Behavior of the Pulmonary Circulation at Rest and During Exercise in Miliary Tuberculosis*

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We studied the hemodynamic behavior of the pulmonary circulation at rest and during exercise in six patients with MTB. As a group, in contrast to advanced fibrocaseous tuberculosis, these patients exhibited normal pulmonary hemodynamics at rest and during exercise. Only minor abnormalities in pulmonary vascular resistance at exercise (increased Pad-PWP gradient) were noted in two of the patients. The increase in Rp during exercise does not appear to be related to acute hypoxic vasoconstruction but rather to functional changes (compliance or recruitment or both) of the pulmonary microvasculature. In the genesis of these functional changes, chronic alveolar hypoxia and the inflammatory-fibrotic process might be interacting.

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MTB = miliary tuberculosis; Pad = diastolic pulmonary arterial pressure; PWP = pulmonary wedge pressure; Rp = pulmonary vascular resistance; PAH = pulmonary arterial hypertension; CI = cardiac index; PAF = pulmonary artery pressure

Pulmonary arterial hypertension and cor pulmonale are well known complications of advanced tuberculosis. Factors implicated in the genesis of PAH are severe abnormalities of pulmonary function (mechanics and gas exchange) and the extensive reduction of the pulmonary vascular bed, either by the disease itself or as a result of surgical therapy. However, in hematogenous (miliary) tuberculosis, knowledge about the abnormalities in cardiopulmonary function, particularly the behavior of the pulmonary circulation, is limited.

The pathology of MTB resembles more that of interstitial than lobar pneumonia. Instead of large numbers of alveoli being filled with exudate, the supporting tissues and the alveolar capillary walls are randomly thickened by cellular infiltration. Also different from fibrocaseous tuberculosis, scarring and fibrosis are less prominent findings. Earlier studies on cardiopulmonary function in MTB have shown that functional abnormalities are different in the acute inflammatory phase and after recovery. In both instances, pulmonary function did not appear to be severely affected; however, there were abnormalities in lung volume and in oxygen transfer at rest and during exercise.

In this anatomic and functional setting, the hemodynamic behavior of the pulmonary circulation would be difficult to anticipate, and therefore we decided to study this aspect.

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Materials and Methods

Patients

We studied six patients with MTB. Diagnosis was based on clinical history and physical examination, on characteristic chest x-ray findings, and mainly on the clinical and radiologic-response in the follow-up to complete specific therapy.

Hemodynamic Studies

All of the procedures were explained to the patients beforehand, and their consent was obtained. The method for cardiac catheterization studies at rest and during exercise performed in our laboratory has been reported elsewhere. Briefly, blood samples were obtained from the pulmonary and brachial arteries over a one-minute period and immediately analyzed using a gas analyzer (Instrumentation Laboratory 127 bath and 213 electrometer). Cardiac output was measured by the thermodilution method, and pressure measurements were obtained through a Swan-Ganz catheter (KMA 9601-7F). Standard formulas were used for calculation of CI and Rp.

Exercise Testing

Patients were familiarized with the exercise technique. After control measurements a supine exercise test was performed with an apparatus similar to that described by Bronfin et al. All pressures were recorded continuously, except during collection of blood samples. Blood and air samples were collected simultaneously, and cardiac output was measured during the final minute of exercise. This degree of exercise increases total body oxygen consumption at rest by at least twofold.

Statistical analysis and significance of results were calculated using standard methods, paired t-test, and linear correlation. All results are expressed as the mean ± SE.

Results

The mean age of the group was 35.6 ± 6.6 years. At the time of the studies, the patients had been symptomatic for an average of three months. Most of them already had been receiving specific treatment for an average of 1.5 months (isoniazid, rifampin, and pyra-
zinamide). They were nonsmokers. Two of the patients were diabetic, and one was an alcoholic; all of them were severely undernourished.

Regarding pulmonary function testing, the mean values of the group, expressed as a percentage of the predicted value, were as follows: VC, 62.5 percent; TLC, 79.5 percent; FEV₁, 50 percent; and FVC/FEV₁, 76 percent.

Normal resting pulmonary artery pressures were found in all patients. The CI and the Rp and Pd-PWP (pulmonary diastolic minus pulmonary wedge pressure) differences were also within normal limits. The calculated resting Rp correlated significantly with the PaO₂ at rest (r = -0.89; p < 0.05; Fig 1). As a group, the hemodynamic response to exercise was characterized by a significant increase in both mean PAP and CI. In most of the patients, Rp remained within normal limits. In two of the patients (cases 2 and 5), there was an abnormal widening of the Pd-PWP difference (from 1.0 and 4.5 to 11.0 and 11.5 mm Hg, respectively). In these two patients the PWP during exercise was low, and this fact could have been the cause of the Pd-PWP difference (false gradient). Therefore, in order to assess the relative contribution of hypovolemia, an IV infusion of dextran 40 (500 ml over a 20-minute period) was given to these patients. By this maneuver, PWP, cardiac output, and PAP increased in both patients, and an abnormal widening of the Pd-PWP difference was again noted. Although these two patients were the most hypoxemic at rest, neither at exercise nor during dextran infusion did the patients become more hypoxemic.

At rest, hypoxemia (mean PaO₂, 59 ± 3 mm Hg) without hypercapnia and normal pH were found in the group as a whole (normal values for Mexico City are as follow: PaO₂, 67.5 ± 2.5 mm Hg; PaCO₂, 32.5 ± 2 mm Hg; and arterial pH, 7.33 to 7.43). The P(A-a)O₂ and the Vd/Vₜ ratio were increased. Venous admixture (QVA/QT) was increased in the more hypoxemic patients (patients 2, 4, and 5). No significant correlation was found between the gas exchange variables and the lung mechanics values. The hematocrit level was low in all patients. During exercise, no significant changes occurred in the gas exchange variables, except for oxygen consumption, respiratory rate, and minute ventilation.

**DISCUSSION**

Years ago, when an early and effective treatment for pulmonary tuberculosis was not readily available, PAH and cor pulmonale were not infrequent complications in patients with severe disease and extensive lung destruction. Both functional and anatomic vascular changes are the factors involved in the genesis of the raised pulmonary artery pressures. In hemogenous (miliary) tuberculosis the behavior of the pulmonary circulation is, by far, less known. In the early study of McClement et al on cardiopulmonary function in a group of 11 patients with MTB, a parallel finding was the demonstration of almost normal pulmonary artery pressures, both at rest and during exercise. Only one out of the seven patients who underwent catheterization had PAH on mild exercise. This patient had the most extensive pulmonary involvement of any of the patients in the series. Nine months after treatment, despite the normal appearance of the chest x-ray film, the patient had a reduced oxygen diffusing capacity and showed, on exercise, a significant increase in PAP despite only a slight increase in cardiac output. McClement et al concluded that the pulmonary vascular bed was markedly reduced in this case and that pathologic residues (fibrosis) were present. The patient eventually died from tuberculous meningitis, and the postmortem pathologic vascular changes in the pulmonary circulation verified the previous conclusion.

In the present study the hemodynamic behavior of the pulmonary circulation of the patients at rest was normal. Four out of the six patients had mild resting hypoxemia, mainly as a result of the V/Q mismatching imposed by the abnormalities in pulmonary function. Although the hemodynamic response to exercise in the group as a whole could be considered to be normal (ie, the increase in PAP was within the normal range of that expected for the observed increase in cardiac output), there were some individual abnormalities that have to be pointed out. Patients 2 and 5 had an increase in the Pd-PWP difference to an abnormal value during exercise. This gradient represents the resistance to flow in the pulmonary microvasculature during diastole, and its normal value is below 5 mm Hg. The possible role of relatively low PWP as the explanation for this vascular pressure gradient ("false
gradient”) was ruled out by the dextran infusion maneuver. The increase in resistance to flow at the microvascular level could be the result of either vasoactive factors (i.e., hypoxia or acidosis) or the result of an abnormal function (compliance or recruitment or both) of the microvasculature.

Although there was not more hypoxemia at exercise and, therefore, acute hypoxic vasoconstriction cannot be invoked, chronic hypoxia may be relevant. The role of chronic alveolar hypoxia in the genesis of the hemodynamic abnormalities that we found is suggested by the significant negative correlation between resting PaO₂ and Rp in the group as a whole, as well as by the fact that the patients who had increased Rp and PAd-PWP at exercise were those with the lowest baseline PaO₂. There is a considerable bulk of experimental and clinical evidence showing that chronic alveolar hypoxia remodels pulmonary circulation in such a way that the resistance vascular segment increases. The abnormal function of the pulmonary circulation in these patients, on the other hand, might traduce a more severe involvement (i.e., inflammation-fibrosis) of the pulmonary vessels. Although these patients had evidence of more severe functional abnormalities than the rest of the group (i.e., resting hypoxemia), we lack anatomic support for more vascular damage in them. Thus, although it is difficult to draw any firm conclusion from such limited observations, it is likely that in the genesis of the abnormalities of the pulmonary circulation in some patients with MTB, the vascular changes imposed by chronic alveolar hypoxia and those related to the inflammatory-fibrotic process might be interacting.

REFERENCES