RESPIRATORY DISEASE IN THE IMMUNOSUPPRESSED HOST

J. B. Lippincott Company *Philadelphia*

New York St. Louis London Sydney Tokyo

Acquisitions Editor: Charles McCormick
Production Manager: Janet Greenwood
Production: P. M. Gordon Associates
Compositor: Achorn Graphics
Printer/Binder: Murray Printing Company

1 3 5 6 4 2

Library of Congress Cataloging-in-Publication Data

Respiratory disease in the immunosuppressed host / James Shelhamer . . . [et al.].
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-397-51008-X
1. Respiratory system—Diseases. 2. Immunosuppression—Complications and sequelae. 3. Lungs—Infections. 4. Pneumonia. I. Shelhamer, James.
[DNLM: 1. Communicable Diseases. 2. Immunologic Deficiency Syndromes. 3. Lung Diseases. 4. Respiratory Tract Diseases. WF 140 R4341026]
RC732.R464 1991
616.97'92—dc20
DNLM/DLC
for Library of Congress *90-13399*
CIP

The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

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The high frequency of pulmonary disease in patients with the acquired immunodeficiency syndrome (AIDS) has led to increased interest in pulmonary function tests (PFTs) in the immunosuppressed host. Office and bedside spirometry, previously directed primarily at the patient with obstructive airways disease, is a simple and sensitive screening test for lung disease in immunosuppressed patients. Arterial blood gas determination can now be supplemented with noninvasive measurements of continuous oxygen saturation (SaO_2) by pulse oximetry to test the adequacy of oxygenation at rest and during exercise. Abnormalities of oxygenation during rest and exercise and abnormalities of the lung's diffusing capacity (DLco) are very sensitive indices for detecting and monitoring the most common pulmonary disease in the AIDS patient, *Pneumocystis carinii* pneumonia. However, the specificity of PFTs generally is poor, and the appropriate use of the more costly and technically demanding tests, such as DLco, remains in question.

This chapter describes the pathophysiologic correlates of the commonly used PFTs from the standpoint of lung mechanics or ventilatory lung function and considers gas exchange abnormalities. The sensitivity and clinical usefulness of PFTs relative to the specific infectious and noninfectious diseases will then be discussed. Finally, an algorithm is proposed as a guide to the use of PFTs in immunosuppressed patients.

PULMONARY FUNCTION TESTS

Mechanics: Volume and Flow Measurements

The most fundamental ventilatory test is spirometry.[1–5] Volume displacement devices that trace volumes over time are technically simple to use, even by inexperienced personnel, and provide reliable data. The most useful and common measurements are the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC) (Fig. 12-1). Electronic devices that measure flow directly, especially when used in conjunction with microcomputers, provide a full array of automated data, including the flow–volume loop, described in Figure 12-2.[6] The validity of these measurements requires careful calibration.[1,7] In addition to the usual electronic calibration, use of a syringe of known volume or performance of the test by a reliable technician are the best ways to ensure accuracy. The variation in FVC and FEV_1 should be less than 5% or 100 mL (whichever is greater), on repeated measurements.[7] The range of predicted values for VC is wide (100% ± 20%, or approximately ±800 mL); since VC can be reproducibly measured to within ±5%, and since a loss of 10% or 400 mL may be clinically significant, it is useful to have baseline measurements for future reference in immunosuppressed patients, who often develop pulmonary complications.

The VC can be obtained with a slow, inspiratory maneuver, the slow vital capacity (SVC or IVC), or a rapid, forced expiratory maneuver (FVC). The former is generally higher in the patient with obstructive airways disease or a tendency to cough or develop bronchospasm with the FVC maneuver (see Fig. 12-2,E).

To reduce the cost of equipment and personnel time, simple, inexpensive, disposable incentive spirometers can be used. Although the measurements will not be equivalent to the VC, they can be used to monitor a given patient with restrictive lung disease over time. Such devices avoid cross-contamination from a spirometer. In addition, these devices provide a mechanism for the treatment or prevention of atelectasis, so common in the immunosuppressed host with pulmonary complica-

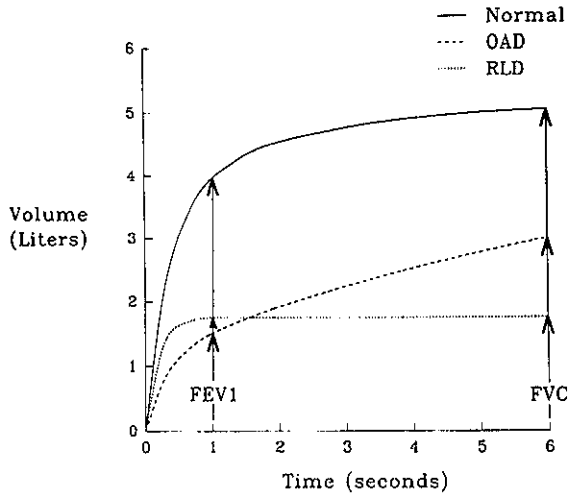

Figure 12-1. Three forced vital capacity maneuvers shown as volume vs time curves for a normal subject, a patient with restrictive lung disease (RLD), and a patient with obstructive airways disease (OAD). Note the low FEV_1 in both obstructive airways disease and restrictive lung disease, but the high FEV_1/FVC ratio in restrictive lung disease. Note also that exhalation is not complete at 6 seconds in obstructive airways disease.

tions. The inability of an adult patient to reach a VC of at least 1 L or 25% of predicted is likely to be associated with impaired gas exchange.[8]

Use of PFTs in Differential Diagnosis

Spirometry alone can often provide a definite diagnosis. A reduced VC with a high FEV_1/FVC ratio (>80%) and absence of curvature in the flow–volume loop suggests restrictive lung disease (see Fig. 12-2,B). Rigorous confirmation of restrictive lung disease requires the measurement of residual volume (RV) and total lung capacity (TLC) using more complex techniques such as the washout of nitrogen from the lungs with oxygen, equilibration of helium in a closed rebreathing system, or body plethysmography. A less accurate TLC is obtained during the DLco measurement and is referred to as alveolar volume (V_A). All of these methods provide RV and TLC with a coefficient of variation in excess of 25% (see references 8 and 9 for descriptions of these methods).

When the FEV_1/FVC is lower than predicted and there is downward curvature on the flow–volume loop, airway obstruction is diagnosed (see Fig. 12-2,C). The VC may be reduced due to obstructive airways disease and may not necessarily indicate restrictive lung disease. To definitively diagnose restrictive lung disease in the presence of airways obstruction, it is necessary to show the RV and TLC to be decreased, or at least not increased, as expected when significant airway obstruction is present.

Combined restrictive lung disease and obstructive airways disease is common in the immunosuppressed host. Even with a marked decrease in VC, significant airway obstruction may be present. The FEV_1/FVC ratio may be normal and wheezes absent since all flows are low; however, obstructive airways disease can be diagnosed from the curvature of the flow–volume loop, with low flows as exhalation approaches RV (see Fig. 12-2,D). Improvement after the administration of bronchodilator aerosol may also confirm the presence of obstructive airways disease as well as indicate the need for treatment with these agents.

A common problem in spirometry is failure of the patient to exhale fully. Frequently the patients are weak and fatigued or have hyperreactive airways with sensitive cough reflexes that prevent such maneuvers (see Fig. 12-2,E).[7] The reduced VC is artifactual and may be misleading by exaggerating the degree of restriction.[7] Also, the airway obstruction may not be revealed, as the slow flows or "tail" of the flow–volume loop that are indicative of disease in the peripheral or smaller airways are not present (see Fig. 12-2,D).

Gas Exchange Measurements

Determination of pH and O_2 and CO_2 tension in arterial blood is used to diagnose alveolar hypoventilation ($Paco_2 > 50$ mmHg) and hypoxemia ($Pao_2 < 80$ mmHg on room air). The alveolar O_2 (P_{AO_2}) is approximated by the $Fio_2 \times 700$ mmHg $- Paco_2$ (assuming a respiratory quotient of 1.0). The difference between the P_{AO_2} and Pao_2, called the alveolar–arterial oxygen gradient ($A–ao_2$), is less than 20 mm Hg when the subject is breathing room air, should not increase with exercise, and should remain less than 50 mm Hg even with a high Fio_2.[4,10] In the earlier phases of lung disease, Pao_2 may be normal at rest; only under the stress of increased blood flow and decreased venous oxygen during exercise does the Pao_2 decrease and $P_A–ao_2$ increase. Such measurements serve to quantify the severity of the gas exchange impairment and direct management, and in many conditions have been correlated with prognosis and survival.

Although arterial blood gas values are useful and reliable monitors of gas exchange, the measurements are invasive, expensive, and static. Pulse oximetry is a noninvasive technique where transmission of two wavelengths of infrared light through a finger or ear lobe provides a continuous measure of oxygen saturation (Sao_2). It is a reliable test when the cardiovascular state of the patient is not compromised.[11] Normal values for Sao_2 are above 95% on

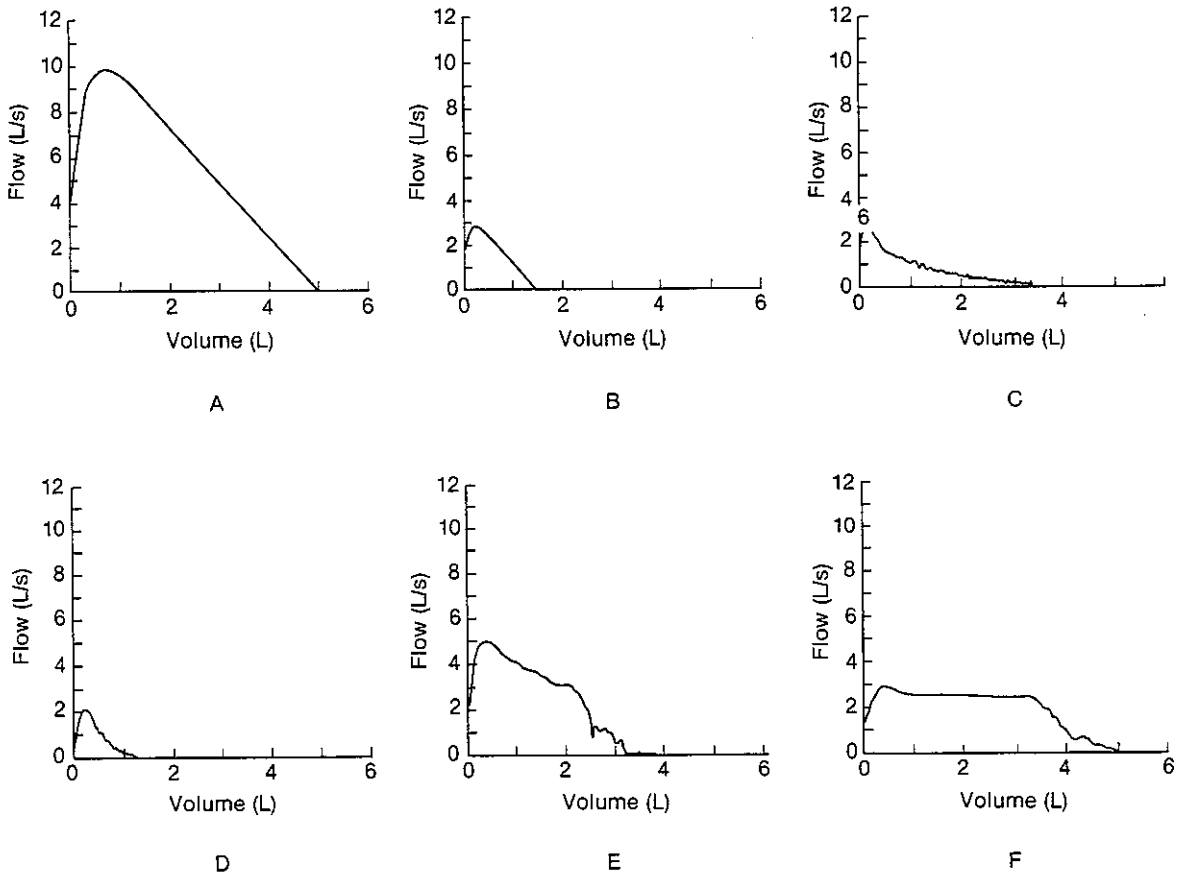

Figure 12-2. Six examples of flow–volume loops during a forced expiratory maneuver: **(A)** normal subject; **(B)** severe restrictive lung disease; **(C)** severe obstructive airways disease (note downward concavity of the curve); **(D)** combined restrictive lung disease and obstructive airways disease (note downward concavity here but absence in **B** and **E**); (E) patient making less than maximal effort (lack of peak, erratic appearance, and premature termination of exhalation), giving erroneously low flows and VC; (F) wide plateau characteristic of fixed extrathoracic or endobronchial obstructive lesion.

room air and should not decrease with exercise. Values below 90% on room air can be corrected with increased Fio_2, which can be monitored and adjusted by oximetry. Such measurements at the bedside or in the clinic or office are used with increasing frequency. Some have called it a "fifth vital sign"[12]; others debate its utility over signs and symptoms[13]; still others point out the potential errors in its use.[14] All agree, however, that it is a readily available, relatively inexpensive, and potentially useful measurement that complements and in many instances replaces arterial blood gas determinations.

Diffusing Capacity

The affinity of CO for hemoglobin has provided a convenient noninvasive estimate of gas exchange from exhaled gas analysis. When done with continuous ventilation with low CO concentrations (<0.5%), a "steady-state DLco" can be measured that correlates well with P_A–ao_2.[4] This method is cumbersome and requires an arterial blood sample to measure $Paco_2$ or approximation of $Paco_2$ using end-tidal CO_2 values. This method has largely been replaced by a noninvasive single breath technique.

A full VC single breath of a mixture of 0.5% CO and either neon or helium held for 10 seconds in the lung followed by measurement of the concentrations in the exhaled gas, is the most common method of measuring the DLco.[15–18] This "single breath DLco" describes the uptake of CO; in addition, the dilution of the inert gas measures the TLC, usually referred to as alveolar volume (V_A = TLC). When the abnormality is limited to the pulmonary