## SUMMARY

Twenty patients with diffuse pulmonary lesions caused by **Paracoccidioides brasiliensis** underwent basic pulmonary function tests before and after the beginning of specific therapy. One or 2 months after the beginning of therapy, the Vital Capacity of Forced Vital Capacity had increased by more than 10% in 7 of 19 patients (36.8%), and the difference for the whole group was significant ($P < 0.05$). After 4 to 10 months, 5 of 6 patients had an increase of more than 10%. The progress of the Forced Expiratory Volume in 1 second, or its ratio to the Vital Capacity, and of the arterial oxygen tension was variable. These findings show that the pulmonary function tests are not an adequate resource for the control of therapy in these cases. They also suggest that the pulmonary infiltrations secondary to **P. brasiliensis** do not play a consistent role in obstruction, which is often the main functional defect in PM, and seems to be caused by underlying COPD.

## INTRODUCTION

Paracoccidioidomycosis (South American blastomycosis) is the most important systemic mycosis seen in Latin America. The lung is often involved by a usually diffuse, polimorphic granulomatous pneumonitis (PM), with infiltrations, areas of consolidation and occasional small sized cavitation [10,11,13,14,17,18,22].

As if to match the anatomic polimorphism of the lesions, pulmonary function studies show a variable pattern, particularly with respect to the magnitude and mechanisms of the gas transfer defect [1,2,4,6,15,20,21]. Spirometry most often demonstrates an obstructive defect, which is difficult to attribute to PM alone, since almost all of these patients are chronic smokers and usually qualify as chronic bronchitics.

There are very few published data on the effect of specific treatment on the pulmonary function results. A few comments have been made on the basis of a patient who was tested before and after treatment [8], and some information may be obtained in a thesis concerning the possible influence of anti-alfa$_1$-trypsine serum levels on emphysema in PM [9]. Besides the relevance to the management of these patients, knowledge of the effect of specific therapy on pulmonary function may help to clarify the role the pneumonits plays in the physiological defect.

In this study, spirometry and arterial blood gas studies were performed on 20 patients with PM, consecutively seen at our services, before and after the beginning of specific treatment. Nineteen were available for reevaluation after 1 to 2 months of therapy, but only 6 remained in the area after that, a few up to 8 or 10 months. The Vital Capacity improved somewhat, whereas obstruction and hypoxemia responded variably.

(1) Associate Professor, Department of Medicine, Federal University at Rio de Janeiro, School of Medicine
Reprints: Alfred Lemle, M.D., R. Fadel Fadel, 20 ap. 1402. 22430 Rio de Janeiro, RJ, Brasil
(2) Assistant Professor, Department of Preventive Medicine, Federal University at Rio de Janeiro, School of Medicine

## CASE MATERIAL

Twenty patients with PM, all with a mycologically confirmed diagnosis and consecutively seen at the Hospital Escola São Francisco de Assis, had their lung function tested before and after the beginning of specific therapy. This consisted of sulpha compounds in all cases except one (case number 20, on Table II), who received Amphotericin B. Nineteen patients were restudied at 1 to 2 months of therapy, but only 6 were available after 4 to 10 months, because the others returned to their hometowns in the interior of the country.

Clinically, the group was typical of the PM population. All were, men aged 37 to 69 (mean 49.3 ± 9.3), with no racial predominance. All had been farmhands at one time or another, all smoked and had diffuse infiltrations on X-ray.

Fifteen had not been treated before (Table I, numbers 1, 2, 4, 6 — 8, 11 — 18 and Table II, number 20). Thirteen had cough and expectoration, 2 of recent onset. Six had dyspnea, 5 of recent onset. Eight showed rales, and 9 and mild signs of hyperinflation. None displayed cyanosis, clubbing or signs of cor pulmonale. All had extrapulmonary manifestations of paracoccidioidomycosis.

## METHODS

Eleven patients were studied according to previously described methods [6]. They are singled out by the letter G on Tables I and II. Essentially, spirometry was performed on a water spirometer with a 9 liter bell (Pulmonet, Godart, Utrecht), in recumbency. Tests were repeated until there were at least two satisfactory trials, and the highest values for each parameter were reported, after correction to BTPS. Predicted values were calculated according to BALDWIN et al.'s equations [3], which correlate well with Latin America's normals. Arterial blood was obtained at rest and after a step-up exercise from the umeral artery with a Cournand needle. The blood aliquots were analyzed for gas contents with the Radiometer equipment.

For technical reasons, the remaining 9 patients (letter C, on Tables I and II) had their spirometry performed on another water spirometer with a 7 liter bell (Recording Vitalometer, Collins, Braintree, Mass) in the sitting position and without BTPS correction. Also, in this group the inspiratory Vital Capacity was not determined. These methodological differences in relation to the other 11 patients are irrelevant to this protocol, since in all calculations each patient functioned as his own control. Arterial blood gas studies were identical to those of the other 11 patients. Only the most relevant parameters are reported: Vital Capacity (VC) or Forced Vital Capacity (FVC) for the G patients, FVC for the C patients, Forced Expiratory Volume in 1 second ($FEV_1$) and the $FEV_1$/VC or $FEV_1$/FVC ratio: resting ($PaO_2R$) and exercise ($PaO_2Ex$) oxygen tensions are reported. $CO_2$ tensions are not reported because in agreement with previous observations [6], they showed practically no abnormalities.

The significance of the pre and post therapy differences in pulmonary function results were analyzed by the Wilcoxon test.

## RESULTS

Table I displays the results of the pulmonary function tests before and 1 to 2 months after the beginning of specific therapy. One patient was only studied before and 4 months after the beginning of therapy, and he therefore only appears on Table II, which shows the results after more than 2 months of treatment (number 20 on Table II).

The initial results show that in this series there were more patients with pure restriction (VC or FVC below 80% of predicted, no obstruction-6 cases) and more patients with normal spirometry (7 cases) than is usually the case in PM. Seven patients were obstructives ($FEV_1$/VC) ratio below (70%) and 3 of those also had restriction. Arterial blood oxygen tension at rest was below 80 mmHg in 9 patients.

One or 2 months after the beginning of therapy, 7 (36.8%) of the patients showed an increase in VC of FVC greater than 10%, and the increase for the group as a whole was significant ($P < 0.05$). The larger increments occurred with the lower initial values. There was no correlation of this increase with the interruption of smoking (which occurred in 9 patients), radiological improvement (12 patients) or the existence of previous courses of therapy.

T A B L E I

Spirometry and arterial blood oxygen tension in patients with diffuse lung infiltrations due to **P. brasiliensis**, measured before and after 1 to 2 months of specific therapy

| | Stopped or reduced smoking | Improved X-ray | Initial | | | | 1 - 2 MO | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | VC or FVC | $FEV_1$ | $Pa0_2R$ | $Pa0_2Ex$ | VC or FVC | $FEV_1$ | $Pa0_2R$ | $Pa0_2Ex$ |
| | | | % Pred/cc | % VC or FCV / cc | mmHg | mmHg | % Pred/cc | % VC or FVC / cc | mmHg | mmHg |
| 1 (G) | + | - | 70/2770 | 69/1920 | 69 | 53 | 72/2840 | 69/1970 | 82 | 56 |
| 2 (G) | - | - | 96/3290 | 42/1370 | 83 | 71 | 100/3430 | 35/1210 | 75 | 66 |
| 3 (G) | - | + | 78/3020 | 76/2300 | 67 | 57 | 86/3360 | 76/2580 | 85 | 75 |
| 4 (G) | + | - | 64/2270 | 59/1350 | 87 | 80 | 66/2380 | 65/1560 | 98 | 91 |
| 5 (G) | - | - | 92/3480 | 62/2180 | 68 | - | 88/3320 | 69/2320 | 70 | 70 |
| 6 (G) | + | + | 115/5100 | 78/3980 | 72 | 76 | 118/5120 | 69/3570 | 77 | 79 |
| 7 (G) | - | + | 97/3480 | 80/2790 | 73 | 65 | 110/3920 | 73/2900 | 82 | 82 |
| 8 (G) | - | - | 83/2540 | 82/2100 | 85 | 79 | 83/2500 | 74/1860 | 89 | 84 |
| 9 (G) | + | - | 88/3140 | 90/2830 | 100 | 68 | 94/3340 | 89/2980 | 89 | 68 |
| 10 (G) | - | - | 67/2500 | 49/1240 | 76 | 65 | 79/3000 | 55/1650 | 72 | - |
| 11 (C) | - | ? | 54/1950 | 93/1800 | 79 | - | 52/1880 | 88/1650 | 89 | 64 |
| 12 (C) | + | + | 64/2130 | 84/1800 | 68 | 64 | 64/2150 | 84/1800 | 57 | 62 |
| 13 (C) | - | - | 91/2980 | 74/2200 | 83 | - | 88/2880 | 74/2150 | 92 | 70 |
| 14 (C) | + | - | 77/3000 | 91/2750 | 82 | 78 | 88/3400 | 93/3200 | 92 | 86 |
| 15 (C) | - | + | 56/1880 | 86/1650 | 82 | 73 | 68/2300 | 80/1850 | 77 | 67 |
| 16 (C) | + | - | 72/2600 | 85/2250 | 89 | 105 | 85/3100 | 74/2300 | 82 | 87 |
| 17 (C) | + | - | 83/3100 | 67/2100 | 82 | 64 | 100/3750 | 58/2200 | 76 | 63 |
| 18 (C) | + | + | 98/3250 | 60/1950 | 69 | 57 | 107/3530 | 61/2180 | 71 | 65 |
| 19 (C) | + | ? | 126/5000 | 73/3650 | 91 | 85 | 126/5000 | 67/3350 | 96 | 86 |

G - Spirometry performed on Pulmonet, Godart, in recumbency, B.T.P.S.; C - Spirometry performed on Recording Vitalometer, Collins, sitting up, not corrected for temperature; VC - Vital Capacity, and Pulmonet; FVC - Forced Vital Capacity, on Recording Vitalometer; $FEV_1$ - Forced Expiratory Volume, one second; $Pa0_2R$ - Resting arterial blood oxygen tension; $Pa0_2Ex$ - Arterial blood oxygen tension after exercise.

Six patients (35.5%) had a larger than 10% increase in $FEV_1$, and the increment for the group as a whole was not significant ($P > 0.05$). There was no correlation between the interruption of smoking and the $FEV_1$ increase ($P > 0.05$). The $FEV_1$/VC or $FEV_1$/FVC ratio increased in 3 patients (15.8%), decreased in 9 (47.4%) and remained unchanged in 7 (36.8%).

Nine patients (47.3%) had a larger than 5 mmHg increase in $PaO_2R$, and 6 (35.5%) had a decrease. The difference for the group as a whole was not significant ($P > 0.05$). Five patients (33.3%) had a greater than 5 mmHg increase in $PaO_2Ex$, and 3 (20%) had a decrease. The difference for the whole group was not significant ($P > 0.05$).

Four to 10 months after the beginning of therapy, the increase in VC or FVC became more evident — 5 of the 6 available patients had an increase greater than 10%. The inpredictable response of the $FEV_1$ also was confirmed, since only 3 had an increase greater than 10%. Only 2 had a larger than 5 mmHg increase in $PaO_2R$, but another (number 1) had an intermediate value, at 5 months, larger than the initial value (76 mmHg).

## COMMENTS

These data clearly show that 1 to 2 months after the beginning of specific treatment for paracoccidioidomycosis in patients with the

TABLE II

Spirometry and arterial blood oxygen tension in patients with diffuse lung infiltrations due to **P. brasiliensis**, measured before and after more than 2 months of specific therapy

| | Initial | | | | | 4 - 10 MO | | | |
|---|---|---|---|---|---|---|---|---|---|
| | VC or FVC | $FEV_1$ | $Pa0_2R$ | $Pa0_2Ex$ | MO | VC or FVC | $FEV_1$ | $Pa0_2R$ | $Pa0_2Ex$ |
| | % Pred/cc | % VC or FVC / cc | mmHg | mmHg | | % Pred/cc | % VC or FVC / cc | mmHg | mmHg |
| 1 (G) | 70/2770 | 69/1920 | 69 | 53 | 8 | 84/3300 | 56/1850 | 71 | - |
| 3 (G) | 78/3020 | 76/2300 | 67 | 57 | 5 | 114/4360 | 76/3320 | 86 | 76 |
| 4 (G) | 64/2270 | 59/1350 | 87 | 80 | 10 | 71/2540 | 51/1300 | 99 | 91 |
| 7 (G) | 97/3480 | 80/2790 | 73 | 65 | 6 | 117/4170 | 77/3210 | 72 | 66 |
| 11 (G) | 54/1950 | 93/1800 | 79 | - | 6 | 93/2600 | 82/2150 | 83 | 66 |
| 20 (G) | 83/3200 | 76/2460 | 80 | - | 4 | 88/3440 | 61/2120 | 81 | - |

Numbers of cases are the same as in Table I. Patient number 20 did not have intermediate studies, used Amphothericin B, did not stop smoking and improved his X-ray. G - Spirometry performed on Pulmonet, Godart, in recumbency B.T.P.S.; C - Spirometry performed on Recording Vitalometer, Collins, sitting up, not corrected for temperature; VC - Vital Capacity, and Pulmonet; FVC - Forced Vital Capacity, on Recording Vitalometer; $FEV_1$ - Forced Expiratory Volume, one second; $Pa0_2R$ - Resting arterial blood oxygen tension; $Pa0_2Ex$ - Arterial blood oxygen tension after exercise.

diffuse pulmonary form of the disease the only significant change in pulmonary function was an increase in Vital Capacity, especially in those cases with low initial values for this parameter. Obstruction, measured by the $FEV_1$, and its ratio to VC or FVC, as well as arterial blood oxygenation were not consistently affected by therapy.

It is to be noted that at this point radiological improvement had already occurred in 12 of 19 patients, without any correlation to the VC-FVC increase. Also, it must be remembered that an isolated increase in VC is a very unspecific datum, which might have been accomplished by a combination of improved nutrition in the hospital, cessation of smoking (9 cases, no correlation to the VC-FVC increase) and the unspecific action of sulpha compounds on pyogenic infection concomitant with or complicating the mycosis.

After 4 to 10 months, there were only 6 patients available. Almost all the paracoccidioidomycosis patients who are seen in Rio de Janeiro come from the interior of the country, and they return to their homes to finish the treatment as soon as the first signs of improvement appear. Although insufficient for final conclusions, this group of results is nevertheless adequate to confirm the increase in VC or FVC and to stress the variability of the progress of obstruction, as expressed by the $FEV_1$ and blood oxygenation.

There is very little information in the literature to check these results. Besides the previous publication of case number 20 of this series[8], there is only Lima Neto's recent thesis concerning the role of $alpha_1$-antitrypsin deficiency in the development of emphysema in PM[9]. This Author drew a sample of cases from a very large series of unpublished observations, with follow-up lung function studies up to a few years in duration, including one or more series of therapy. Although this study is based on a selected group of patients retrospectively studied for other purposes, it also shows an increase in VC and a variable course of the $FEV_1/VC$ ratio, the RV/TLC ratio and $PaO_2$ after treatment.

The first implication of the findings in the present study is that pulmonary function studies are not an adequate resource for the control of therapy in PM.

The second implication is that the impact of the pulmonary infiltrations secondary to PM on pulmonary function seems to be limited, since their radiological clearing only had a consistent effect in the VC. Obstruction and, most significantly, the gas transfer defect were not consistently influenced by specific therapy and X ray improvement.

Careful studies of the radiological progress of the pulmonary lesions under treatment have shown that reabsorption, frequently incomplete, is also slow, stabilization of the X-ray picture occurring sometimes as late as at 6 months of therapy [12]. Therefore, the absence of clear cut effects of therapy on pulmonary function was to be expected after 1 to 2 months, although many cases in this series had improved their X-ray appearances at this time. However, a more evident effect was to be expected at 4 to 10 months, or later.

These observations may have an important bearing on the interpretations of the pulmonary function changes in PM. These changes are variable, because of the polimorphism of the lesions themselves and the association with variable degrees of chronic obstructive pulmonary disease (COPD), since almost all of these patients are chronic smokers and usually qualify as chronic bronchitics.

The most common ventilatory defect in PM is obstruction [2,4,6], but one is hesitant to attribute obstruction to the disease itself, both because of the association with COPD as well as because anatomic studies have not yet established a clear link between the mycotic lesions and diffuse obstruction [5,16,19].

In a recent study, 17 patients with PM and COPD manifestations were matched against 17 clinically similar patients with pure COPD and otherwise clear lungs [7]. There was no significant difference between the spirometric and gas transfer parameters of both groups, suggesting that COPD and not the fungal infiltrations caused the functional defect.

The finding, in this study, that specific therapy with radiological improvement did not consistently relieve obstruction is in agreement with the concept that obstruction is secondary to underlying COPD rather than to PM itself.

This series of patients had a higher incidence of pure restriction than is usually found in PM. The improvement of VC, particularly after more than 4 months of therapy, was therefore very consistent. It is, therefore, particularly surprising that $PaO_2$ improvement was so erratic. This may be explained by the fact that the COPD component of the functional disorder was frequently not affected by therapy.


## RESUMO

### Localização pulmonar da paracoccidioidomicose: estudos da função pulmonar antes e depois do tratamento.

Vinte doentes com lesões pulmonares difusas causadas pelo **Paracoccidioides brasiliensis** foram submetidos a provas de função pulmonar básicas antes e depois do início de tratamento específico. Após 1 ou 2 meses de tratamento, a Capacidade Vital ou a Capacidade Vital Forçada haviam aumentado em mais de 10% em 7 de 19 doentes (36,8%), e a diferença para o grupo todo foi significativa ($P < 0,05$). Após 4 a 10 meses, 5 de 6 doentes apresentaram aumentos superiores a 10% nesse parâmetro.

A evolução do Volume Expiratório Forçado em 1 segundo, ou de sua relação com a Capacidade Vital, e a da pressão parcial do oxigênio no sangue arterial foi variável.

Estes resultados evidenciam que as provas de função pulmonar não representam meio adequado para o controle do tratamento dessa condição mórbida. Por outro lado, sugerem que os infiltrados pulmonares causados pelo **P. brasiliensis** têm pouca influência sobre o componente obstrutivo, que é frequentemente o principal elemento do distúrbio funcional na forma pulmonar difusa da paracoccidioidose, mas parece ser causado pela doença pulmonar obstrutiva crônica frequentemente subjacente.


### REFERENCES


1. ADRIANZA, M.; RECAGNO, A. & ASCANIO, R. — La función ventilo-respiratoria en paracoccidioidomicosis de localización pulmonar. **Mycopathologia** (Den Haag) **15:** 163-170, 1961.

2. AFONSO, J. E.; NERY, L. E.; ROMALDINI, H.; BOGOSSIAN, M. & RIBEIRO-RATTO, O. — Função pulmonar na paracoccidioidomicose (blastomicose sul-americana). **Rev. Inst. Med. trop. São Paulo 21:** 269-280, 1979.

3. BALDWIN, E. F.; COURNAND, A. & RICHARDS Jr., D. W. — Pulmonary insufficiency: I — Methods

of analysis, physiologic classification, standard values in normal subjects. **Medicine** (Baltimore) **27**: 243-278, 1948.

4. CHIBANTE, A.; PEREIRA RÊGO, A.; SANTOS LIMA, N.; TEIXEIRA, G. & BETHLEM, N. — A espirometria na blastomicose sul-americana. **J. Pneumol. 3**: 16-19, 1977.

5. FIALHO, A. S. — **Localizações pulmonares da micose de Lutz — anatomia patológica e patogenia.** [Thesis]. Faculdade Nacional de Medicina da Universidade do Brasil, Rio de Janeiro, 1946.

6. LEMLE, A.; VIEIRA, L.; MILWARD, G. & LISBOA MIRANDA, J. — Lung function studies in pulmonary South American blastomycosis. Correlation with clinical and roentgenologic findings. **Amer. J. Med. 48**: 434-472, 1970.

7. LEMLE, A. & LIMA NETO, J. A. — Paracoccidioidomicose: localização pulmonar. In preparation.

8. LEMLE, A.; LIMA NETO, J. A.; MANDEL, M. B. & GAENSLER, E. A. — South American blastomycosis: a treated case with control lung function studies. **Respiration 34**: 85-96, 1974.

9. LIMA NETO, J. A. — **Deficiência de alfa$_1$-antitripsina na paracoccidioidomicose pulmonar.** [Thesis]. Instituto de Tisiologia e Pneumologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 1979.

10. LONDERO, A. T. — The lung in paracoccidioidomycosis. In: **Paracoccidioidomycosis.** PAHO Scientific Publication n. 254. Pan American Health Organization, Washington, 1972, pp. 109-117.

11. LONDERO, A. T. & RAMOS, C. D. — Paracoccidioidomycosis. A clinical and mycologic study of forty-one cases observed in Santa Maria, RS, Brazil. **Amer. J. Med. 52**: 771-775, 1972.

12. MACHADO FILHO, J. & LISBOA MIRANDA, J. — Considerações relativas à blastomicose sul-americana — evolução, resultados terapêuticos e moléstias associadas em 394 casos consecutivos. **Hospital** (Rio) **60**: 374-412, 1961.

13. MACHADO FILHO, H. & LISBOA MIRANDA, J. — Considerações relativas à blastomicose sul-americana — localizações, sintomas iniciais, vias de penetração e disseminação em 313 casos consecutivos. **Hospital** (Rio) **58**: 99-137, 1960.

14. MACHADO FILHO, J. & LISBOA MIRANDA, J. — Considerações relativas à blastomicose sul-americana — da participação pulmonar entre 338 casos consecutivos. **Hospital** (Rio) **58**: 431-449, 1960.

15. MACHADO FILHO, J.; MARQUES LISBOA, R.; DARWIN DE MATTOS, A.; JANUZZI, A. & LISBOA MIRANDA, J. — Considerações relativas à blastomicose sul-americana. As repercussões cardiovasculares das lesões pulmonares. Dados hemodinâmicos, oximétricos e angiopneumográficos. **Hospital** (Rio) **60**: 241-259, 1961.

16. PENA, C. — Deep mycotic infiltrations in Colombia. **Amer. J. Clin. Path. 47**: 505-520, 1966.

17. RESTREPO, A.; ROBLEDO, M.; GIRALDO, R.; HERNANDEZ, H.; SIERRA, F.; GUTIÉRREZ, F.; LONDOÑO, F.; LOPEZ, R. & CALLE, G. — The gamut of paracoccidioidomycosis. **Amer. J. Med. 61**: 33-42, 1976.

18. RESTREPO, A.; ROBLEDO, M.; GUTIÉRREZ, F.; SANCLEMENTE, M.; CASTAÑEDA, E. & GALLO, G. — Paracoccidioidomycosis (South American blastomycosis). A study of 39 cases observed in Medellin, Colombia. **Amer. J. Trop. Med. & Hyg. 19**: 68-76, 1970.

19. SALFELDER, K.; DOEHNERT, G. & DOEHNERT, H. R. — Paracoccidioidomycosis. Anatomic study with complete autopsies. **Virch. Arch. Abteilung A Pathol. Anatomie 348**: 51-76, 1969.

20. TUFFIK-SIMÃO, A.; TAVARES, W.; TOMASSINI, M. C. C.; KRAKOWSKI, D. & RODRIGUES DA SILVA, J. — Alterações da função ventilatória na blastomicose pulmonar. **Rev. Soc. Brasil. Med. Trop. 1**: 79-92, 1967.

21. VÉLEZ, L. A. C.; RESTREPO, J. M. & LONDOÑO, F. P. — Pulmonary function in paracoccidioidomycosis. In: **Paracoccidioidomycosis.** PAHO Scientific Publication n. 254. Pan American Health Organization, Washington, 1972, pp. 170-175.

22. VIEIRA, LOBD & LEMLE, A. — A localização pulmonar da blastomicose sul-americana. **Rev. Brasil. Med. 25**: 403-409, 1968.

Recebido para publicação em 15/4/1982.