PREFACE

In a landmark paper published in 1995, Dr. Joel Cooper reported the initial results of a procedure that he termed "bilateral pneumectomy." A modern reincarnation of an operation conceived nearly a half century earlier by Otto Brantigan, Dr. Cooper's technique involved bilateral resection of significant amounts of diseased lung tissue in emphysema patients, in an effort to improve respiratory function by decompressing the thoracic cavity and increasing pulmonary elastic recoil. Almost instantaneously, worldwide interest and enthusiasm were directed toward this potential panacea for the millions of patients suffering and dying from end-stage emphysema. Lung volume reduction surgery (LVRS), as the new procedure soon came to be known, became the subject of numerous articles in the lay media, if not in scientific journals, gaining the attention of patients, physicians, and the general public. Despite a paucity of objective data, surgeons willing to perform the procedure were inundated by hundreds of self-referring patients desperate for a new lease on life.

Dozens of centers began to perform LVRS, in the manner described by Cooper, and a trickle of scientific reports eventually ensued. According to these early reports, short-term results were promising, although outcomes had not been positive in all patients. Nonetheless, before long, the operation was being performed across the country, fueled by positive reports from centers operating on highly selected patient cohorts, and more importantly, by patient and physician enthusiasm.

This enthusiasm for LVRS had several effects. Almost suddenly, questions about how our society should implement new surgical technology and about the role of insurers in determining coverage, and thereby access, to new procedures became central issues. The ethics of randomized trials for the study of apparently beneficial surgical treatments became hotly debated. Fundamental questions were raised concerning the long-term efficacy, cost-effectiveness, selection criteria, timing, and optimal surgical approaches for LVRS. The previously quiescent field of pulmonary physiology was reinvigorated.

In 1996, after a review of preliminary data failed to provide conclusive evidence of a clear benefit of LVRS for emphysema, the Health Care Financing Administration (HCFA) imposed a moratorium on Medicare reimbursement for the new procedure until a properly designed, randomized trial could be performed. Thus, through the collaboration of HCFA and the NHLBI, the multicenter National Emphysema Treatment Trial (NETT) was conceived. As of the writing of this book, the trial is underway, with results still several years away. It is the hope of the physicians and patients involved in this trial that valuable information is gained, with the ultimate goal of determining if (and for whom) the operation is in fact beneficial.

Lung Volume Reduction Surgery was conceived in response to the enthusiasm, controversy, confusion, and disappointment that, in the experience of the editors, have variously (and often simultaneously) characterized the attitudes of clinicians and scientists toward this novel and potentially revolutionary operation. In the chapters that follow, we attempt to elucidate the current state of knowledge surrounding LVRS, in order to define the clinical and scientific landscape for those interested in this field. In Part One, experts in clinical medicine and the basic sciences review the diagnosis, pathophysiology, and medical management of emphysema, in order to ground the reader in the disciplines that

form the basis of our current knowledge. In Part Two, the technical aspects and clinical results of LVRS are reviewed, with additional emphasis on organizational issues important for those involved or planning to be involved in LVRS programs. This book is intended for readers of diverse backgrounds, including surgeons, pulmonologists, primary care physicians, physiologists, radiologists, basic scientists, physical and occupational therapists, and nurses. It is the hope of the editors that the information contained in this book will be of help to these professionals and to all those who share the mission of providing the best possible care to patients with emphysema.

The question of whether LVRS will have a future role in the treatment of emphysema is currently unanswered. A clear and complete answer to this question will likely require years of clinical experience, careful analysis of properly designed randomized trials, and perhaps most importantly, a redefinition by society of the importance of palliation in the treatment of incurable diseases. Despite the controversy that is certain to surround LVRS in the coming years, the debate that has been generated has already had positive effects. The enthusiasm generated by this novel operation has brought a fresh perspective and a new generation of researchers into the fields of pulmonary physiology and end-stage lung disease. In this environment, a unique opportunity exists for both clinicians and researchers to uncover the physiologic and molecular determinants of this devastating disease. Although LVRS may one day be shown to improve (and perhaps prolong) the lives of patients suffering from emphysema, it is far more exciting to think that the research initiated in these early LVRS years might one day lead to an actual cure of the disease.

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2 Cardiopulmonary Exercise Testing in the Evaluation of the Patient with Emphysema

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INTRODUCTION

Comprehensive exercise testing offers an opportunity to study the cellular, cardiovascular, and ventilatory systems' responses simultaneously under controlled conditions *(1)*. Physical exercise requires the interaction of physiologic mechanisms that enable the cardiovascular and respiratory systems to supply exercising muscles with the fuel

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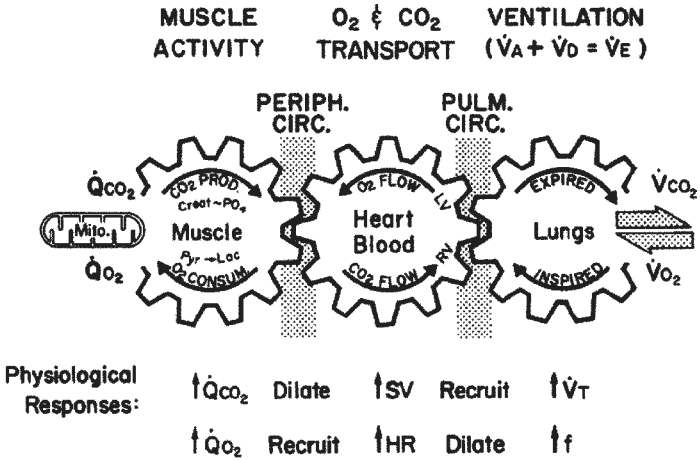

Fig. 1. Gas transport mechanisms for coupling cellular to pulmonary respiration. The gears represent functional interdependence of the physiological components of the system. (Printed with permission from Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ, Principles of Exercise Testing and Interpretation 1999, 3rd ed., Lipincott, Williams & Wilkins.)

required to meet increased oxygen demand (VO_2) and remove excess carbon dioxide production (VCO_2). This coupling of respiratory, cardiovascular, and muscle gas transport systems is illustrated in Fig. 1 *(1)*. The physiologic reserve capacity of the cardiovascular and respiratory systems is significantly high enough that even if much of this capacity is lost, demands of daily living will be met adequately *(2)*. Abnormalities of exercise performance may be influenced by diseases of the heart, lungs, pulmonary and peripheral circulation, hemoglobin, muscles and/or cytochrome systems *(3)*. In this chapter, we will initially discuss various methods of cardiopulmonary testing, and later we will discuss its applications in patients undergoing lung volume reduction surgery.

BROAD OVERVIEW OF METHODS OF CARDIOPULMONARY EXERCISE TESTING

Exercise testing allows the objective measurement of exercise capacity that can be compared with the ideal exercise capacity corrected for age, gender, height, and weight. In addition, symptoms that limit exercise can be elucidated and the physiologic responses to exercise can be analyzed in order to highlight patterns suggesting underlying organ dysfunction. Unfortunately, there is a lack of standardization concerning

the performance of clinical exercise testing *(2)*. This applies to the methods used, variables being measured, and interpretive techniques. There are a number of predicted formulas that can be used to calculate the maximum VO_2, work rate, heart rate, and minute ventilation *(1,2,4)*. Exercise tests can be noninvasive, symptom limited, steady state, performed with arterial blood sampling, or with the presence of a pulmonary artery catheter *(2)*. In addition, the tests can be conducted on various types of equipment: treadmill, cycle ergometer, step testing, or using an arm ergometer. The tests can be performed on room air or on supplemental oxygen. Using an electrically braked cycle ergometer leads to a more predictable increase in oxygen uptake than with a treadmill *(2)*, using a treadmill results in an approx 7 % higher oxygen consumption than a cycle *(5)*, increases in ventilation and blood lactate levels tend to be higher in cycling *(6)*. The work performed on a treadmill is dependent on the weight of the subject, but this is not as significant with the cycle ergometer *(7)*.

SAFETY ISSUES IN CARDIOPULMONARY EXERCISE TESTING

The safety of exercise testing has been well established and the risks to the patient are very small as long as simple precautions are observed. The risk of a myocardial infarction (MI) or serious arrythmia is estimated at 1/10 000 submaximal tests *(8)*, increasing to 1/2500 maximal tests if the patient has a history of MI *(9)*. We feel that the test should be supervised by an experienced physician who is familiar with the patient's history and physical examination, and who is knowledgeable in resuscitative techniques. Before 1980, exercise tests were supervised by physicians 90% of the time. However, over the past 15 yr, cost containment initiatives have encouraged more extensive use of specially trained health professionals (nurses, exercise physiologists, physician assistants, and physical therapists) *(10–12)*.

<u>Absolute contraindications to exercise testing</u>

1. The presence of an acute febrile illness.
2. EKG features of myocardial ischemia.
3. Uncontrolled heart failure.
4. Pulmonary edema.
5. Unstable angina.
6. Acute myocarditis.
7. Uncontrolled hypertension (> 250 mm systolic, 120 mm diastolic).
8. Uncontrolled asthma *(2)*.

Relative contraindications to exercise testing

1. Recent (less than 4 wk previously) MI.
2. Aortic valve disease.
3. Resting tachycardia (HR >120/min).
4. Resting EKG abnormalities.
5. Poorly controlled diabetes.
6. Poorly controlled epilepsy.
7. Cerebrovascular disease.
8. Respiratory failure *(2)*.

SPECIFIC ISSUES RELATING TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND EMPHYSEMA

Chronic obstructive pulmonary diseases (COPD) are characterized by reduced maximal expiratory flow and include various disease entities such as chronic obstructive bronchitis, asthmatic bronchitis, and emphysema. At least 14 million people in the United States suffer from COPD, and the prevalence of this disease seems to be increasing *(13–16)*. As many as 2 million people suffer from emphysema, and the overall death rate for emphysema in the United States has been estimated at 20 000/yr, the fifth leading cause of death in North America *(13,16–18)*. Exercise testing in patients with COPD has been stimulated by the increasing numbers of patients entering pulmonary rehabilitation programs *(19)*, in addition to the availability of specific treatments for this condition, i.e., pulmonary transplantation and lung volume reduction surgery (LVRS).

TYPES OF CARDIOPULMONARY EXERCISE TESTING FOR PATIENTS WITH COPD

The simplest validated exercise test is the 6-min walk test performed either on or off oxygen. The inability to walk at least 200 m during this test has been shown to correlate with increased postoperative mortality *(20)*. Patients with severe COPD present a number of difficulties when an incremental exercise test is performed. Their exercise capacity is frequently extremely limited *(21)*, it is therefore difficult to obtain sufficient physiologic data. The exercise duration can be improved, however, by using small increments in the exercise load *(21)* and by using supplemental oxygen. Currently, the National Emphysema and Treatment Trial (NETT) is comparing the efficacy of LVRS and maximal medical therapy. Exercise tolerance is an important outcome measure in the study and the exercise techniques used in the NETT trial could serve as a standardized way of performing an incremental exercise test in patients with severe COPD.

Patients are exercised on an electrically braked cycle ergometer, which has the capability for electronic computer control to provide ramp workloads as low as 5 W/ min. The test is initially performed with arterial blood sampling, whereas subsequent tests during the trial may or may not use arterial sampling. The exercise tests are performed on an FIO_2 of 30%, the patients breathing in the O_2 and air mixture delivered from a high-flow blender to a large Douglas bag (>30 L). After being connected to the exercise equipment and getting on the cycle ergometer, the patient is observed for 5 min at rest, 3 min at 0 W cycling, and subsequently during a symptom-limited incremental exercise test (5 W/ min increments) *(22)*. Exercise is considered maximal if one or more of the following criteria are met:

1. The patient's predicted maximal VO_2 is reached.
2. A clinically significant EKG abnormality develops.
3. Serum lactate increases to greater than 8 mmol/L.
4. Breathing reserve is less than 15 L /min.
5. The heart rate reserve is less than 10 beats/min.
6. The arterial PO_2 falls below 50 mmHg or the oxygen saturation falls below 84%.

The following parameters are measured:

1. Level of work (WR).
2. Heart rate (and the difference between heart rate and maximal predicted heart rate—the heart rate reserve).
3. EKG.
4. Blood pressure.
5. Respiratory rate.
6. Tidal volume (and the tidal volume to inspiratory capacity ratio).
7. Minute ventilation (VE) (and the difference between VE and maximal voluntary ventilation—the breathing reserve).
8. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and the relationship of these measures to the minute ventilation (VE/VO_2 and VE/VCO_2).
9. The VO_2/WR relationship.
10. The VO_2/heart rate response—the oxygen pulse.

RESPONSES TO EXERCISE IN CHRONIC OBSTRUCTIVE LUNG DISEASE

The two main factors reducing exercise capacity in COPD/emphysema are the reduced ventilatory capacity and the increased ventilatory requirement *(1)*. Other factors include exercise-induced hypoxemia, cardiac dysfunction, and deconditioning *(23)*. Both airway obstruction

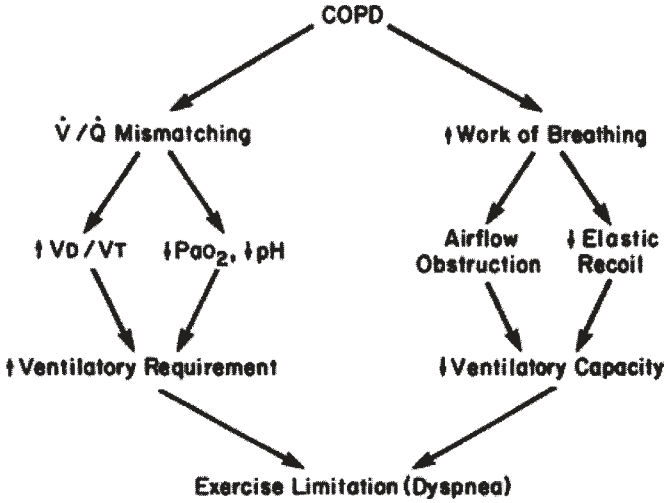

Fig. 2. Factors that play a role in exercise limitation and dyspnea in patients with chronic obstructive pulmonary disease. (Printed with permission from Wasserman K, Hansen JE, Sue DY, Casaburi R, Whipp BJ, Principles of Exercise Testing and Interpretation 1999, 3rd ed., Lipincott, Williams & Wilkins.)

and a reduction in lung elastic recoil are responsible for the decreased ventilatory capacity; the increased ventilatory requirements are a result of inefficient ventilation of the lungs because of mismatching of ventilation to perfusion *(1)* (Fig. 2). There is often a reduction in work that can be performed as a consequence of oxygen demand exceeding the maximal oxygen carrying capacity of the oxygen transport chain *(21)*, and this is largely because of the failure of the available ventilatory reserve to meet the increasing ventilatory demands *(24,25)*. The VO_2/WR response is often normal in patients with COPD, the oxygen cost of breathing, however, is much higher in COPD as compared to normal *(21)*. There is a greater time constant for CO_2 excretion than O_2 consumption (50–60 s vs 30–40 s). Patients with COPD have increased numbers of lung units with high ventilation/perfusion ratios, these regions receiving up to 50% of blood flow, further exacerbating the delay in CO_2 output. The ventilatory response to exercise is dependent on the metabolic rate, the "set point level of arterial CO_2" and the wasted ventilation fraction *(VD/Vt)*. The required minute ventilation at any given time may be calculated using the following equation:

$$VE = (863 \times VCO_2)/(PACO_2 \times (1\text{-}VD/Vt))$$

with the arterial $_pCO_2$ ($PaCO_2$) generally being substituted for the alveolar CO_2 ($PACO_2$) *(21,26)*. Patients with stable COPD regulate

$PaCO_2$ at a reasonably constant level despite increasing work rates, in patients with severe COPD, however, the $PaCO_2$ may increase with exercise, worsening exercise-associated acidosis *(1)*. Minute ventilation is frequently increased at rest in addition to being increased for a given level of exercise *(1,21)*. This is frequently a result of the increased *VD/Vt* ratio, requiring an abnormal level of ventilation to maintain a normal $PaCO_2$ *(27)*.

Many patients with COPD are hypoxemic, either at rest and/or during exercise. The degree of widening of the alveolar-arterial oxygen gradient with exercise is related to the degree of ventilation perfusion mismatching, particularly in regions of low ventilation/perfusion ratios (21).

DYNAMIC HYPERINFLATION AND ITS CONSEQUENCES

In patients with chronic lung diseases, the tidal volume tends to be lower and the respiratory rate tends to be higher at a given level of VE. A close relationship has been noted between measured vital capacity and maximal tidal volume during exercise *(1,21)*. In patients with COPD, flow rates can be shown to reach the envelope of the resting maximal flow volume curve, which may contribute to exercise limitation *(28,29)*. Normal subjects increase respiratory rate by decreasing inspiratory time *(Ti)* fractionally less than expiratory time *(Te)*—as a consequence, the inspiratory duty cycle (*Ti*/total respiratory time) increases. In contrast, patients with COPD often show no increase in the inspiratory duty cycle, preserving greater time for exhalation. This is achieved by increasing inspiratory flow rates. There is, however, an associated increase in intrathoracic gas volume as a consequence of airflow limitation and increased respiratory frequency, eventually leading to a point on the thoracic cage pressure/volume relationship where inspiratory muscles function inefficiently, eventually leading to a large increase in thoracic gas volume with resultant fall in inspiratory flow *(21,30)*. During exercise, the development of dynamic hyperinflation with a progressive increase in end-expiratory lung volume (EELV) imposes an additional elastic load on the ventilatory system, resulting in a reduction in inspiratory capacity, and is closely related to exertional dyspnea *(31–33)*. This is in contrast to normal subjects in whom the EELV decreases with exercise *(33)*. Traditionally, the maximal voluntary minute ventilation (MVV) (or multiple of the FEV1) has been compared to the maximal VE as an estimate of ventilatory capacity. Measuring the MVV in patients with COPD has shortcomings, however. Significant differences exist in the breathing patterns during the 12–15 s MVV maneuver and the breathing patterns during heavy exercise *(33)*.

Ventilatory capacity can vary during exercise because of bronchodilation or bronchoconstriction, and is dependent on the lung volume where the tidal breathing occurs relative to the total lung capacity (TLC) and residual volume (RV). Measurements of the resting inspiratory capacity have been shown to closely correlate with maximal work in COPD patients *(34)*. Breathing at higher lung volumes increases the inspiratory elastic load and, consequently, the work of breathing. Breathing at low lung volumes limits the available ventilatory reserve because of encroachment on the flow volume envelope. Reducing the total lung volume and residual volume, either medically by the use of bronchodilators (medical volume reduction) or surgically (surgical volume reduction), may indeed offer significant benefits by reducing EELV and subsequently availing more inspiratory capacity.

The technique of measuring the exercise inspiratory capacity, which allows superimposition of the exercise tidal volume loop on the maximal flow volume loop allows measurement of the EELV and the end inspiratory lung volume during exercise. This analysis provides more useful information about the cause of ventilatory limitation than analysis of the breathing reserve and breathing pattern (tidal volume and respiratory rate relationship) alone *(33)*. Fig. 3 represents flow volume loops during exercise and compares the pattern in a healthy young male to that in a patient with emphysema.

CARDIOVASCULAR RESPONSE TO EXERCISE IN COPD PATIENTS

Patients with COPD can have coexisting cardiovascular diseases, because smoking is a risk factor for both COPD and ischemic heart disease and hypoxia can exacerbate ischemic heart disease. In patients with COPD, increases in cardiac output with exercise is less in comparison with normal subjects *(35)*. Possible explanations for this phenomenon include cardiac dysfunction and elevations in pulmonary artery pressure with exercise due as a result hypoxia and or capillary destruction or obstruction, even in the absence of cor pulmonale *(21,35,36)*.

EFFICACY OF LVRS

LVRS has been shown to significantly improve forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and MVV, in addition to RV and TLC *(37)*. Furthermore, lung elastic recoil has been shown to increase significantly after LVRS *(38)*. The exercise capacity of patients with emphysema is thought to be determined by the mechanical constraints placed on maximal ventilation *(39)*. Therefore, improvements in lung

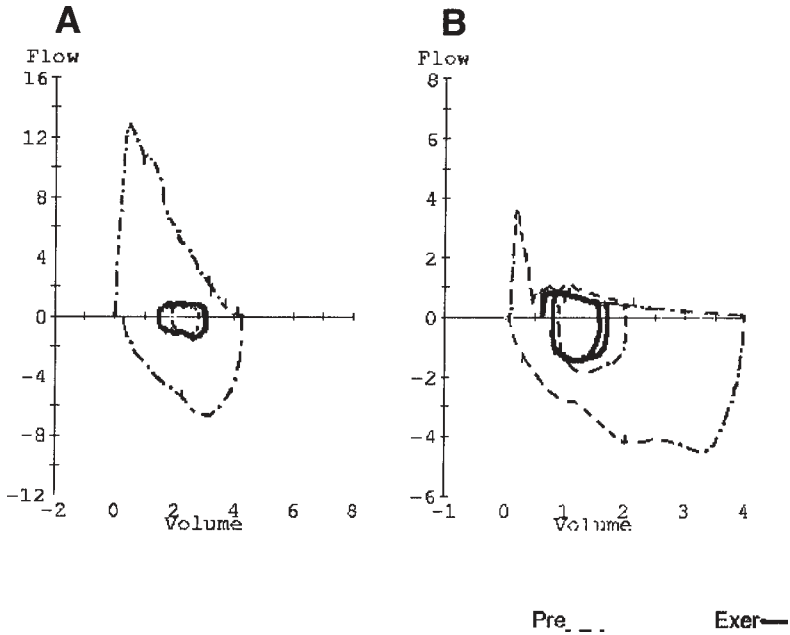

Fig. 3. Exercise flow volumes pre- and during exercise. Graph A represents the normal increase in tidal volume with exercise associated with a reduction in the end expiratory lung volume accompanied by an increase in the end inspiratory lung volume and no encroachment on the maximal resting flow volume loop. Graph B represents a patient with COPD, with an exercise-associated increase in the EELV. In addition, there is encroachment on the expiratory component of the maximal pre-exercise flow volume loop.

mechanics may explain the improvements noted following LVRS, specifically, the combination of the reduction in pulmonary hyperinflation, reduction in breathing frequency, reduction in mechanical constraints on tidal volume and reduction in functional residual capacity (FRC) *(40)*. Improvements in exercise tolerance following LVRS include longer 6-min walk distances, increased maximal workloads, higher maximal VO_2, and improved indices of gas exchange *(41)*. Currently in the NETT trial, the 6-min walk test, maximal VO_2, and maximum work rate are measured, with the maximum work rate as one of two primary outcomes to be analyzed *(13,23,42–45)*.

Significant increases in the 6-min walk test have been noted following LVRS, from 300 to 370 m in normocapnic patients, and from 197 to 274 m in hypercapnic patients. The maximal VO_2 has also been shown to significantly increase in both normocapnic and hypercapnic patients following LVRS, from 14.6 to 17.02 mL/Kg/min and

11.7 to 14.7 mL/Kg/min, respectively *(37)*. The same study also noted significant increases in the maximal *Vt* (0.85 to 1.05 L and 0.8 to1.2 L, respectively, in normocapnic and hypercapnic patients); similarly, maximal minute ventilation increased from 29.2 to 33.5 L/min in normocapnic and 22.5 to 31 L/min, respectively, in hypercapnic patients *(37)*.

The role of cardiovascular adaptations and altered heart–lung interactions in the improvements noted following LVRS is unclear. Most patients with severe emphysema have mild to moderate pulmonary hypertension, which may contribute to their exercise limitation *(46)*. The consequences of LVRS on the pulmonary circulation are felt to be twofold: 1) resection of emphysematous lung tissue could reduce the vascular bed and increase pulmonary vascular resistance; and 2) better mechanical properties of the respiratory system with improved elastic recoil and less dynamic hyperinflation might counteract this effect and lead to a decrease in pulmonary vascular resistance *(43,47)*. Strong correlations have been noted between improvements in gas exchange (the alveolar-arterial gradient) and reductions in mean exercise pulmonary artery pressure following ARDS, although these associations were not evident at rest *(47,48)*. Other investigators have shown a trend to improvement in the *VD/Vt* ratio following LVRS *(44)*. It is of interest that close correlations have been previously noted between the cardiac output and maximal VO_2 at maximal exercise in patients with predominant cardiac dysfunction or pulmonary vascular disease. It is a possibility, therefore, that the increased VO_2 noted following LVRS could, in part, represent an improvement in cardiac output *(48,49)*. A strong association has been noted between the increases in FEV1 and the improvements in VO_2 following LVRS *(47,48)*. Thus it appears that there is a dichotomy between improvement in maximal VO_2 and PaO_2 following LVRS. The former depends on improvements in FEV1, whereas the latter depends on improvement in pulmonary artery pressure.

LVRS has been shown to produce significant improvement in relief of dyspnea in many patients *(44)* in addition to improved quality-of-life scores *(50)*. These improvements are generally associated with improvements in pulmonary function and exercise tolerance. However, the exact mechanism for the improvement in dyspnea is not precisely defined *(50)*. Exercise testing before and after LVRS, including the use of the exercise flow volume loop and, in selected circumstances, invasive hemodynamic exercise testing will continue to improve our knowledge and help to ascertain the nature and duration of improvement in these patients. Moreover, as additional information is obtained from ongoing

clinical trials, the exercise test will help to define which patients are suitable candidates for the procedure *(37)*.

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