LIMITATIONS TO EXERCISE IN PATIENTS WITH CHRONIC LUNG DISEASES

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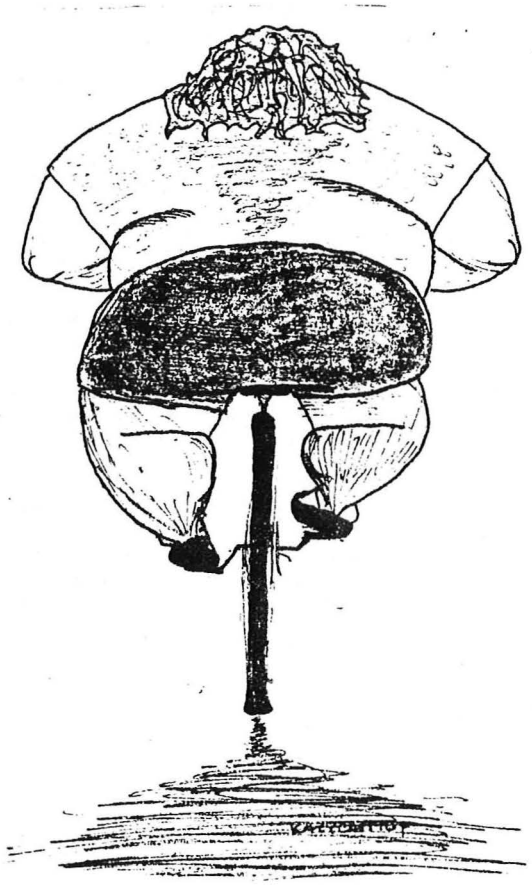

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Exercise intolerance is a leading symptom in patients with chronic respiratory and cardiac diseases. This exercise intolerance is almost always manifest as recognizable breathlessness at levels of physical exertion that had been tolerated, previously. In the context of this presentation the term, exercise, will be used synonomously with physical exertion. Exercise is the activity that allows us the freedom to move within our environment and to physically manipulate the environment.

The physiology of exercise in normal man and elite athletes, as well as in patients with respiratory and cardiac diseases, has been studied extensively by many investigators at this institution for the past 30 years under the leadership of the eminent Jere H. Mitchell. Many aspects of the physiology of exercise have been presented on numerous occasions at Internal Medicine Grand Rounds.

The focus of this Grand Rounds will be centered on the capacity for gas exchange in the lung. The areas that will be considered are:

1. The capacity of the lung to transport oxygen at rest and during exercise;

2. The functional derangements during rest and exercise that are associated with different types of lung diseases;

3. A method to predict exercise performance based on the capacity to transport oxygen and the functional derangements caused by disease;

4. An outline of therapeutic and diagnostic strategies from the perspectives of exercise and the patient with chronic lung disease.

II. **Muscular work** (ref. Johnson, 1980; and Astrand and Rhodal, 1970.)

Exercise is muscular work. In mechanical terms, this work is defined as the force times the distance through which the force acts. Mechanical power is the rate at which the work is performed and can be measured on a treadmill or on a bicycle ergometer. It is usually expressed in units of electrical power (Watts) or mechanical power (kilogram meter per min); 100 Watts is equivalent to 600 kg m/min.

Muscular work requires an energy source. During exercise, chemical energy generated through metabolism is converted into heat and mechanical work, the sum being the metabolic rate. Metabolic rate usually is measured as the rate of oxygen consumption, but the total chemical energy production is dependent upon the substrate being used as the energy source. Chemical energy is expressed in terms of thermal power: kilocalories per min. 1.4 kcal/min is equivalent to 100 Watts. When fat is the substrate, 4.69 kcal of energy is produced per liter of O_2. When carbohydrate is used, 5.05 kcal/liter of O_2 is produced.

Mechanical efficiency is the mechanical power developed per increase in metabolic rate, and generally falls between 20 and 25%.

The immediate source of energy for muscle contraction is that stored in high energy phosphate bonds of adenosine triphosphate (ATP) and creatine phosphate (CP). These small labile energy stores in muscle must be continually replenished by metabolism of carbohydrates, fats, and amino acids. Most of the energy derived from these substrates requires oxidation with molecular oxygen (aerobic metabolism).

A portion of the energy available from carbohydrate metabolism can be released in the absence of O_2. When O_2 delivery to the mitochondria is inadequate, reduced NAD builds up in the cytoplasm. Reduced NAD reacts with pyruvate to produce lactic acid, and lactate production is used as an index of inadequate O_2 delivery during exercise.

Total energy stores are listed for an average 70 kg y/o man with 50% muscle and 10% fat.

TABLE 1

Store	Mass (kg)	Concentration (mM/kg muscle)		Total (Mol.)	Free energy/mol (K cal/mol)	Total free energy (k cal)
Muscle	37.5	ATP	6	.225	7.3	1.6
		CP	17	.637	7.3	4.7
Muscle glycogen			70		700	1,840
Liver glycogen	1.5				700	315
Fat(palmitic)*	7.5			29.3	2340	68,000

*Molecular wt. of Palmitic Acid is 256

These energy stores are important in determining the time interval over which a muscular effort can be sustained. At 75% of maximum work load (or 2.63 L/min $\dot{V}_{O_2}$) enough ATP and CP are available to supply metabolic requirements for about 30 sec. Enough muscle and liver glycogen are present to sustain this level of exercise for about three hours, assuming complete oxidation to CO_2 and H_2O.

However, to sustain exercise or muscular work for a long duration, the energy must be provided by oxidative metabolism, which necessitates an adequate oxygen delivery and carbon dioxide removal system.

Oxygen delivery

It is the capacity of this oxygen delivery system that will determine ability to sustain exercise. This oxygen transport system consists of several functional steps that are linked in series (that is, the steps have to proceed in a given order as follows:)

TABLE 2

1. Ventilation
2. Diffusion
3. Chemical reaction with hemoglobin
4. Cardiac output x O_2 capacity
5. Distribution to muscles,
   Chemical release, and
   Diffusion into cells and mitochondria.

Oxygen consumption continues to rise in proportion to increasing work load until the limits of the oxygen delivery system are exceeded. Healthy, young persons can increase their $\dot{V}_{O_2}$ 9-10 x resting values. This limit is termed the maximal oxygen consumption ($\dot{V}max O_2$) (Mitchell et al., 1958 and Snell and Mitchell, 1984) and varies with age among healthy subjects as shown in Table 3 (from Astrand, 1970).

TABLE 3

Age	0-29	30-39	40-49	50-59	60-69
$\dot{V}max O_2$ (ml O_2/min/kg)					
Female	39.9	37.3	32.5	28.4	
Male	52.2	39.9	39.2	33.1	31.4
Maximum heart rate (beats/min)					
Female	187	185	178	170	
Male	186	181	173	161	159

The bottleneck in the oxygen transport system that sets the limit on $\dot{V}max O_2$ theoretically could occur at any of the steps (Table 2) in the oxygen delivery chain.

III. Functional Capacities of the heart and lungs during exercise.

A. The normal individual

1. Ventilation:

Ventilation is the bulk movement of gas moved into the lungs per min. It is the tidal volume times the frequency of breathing ($\dot{V}_E = V_T \times f$). Ventilation is coupled to metabolic rate and increases nearly linearly with respect to oxygen consumption as the exercise work load increases to moderate levels; thus, alveolar gas tensions ($P_{A_{O_2}}$ and $P_{A_{CO_2}}$) are maintained in accordance with the well-known relationships:

(Eq. 1) $$P_{A_{CO_2}} = \frac{\dot{V}_{CO_2} \text{ ml STPD/min}}{\dot{V}_A \text{ ml BTPS/min}} \quad (863)$$

where 863 = mmHg/atm x STPD to BTPS conversion factor
$\dot{V}_{CO_2}$ = CO_2 production
$\dot{V}_A$ = alveolar ventilation

(Eq. 2) $$P_{A_{O_2}} = (P_B - 47)\, F_{I_{O_2}} - P_{A_{CO_2}} \left(F_{I_{O_2}} + \frac{F_{I_{N_2}}}{R}\right)$$

where P_B = Barometric pressure in mmHg
47 = water vapor tension at 37°C
F_I = fractional inspired concentration
R = respiratory quotient

The relationship between $\dot{V}_E$ and $\dot{V}_{O_2}$ ($\Delta\dot{V}_E/\Delta\dot{V}_{O_2}$) is reportedly 22-25. This is within the range that would be predicted from the alveolar ventilation equation (Eq.1) if dead space ventilation were normal (20% of total volume; $V_D/V_T = 0.2$) and the respiratory quotient were 0.8.

If the Eq: $$P_{A_{CO_2}} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} (863)$$

were rearranged, and $\dot{V}_{O_2} \times R$ was substituted for $\dot{V}_{CO_2}$, and $\dot{V}_E (1-V_D/V_T)$ was substituted for $\dot{V}_A$, the equation could be written as:

$$P_{A_{CO_2}} = \frac{.8\, \dot{V}_{O_2}}{.8\, \dot{V}_E} (863); \text{ or as: } \dot{V}_E/\dot{V}_{O_2} = 863/P_{A_{CO_2}} = 21 \text{ to } 25$$

for a $P_{A_{CO_2}}$ of 36-40 mm Hg.

Normally individuals increase tidal volume linearly as work load and $\dot{V}_{O_2}$ increase with exercise until approx. 70% of the FEV_1 is reached. As $\dot{V}$maxE is neared there is a tendency for the increase in tidal volume to level off (Pierce et al., 1968 and Saltin et al., 1968). Frequency of breathing frequency also increases linearly until approx. 2/3 of $\dot{V}$maxE, then f increases disproportionately when tidal volume begins to level off. Although the reason for shifting ventilation more toward increasing frequency is not known, it is imagined that the force development needed to expand the lungs to larger volumes becomes excessive and preference is given to developing a lesser force more frequently.

When exercise is extended beyond a moderate level in progressive steps, anaerobic metabolism with attendant lactic acid production increases disproportionately as the source of energy. At nearly the same time, ventilation increases out of proportion to the increase in oxygen consumption and work load. It has been proposed that the disproportionate increase in ventilation is caused by the rise in $[H^+]$ from lactic acid in arterial blood, which stimulates aortic and carotid bodies chemoreceptors, which in turn, drives the respiratory center in the brain. This phenomenon has been termed the "anaerobic threshold". The physiological interrelatedness of these two phenomena--the disproportionate increases in ventilation and lactic acid production--is by no means proven and is often the subject of heated controversy.

The important relationships to consider are: what is the maximum possible minute ventilation, and what is the maximum oxygen that can be transported at that level of ventilation. The normal functional capacities of the heart and lungs in a 70 kg healthy male at peak exercise are listed in Table 4.

TABLE 4

Normal Functional Capacities of the Heart and Lungs at Peak Exercise

Step	Functional counterpart	Capacity
1	Ventilatory capacity ($\dot{V}_{max}E$) in liters/min (BTPS)	197
2	Membrane diffusing capacity (DM_{O_2}) in (ml/min)/mmHg	102
3	Specific rate of O_2 uptake by red cells (θO_2) in (ml/min)/mmHg per ml pulmonary capillary blood*	2.8
	Pulmonary capillary blood volume (VC) in ml	205
2 + 3	Transfer coefficient for oxygen (DL_{O_2}) in (ml/min)/mmHg where $\frac{1}{DL_{O_2}} = \frac{1}{DM_{O_2}} + \frac{1}{\theta O_2 Vc}$	87
4	Maximal cardiac output ($\dot{Q}_{max}$) in liters/min	22.8
	O2 Capacity of blood (O_2cap) in ml O_2/ml blood	0.21
5	Maximal fractional O_2 extraction in tissues (O_2ext)	0.85

Source: *Staub et al. [6].

Maximum breathing capacity can be estimated by measuring the maximum voluntary ventilation (MVV) that can be sustained for 15 seconds. MVV also has been estimated from resting spirometric measurements. Various studies report the MVV equivalent to $FEV_{1.0}$ x 35 to 40.

The oxygen transport capacity that can be achieved at maximum ventilation has been approximated (Wehr and Johnson, 1979) and is listed in Table 5.

TABLE 5

Table 6 Approximate Capacity of Each Link in the O_2 Transport Chain at Sea Level

	Step	Approximate O_2 transport capacity (liters/min)
1	Ventilation[a]	$\dot{V}_{maxE}$ (liters/min STPD) $\times (1 - \frac{VD}{VT}) \times FI_{O_2} \times \frac{1}{4}$ = 6.4
2	Diffusion[b]	$DL_{O_2} \left(\frac{\text{liters/min}}{\text{mmHg}}\right) \times$ 70 mmHg = 6.1
3	Chemical reaction	
4	Cardiac output $\times$ O_2cap	$\dot{Q}_{max}$ (liters/min) $\times$ O_2cap $\times$ O_2sat $\times$ O_2ext = 3.9
5	Distribution, chemical release tissue diffusion	

[a] VD/VT = Ratio of deadspace ventilation to total ventilation. FI_{O_2} = Fraction of inspired oxygen (0.2093). 1/4 = Fraction of oxygen which can be utilized without the alveolar O_2 tension falling below 110 mmHg.
[b] 70 mmHg = Difference between alveolar and mean capillary blood O_2 tension which can be achieved at heavy exercise without allowing the end-capillary oxygen saturation to fall below 96%.

The steps required to determine the approximate oxygen delivered by a given level of ventilation are:

1. Estimate $\dot{V}_E$ max by multiplying the $FEV_{1.0}$ x 40. (Eg. if $FEV_{1.0}$ is 5.0 L, $\dot{V}$maxE is 200 L/min)

2. Convert $\dot{V}_E$ from BTPS to STPD. (Eg. at 37° and 750 mmHg atmospheric pressure, conversion factor is 0.8146)

3. Determine alveolar ventilation ($\dot{V}_A$) from $\dot{V}_E$ by subtracting out the dead space ventilation, V_D/V_T. (Eg. nl V_D/V_T is 0.25 and $1-V_D/V_T$ is 0.75)

4. Multiply by the fraction of gas that is O_2 ($F_{I_{O_2}}$). (Eg. ambient air is 21% O_2)

5. Multiply by the fraction of the inspired O_2 that can be removed without lowering the oxygen concentration to a level that would desaturate hemoglobin (Eg. Removing ¼ of the oxygen would reduce alveolar oxygen from 147 to 110 mmHg).

If $\dot{V}$maxE is 200 L/min BTPS in our 70 kg healthy man, then the predicted maximum O_2 transport capacity of the ventilation step is:

$$200 \times 0.8146 \times 0.75 \times 0.21 \times 0.25 = 6.4 \text{ } LO_2/min.$$

This value of 6.4 L/min is far in excess of the presumed $\dot{V}_{maxO_2}$ of 3.65 LO_2/min for this 70 kg man, age 25 yr.(see Table 1; $\dot{V}maxO_2$ = 52.2 ml/kg).

Thus, it is apparent that maximal alveolar ventilation, $\dot{V}$maxA, must be reduced 40-45% before this step alone could limit $\dot{V}maxO_2$ and consequently, maximal exercise.

2. Diffusion of gases and chemical reactions

The second step in the linked oxygen transport system is diffusion. The oxygen that was swept into the alveolae with the ventilatory apparatus now dissolves in the alveolar lining layer and moves across the alveolar-capillary membranes by passive diffusion according to the concentration gradient between alveolar air and capillary blood. The O_2 enters the red cell where it chemically reacts with hemoglobin to, in effect, remove the O_2 from solution, thereby maintaining a favorable gradient for further diffusion, as well as enhancing the O_2 capacity of the blood.

The time interval required for the hemoglobin saturation of the blood in the capillaries to rise to the equilibrium point with alveolar O_2 is a function of the barrier to diffusion and the concentration of O_2 driving the movement of gas across the barrier.

Because of extreme difficulties in knowing capillary O_2 tensions to enable us to determine the concentration gradient across the alveolar capillary membrane, diffusing capacity of O_2 is not frequently measured; rather, we measure the diffusing capacity for carbon monoxide (CO), which behaves similarly to O_2, and we can assume the capillary concentration of CO is zero. Taking into account the difference in solubilities and molecular weights of these two gases, the relative diffusibility of O_2 is 1.23 times that of O_2 (i.e., $D_{M_{O_2}} = 1.23\ D_{M_{CO}}$).

There are two components to the measured diffusing capacity of the lung for CO ($D_{L_{CO}}$): the membrane component (DM) and the red cell component. The red cell component includes the volume of hemoglobin in the capillaries, i.e., the capillary volume (V_C) of a stated Hgb concentration and the reaction rate of CO with hemoglobin, termed θ . The relationship is stated in terms of the resistance to diffusion of each component (Roughton and Forster, 1957):

$$1/D_{L_{CO}} = 1/D_{M_{CO}} + 1/\theta V_C .$$

During exercise, D_L increases (Johnson, 1967; Cassidy and Stray-Gundersen, 1983). This is caused by a nearly proportional increase in the capillary volume, presumably caused either by recruitment of additional capillaries associated with the increased blood flow and/or by distension of the existing capillary bed. The membrane component of diffusion does not change, or increases only slightly with exercise. The net result is that $D_{L_{CO}}$ does not increase as much as $\dot{V}O_2$ increases with exercise.

Once again, it is the capacity of these links to transport oxygen that is important in determining their potential to set a limit on $\dot{V}max O_2$ (Wehr and Johnson, 1976, and Johnson, 1980). The maximal $D_{L_{O_2}}$ is approximated by:

$$1/D_{L_{O_2}} = 1/1.23 \times D_{M_{CO}} + 1/\theta_{O_2} V_C = 87(\text{ml/min})/\text{mmHg}$$

Considering that: maximum V_C for our typical 70 kg man is 205 ml; the affinity of the red cells for O_2 is 2.8[(ml O_2/min)/mmHg]/ml blood; and measured maximal $D_{M_{CO}}$ is 83(ml/min)/mmHg; then:

$$1/D_{L_{O_2}} = 1/(1.23 \times 83) + 1/(2.8 \times 205) = 0.0115$$

$$D_{L_{O_2}} = 87(\text{ml/min})/\text{mmHg} .$$

By this approximation, the estimated maximal driving pressure for oxygen, i.e., the difference between alveolar oxygen tension and mean oxygen tension inside alveolar capillary red cells, which can be sustained without a fall in the O_2 saturation of blood leaving the lung during exercises, is 70 mmHg. Thus, the predicted maximum O_2 transport capacity of the diffusion and chemical reaction step is:

$$87 \times 70 = 6{,}090 \text{ ml } O_2/\text{min} = 6.1 \text{ L/min.}$$

This potential to transport O_2 through the diffusion and chemical reaction steps is still in excess of the $\dot{V}maxO_2$ that could be achieved in this individual. Thus, normal individuals are not limited at sea level by the constraints imposed on the transfer of O_2 from the alveolae to hemoglobin in the red cells.

3. Cardiac output:

Cardiac output, like ventilation, is coupled to metabolic rate through neural regulatory mechanisms that remain ill-defined. Cardiac output increases by 4-5 x resting values. The remainder of the increase in O_2 transport is brought about by an alinear widening of the A-$\dot{V}_{O_2}$ difference from 6.5 to 14.3 ml/100 ml.

The capacity of this link to transport oxygen is a function of maximum cardiac output ($\dot{Q}$), oxygen-carrying capacity of the blood (Hgb conc. x 1.34) x %Sat (96%), and the fraction of O_2 that can be extracted by the tissues. At exercise this fraction approximates 85%; thus,

$$\dot{V}maxO_2 = \dot{Q} \times .85 \times O_2 \text{ Cap} \times Sa_{O_2}$$

If the max $\dot{Q}$ of our 70 kg, 25y/o man is 22.8 L/min [Mitchell et al. (1957)]; then, the predicted maximum O_2 transport capacity of the cardiac-output-times-O_2-capacity step is:

$$22.8 \times .85 \times .21 = 3.9 \text{ L/min}$$

This value approximates the actual maximal $\dot{V}_{O_2}$ of 3.6 L/min. The relationship between the increase in $\dot{Q}$ and the increase in $\dot{V}_{O_2}$ (i.e., $\dot{Q}/\dot{V}_{O_2}$) with exercise was 6.1 (Mitchell et al., 1957), and this agrees with our predictions ($23 \div 3.9 = 5.9$).

4. Pulmonary vascular resistance:

One of the ways that lung disease might impose a limit on exercise performance is by virtue of the possibility of accompanying pulmonary hypertension that could be made worse by exercise. Normal man does not elevate his pulmonary artery pressure (P_{PA}) to any substantial degree with exercise [$P_{PA}/\dot{Q}$ = 0.6 mmHg/(L/min)]; however, pulmonary hypertension may occur with various degrees of severity in all forms of lung disease and needs to be considered separately as an additional, functional impairment that may limit exercise capacity in patients with lung disease.

5. $\dot{V}_A/\dot{Q}$ equality:

When the regional distribution of ventilation is proportional to the regional blood flow, ventilation and perfusion are said to be matched. In this ideal situation, alveolar (A) P_{O_2} would be equivalent to end-capillary or arterial (a) P_{O_2}, and there would be no A-a gradient for O_2, and gas exchange would be maximally efficient. In normal persons at rest, there is slight inequality in the relative distribution of $\dot{V}_A$ and $\dot{Q}$, which is thought to be caused by gravity. This is responsible for the normal resting A-a O_2 gradient of 5-15 mmHg. This small degree of inequality of $\dot{V}_A/\dot{Q}$ becomes even less during exercise; thus, efficiency of gas exchange approaches 1 with exercise in normal persons and does not noticeably lower our expectations for O_2 transport capacity in the preceding steps.

In summary

Normal individuals have the following responses to exercise:

1. Oxygen consumption increases in proportion to mechanical work load. An average, young man has

$$\dot{V}maxO_2 = 3.64 \text{ L/min.}$$

2. Ventilation is increased through neural control mechanisms in proportion to the increase in $\dot{V}_{O_2}$ up to moderate work loads;

$$\Delta\dot{V}_E/\dot{V}_{O_2} = 22\text{-}25.$$

At heavy work loads, $\dot{V}_E$ increases at a steeper slope. Max O_2 transported by ventilation in this average, young man is 6.4 L/min.

3. Diffusing capacity increases passively with exercise because capillary volume expands in proportion to the blood flowing through the lungs. Max O_2 transported through the diffusion steps in a young man is 6.1 L/min.

4. Cardiac output increases linearly with oxygen consumption; $\Delta\dot{Q}/\Delta\dot{V}_{O_2}$ = 6.0, and the arterial to mixed-venous oxygen difference widens alinearly. The Max O_2 transported by the cardiac output with normal O_2 capacity of blood in one average, young man is 3.6 L/min.

5. Pulmonary artery pressures increase minimally, but linearly, with exercise because pulmonary vascular resistance falls.

$$\Delta\bar{P}_{PA}/\Delta\dot{Q} = 0.6 \text{ mmHg/(L/min)}.$$

6. $\dot{V}_A/\dot{Q}$ matching improves with exercise, further enhancing the efficiency of the steps above.

Thus, the apparent bottleneck to maximum oxygen transport during exercise in normal individuals is cardiac output x oxygen-carrying capacity.

b. Obstructive lung disease

Diseases classified as chronic obstructive lung diseases (COPD) fall into one of three categories: asthma, chronic bronchitis, and emphysema. They all have in common expiratory flow limitation, and this is commonly quantified according to the degree of reduction in the fractional volume exhaled in 1 sec:

$$FEV_{1.0}/FVC$$

Values < 75% represent abnormal reduction in expiratory airflow.

Patients with asthma, which is defined as reversible airways obstruction, can experience unpredictable worsening of their obstruction with exercise, and this inconsistency of airways obstruction poses unique management considerations related to mediators of airways obstruction which will not be considered in this presentation, which relates pulmonary functional impairment to exercise limitation.

1. Work load

Patients with advanced COPD have a reduced capacity to perform muscular work (to exercise). Since normal individuals do not appear to be limited by the various respiratory functional capacities, our aim is to determine what derangements are responsible for the reduced capacity to exercise in these patients. The importance of this in the clinical setting is to be more knowledgeable with regard to individual patients' abilities and limitations, and to identify specific causes to which therapy could be directed. Capacity to exercise will be judged in comparison to that predicted from maximum oxygen consumption (Table 2) or maximum work loads. Several studies have examined the maximum exercise capacity in patients with COPD (Wehr and Johnson, 1976; Jones, et al., 1971; Hickam and Cargill, 1947; Nery et al., 1983; Blount, 1959; Raffestin et al., 1982).

On the average, the patients that have been reported have had a moderate-to-severe obstruction, meaning that $FEV_{1.0}$ was reduced to less than 50% of predicted values based on age, height, and sex, and that fractional reduction of $FEV_{1.0}$, compared to FVC, demonstrates an obstruction. In such patients, max work load was reduced, and the reduction was proportional to the reduction in $FEV_{1.0}$ ($r = 0.621$). In these patients of Jones (1971), predicted $\dot{V}maxO_2$ was 910 ml/min. However, there is tremendous variability, which suggests that factors other than obstruction to airflow limited the work capacity of these patients.

The lactic acid production is high for the work load imposed on these patients with COPD. This could mean that the patients were very unconditioned, which is a reasonable possibility in chronically ill patients. However, the high lactates also could reflect that some muscle groups, perhaps the respiratory muscles, were operating beyond their aerobic capacity.

Early in the studies of exercise limitation in COPD, it became apparent that patients with emphysema behaved differently from those with chronic bronchitis. Emphysema (also called Type A COPD) can be defined on a functional basis, demonstrating a loss of elastic recoil; whereas, chronic bronchitis (also called type B) demonstrates high airways resistance. Both derangements are associated with expiratory flow limitation. These two types of obstructive

lung disease can also be differentiated based on radiological criteria. In Jones' (1971) study, patients were divided into two groups, using both types of criteria. Patients with emphysema had worse limitation (max. workload, 442 kgm/min) compared to the chronic bronchitics (max. work load, 475 kgm/min) in spite of a less severe reduction of $FEV_{1.0}$ ($FEV_{1.0}$ = 1.01 L in emphysema, vs 0.77 L in chronic bronchitics).

2. Ventilation

If $\dot{V}maxE$ can be estimated from the $FEV_{1.0}$ (FEV_1 x 35), we would expect that the maximal ventilation would be higher in emphysematous patients compared to chronic bronchitics. Indeed, Marcus (1970) showed that $\dot{V}maxE$ was lower in chronic bronchitics as was ventilation for any work load. Using a uniform level of increased lactic acid production, Marcus et al. (1970) normalized the work load associated with a uniform level of anaerobic muscle metabolism. They found that ventilation at this level of work correlated closely (r = 0.78) with $\dot{V}_{O_2}$ in chronic bronchitics, but ventilation did not correlate (r = 0.059) with $\dot{V}_{O_2}$ in emphysematous patients. This was interpreted to mean that ventilation probably was a limiting factor in determining the exercise capacity in chronic bronchitics, but that other functional derangements were responsible for limiting exercise capacity in patients with emphysema.

These patients with emphysema have a higher ventilatory response to incremental $\dot{V}_{O_2}$ ($\dot{V}_E/\dot{V}_{O_2}$ = 36.6) compared to normals (25.9) and to chronic bronchitics (22.6). This difference in ventilatory responses to oxygen consumption is not because of a systematic difference in work loads, because Jones (1971) showed that ventilatory response to incremental work loads also was higher in emphysematous patients compared to chronic bronchitics ($\dot{V}_E/$ 100 kgm = 6.7 vs 4.6 L/kgm). The reason for this deviant control of ventilation is not clear, and will be addressed again later. When attempting to determine the cause of arterial desaturation with exercise, Minh et al. (1979) found the FEV_1 to be lower in the group that desaturated, but exercise Pa_{CO_2} was not different, 42 vs 41 mmHg. They did not measure D_{LCO}, but did find that mixed venous saturation was the same in both groups (33.6 vs 33.8%), and concluded that hypoventilation and a lowered mixed venous O_2 were excluded as causes, and presumed that worsening of this matching of ventilation with respect to perfusion accounted for the desaturation. Cardiac output was the same (8.3 vs 8.4 L/min).

Presumably, if patients are limited in their ability to perform exercise as a consequence of their lung disease, exercise would be terminated because of arterial desaturation, carbon dioxide retention, or limiting elevations in PA pressure. In many of studies, none of these hallmarks were present. This could have been because the subjects were unconditioned to perform either treadmill or cycle ergometer exercise.

In at least one study (Wehr and Johnson, 1979), the individuals underwent a three-week training program until maximum $\dot{V}_{O_2}$ was reproducible. In all six patients with COPD (not categorized as to Type A or B), CO_2 retention occurred at $\dot{V}max O_2$ (avg. Pa_{CO_2} 42±4 mmHg at rest and 62±9 during max exercise). Arterial desaturation was variable, sometimes increasing, sometimes decreasing.

3. Diffusing Capacity

D_{LCO} measured at rest also was different between the group of patients whose lung disease was classified as emphysema vs those whose disease was classified as chronic bronchitis.

Using physiological criteria (excluding D_L) to classify patients, Marcus (1970) found complete separation of the pure forms of the two types of patients based on their D_L. A group meeting criteria for both chronic bronchitis and emphysema overlapped with the two groups somewhat, but largely were representative of the emphysematous patients. In Jones' patients, also, D_L was lower in the patients classified as having emphysema in comparison to the chronic bronchitics [10.81 vs 15.59 (ml/min)/mmHg]. This reduction of D_L in the patients with emphysema was very nearly 35% of predicted values. This severe of a reduction in D_L would be expected to cause desaturation with exercise because, with exercise, the time spent in the pulmonary capillaries by the red cell is not long enough to reach equilibration with the alveolar oxygen tension at the reduced rate of oxygen transfer. Owens et al. (1984) found the diffusing capacity to be a good predictor of the patients that would desaturate on exercise. In 48 patients who were not classified as to type of COPD, not one of the 20 patients (0%) with a D_{LCO} greater than 55% of that predicted, desaturated on exercise, while 19 out of 28 patients (68%) with a D_{LCO} lower than 55% of that predicted, desaturated (i.e., lowered Sa_{O_2} > 3%). This contrasts with the $FEV_{1.0}$ in which two out of eleven patients whose $FEV_{1.0}$ was above 55% of that predicted, desaturated with exercise; and two out of sixteen (13%) of those with FEV, between 35 and 55% of that predicted, desaturated on exercise. Over 80% of the patients with either a D_{LCO} or FEV_1 < 35% of that predicted, would desaturate on exercise. Thus, a D_{LCO} > 55% was 100% specific in excluding arterial desaturation on exercise.

4. Cardiac output

Similar to many previous investigators, Jezek et al. (1973) found cardiac output to be proportional to $\dot{V}_{O_2}$ in 50 patients with COPD, and that there were no differences in cardiac output responses to exercise among three groups (no, mild, or severe cor pulmonale). The A-$\dot{V}_{O_2}$ difference widens in the range of normal.

This contrasts with the primary limitation in patients with heart disease who fail to increase cardiac output in the normal relation to $\dot{V}_{O_2}$. Rather, they widen their A-$\dot{V}_{O_2}$ difference (Hickam and Cargill, 1947). This evidence may seem weighted against cardiac output being a limiting factor to exercise through either an LV or an RV mechanism. However, of Jezek's patients, the group with severe cor pulmonale secondary to COPD did not increase stroke volume with exercise. Khaja and Parker also found that those patients with COPD who were in cor pulmonale at the time of the study did not increase their stroke volumes with exercise. This is in contrast to equally severe COPD patients who were not in cor pulmonale and who did increase stroke volume appropriately.

a) Pulmonary vascular resistance

Pulmonary arterial pressures are elevated in virtually all patients

with COPD who were studied with exercise (Blount, 1959; Hickam and Cargill, 1947; Burrows et al., 1972; and Mahler et al., 1984), but few investigators have studied patients with mild lung disease. At rest, the elevations of pulmonary arterial pressures may seem minimal in patients not in cor pulmonale.

The rise in pulmonary arterial pressure in response to exercise is much greater in most patients with COPD compared to normals. The higher the vascular resistance, the greater will be the increase in pulmonary arterial pressure with exercise. Pulmonary vascular resistance did not change with exercise in Burrows' (1972) patients, but did increase slightly by about 25% in Mahler's (1984) patients. In the patients with COPD, who had severe cor pulmonale that were studied by Rubin and Peter (1981), PA pressures increased from 52-68 mmHg in response to exercise, and the pulmonary vascular resistance did not change (10.8 vs 10.1 units). They found that when $\dot{V}_{O_2}$ was increased from 336 to 717 ml/min, stroke volume rose by only 6 ml (from 42 ml at rest to 48 ml at exercise). In those patients, the $\Delta\dot{Q}_C/\Delta\dot{V}_{O_2}$ was 4.7 which is lower than expected (6.1). Thus, the increase in pulmonary arterial pressure with exercise is predictable from resting measurements of pulmonary vascular resistance.

The important question is to what extent the rise in pulmonary arterial pressure will limit exercise performance. Matthay et al. (1980) evaluated similar patients with regard to RV function as assessed by first pass radionuclide studies. RVEF was abnormal at rest in 8/30 patients. RVEF failed to rise or actually decreased in 23/30 patients. $\dot{V}_{O_2}$ and heart rate were equivalent among those patients classified as having normal vs abnormal RV responses to exercise; however, the work load achieved was much higher in the group with the normal RV function, 418 vs 274 kp m/min. All patients with severe airways obstruction had abnormal RV responses to exercise. In the patients with mild-to-moderate obstruction (FEV_1/FVC between 40 and 70%), there was no discernible difference in FEV_1 between the normal and abnormal responders. Resting Pa_{O_2} tended to be lower in the abnormal responders, and one might suppose that this would correlate with higher vascular resistance. However, Sa_{O_2} did not fall in either group with exercise, 93% vs 96%; nor did Pa_{CO_2} rise in either group with exercise, 34 vs 32 mmHg. Thus, while it is clear that the elevated pulmonary vascular resistances and pulmonary artery pressures adversely influence right ventricular function in patients with COPD, it is not apparent that their exercise potential is primarily limited by the altered right ventricular function.

Even though control mechanisms linking cardiac output to oxygen consumption remain normally operative, the increase in cardiac output is accomplished with a small stroke volume and relatively higher heart rate. Thus, at maximal heart rate, it can be predicted that maximal cardiac output will be reduced.

b) LV function

The issue as to whether the left ventricle functions normally in patients with COPD has been raised repeatedly over many years. Khaja and Parker (1971) examined left ventricular function in patients with COPD; and, regardless of whether cor pulmonale was present, LVEDP was normal at rest, 6.9-7.0 mmHg, and increased normally with suppine exercise to 11.0-12.2 mmHg. On the other

hand, RVEDP increased to abnormal levels with exercise, changing from 3.3 mmHg to 9.5 mmHg in the absence of cor pulmonale and from 4.8 mmHg, rising to 11.1 mmHg in the presence of cor pulmonale. In the latter group, stroke volume did not change with exercise, implicating a cardiac limitation in this group.

This reduced LV stroke volume could be the consequence of reduced left ventricular filling caused by a limited RV output or by the encroachment of the overly-filled RV at end-diastole on the LV chamber (the phenomenon of ventricular interdependence). However, it has been suggested that LV function might be adversely altered in patients with COPD.

To address that issue, Matthay (1980) employed radionuclide assessment of RV and LV function to determine the cardiac response to exercise in 30 patients with COPD, four of which had cor pulmonale, and in 16 normal subjects. Normal LVEF was 67%; range 55-80%; response to exercise was +7% to +17%. Normal RVEF was 54%; range 48-63%; response to exercise was +6% to +26%. LVEF showed an abnormal response to exercise in six out of 30 patients, four of which were normal at rest. In the remaining 24 patients, 22 demonstrated a normal response to exercise, increasing by +5 to +18%. The other two had ejection fractions of 75% at rest, and the failure to rise with exercise was considered probably normal. Thus, normal LV function and reserve were present in the majority, 80%, of patients with COPD. The patients with abnormal LV function and reserve were equally distributed among the mild, moderate, and severe classifications of COPD, and between those with and without abnormal RV function. Also, there were no significant differences with respect to blood gas values. Thus, it was not felt that the occasionally impaired LV function was related in any way to the lung disease or the associated RV disease.

5. $\dot{V}_A/\dot{Q}$ inequality

We have learned that certain types of $\dot{V}_A/\dot{Q}$ inequality, those in which a large proportion of blood perfuses regions with $\dot{V}_A/\dot{Q}$ ratios < 0.1, is responsible for the hypoxemia associated with chronic bronchitis. Patients with emphysema are not often hypoxemic at rest. This is because they have very little blood flow perfusing regions of low $\dot{V}_A/\dot{Q}$; rather, they have an inordinately large number of regions with high (> 3.0) $\dot{V}_A/\dot{Q}$ ratios. These $\dot{V}_A/\dot{Q}$ inequalities explain the relatively high $\dot{V}_E/\dot{V}_{O_2}$ in patients with emphysema and the low-to-normal $\dot{V}_E/\dot{V}_{O_2}$ ratios in patients with chronic bronchitis. Wagner et al. (1977) showed that patterns of $\dot{V}_A/\dot{Q}$ inequality did not change in either direction during exercise in a group of patients with COPD. They found that with exercise as with resting measurements, all of the abnormalities in arterial P_{O_2} could be explained by the $\dot{V}_A/\dot{Q}$ inequalities. They did not feel that diffusion was a limiting factor to exercise in these patients. This may have been because only a small fraction, 3/10, of their patients that were exercised, had substantially lowered D_{LCO} (< 50% predicted). Based on more recent studies on normal subjects at high altitude, where exercise-induced desaturation occurs, Wagner recently has softened his position on this question and now believes that a diffusion impairment can cause exercise-induced desaturation.

In summary

1. Patients with emphysema (Type A) differ from chronic bronchitics

(Type B) not only in their physiological dimensions, but also in their responses to exercise.

2. Both types of COPD (A and B) display a reduced capacity to perform muscular work.

3. The ventilatory response, $\dot{V}_E/\dot{V}_{O_2}$, tends to be elevated in Type A and normal to reduced, in Type B: Both types exhibit ventilation-limited exercise performance and retain CO_2 at $\dot{V}max O_2$.

4. Diffusing capacity is reduced in patients with a component of emphysema. With exercise, 85% of these patients will develop arterial desaturation if the D_{LCO} is < 55% of predicted. Above 55%, desaturation is not likely to occur

5. Cardiac output responses to exercise were normal in relation to $\dot{V}_{O_2}$ when cor pulmonale was absent. This suggests that the heart, and particularly, the RV were able to generate appropriate cardiac output responses to increased work loads in spite of increasing PA pressures and lowering the RV ejection fractions.

6. Pulmonary vascular resistance changes very little with exercise in patients with COPD. At rest the PVR is variably elevated, in part influenced by the level of desaturation and the level of P_{CO_2}. Thus, elevated PVR is more prevelant in Type B COPD, and Type B patients are more likley to develop cor pulmonale.

7. $\dot{V}_A/\dot{Q}$ inequality is different between the two types of COPD, also. Patients with emphysema have a large proportion of regions with high $\dot{V}_A/\dot{Q}$ ratios (also called physiological dead space ratios), which are responsible for the high ventilation with respect to the work load ($\dot{V}_A/\dot{V}_{O_2}$). Patients with emphysema do not have regions of low $\dot{V}_A/\dot{Q}$ ratios or shunts; therefore, they are not hypoxemic at rest. Patients with chronic bronchitis have large proportions of low $\dot{V}_A/\dot{Q}$ ratios and no high $\dot{V}_A/\dot{Q}$ ratios; and, therefore, chronic bronchitics are hypoxemic at rest. $\dot{V}_A/\dot{Q}$ ratios do not change with exercise.

C. Interstitial Lung Disease

Patients with interstitial lung diseases are characterized physiologically as having reduced lung volumes with increased elastic recoil. This is reflected in a reduced FVC measured by spirometry. The FEV_1 is reduced proportionally unless airways disease is a complicating feature of the illness. Although not essential to making a diagnosis of interstitial lung disease, a reduced diffusing capacity is found in many of these patients. Pulmonary hypertension, which may be caused indirectly by the fibrosing process or may be the result of primary involvement of the pulmonary vascular bed, is a variable, complicating feature of interstitial lung disease. Thus, the same potential limitations to exercise that were observed in patients with COPD are present:

1) A limited ventilatory response;
2) Desaturation caused by failure of end-capillary oxygen tension to reach equilibrium with alveolar gas (i.e., a diffusion impairment); and

3) Inability to augment right ventricular stroke volume because of pulmonary hypertension.

In addition, patients with interstitial lung diseases, especially those associated with connective tissue disorders, may have cardiac involvement of the primary disease process. The responses to exercise of this group of patients has not been as extensively studied as has exercise in patients with COPD.

1. Work performed (Power output)

Often these patients are studied at designated rather than maximal work loads. Maximal work load was reduced to approximately 64% in 16 patients with ILD, studied by Bye et al. (1982). In these patients, FVC was reduced comparably (60%); but the correlation ($r = .546$), while significant ($p < .05$), is not tight and suggests that factors other than vital capacity influence the work output. $\dot{V}maxO_2$ was reduced 56% in their study. In similar patients who had a more severe restriction in lung volume (reflected in an FEV_1 = 50% predicted), studied by Wehr and Johnson, $\dot{V}maxO_2$ was reduced even further (45% predicted), consistent with the direct relationship between lung volumes and $\dot{V}maxO_2$.

2. Ventilation

This reduction in $\dot{V}maxO_2$ paralleled the reduction in maximal ventilation, $\dot{V}_E$ (Wehr and Johnson). $\dot{V}_E/\dot{V}_{O_2}$ was increased (34.8 L/L; normal = 25 L/L) just as it was for the emphysematous patients, which indicates a large number of regions with high $\dot{V}_A/\dot{Q}$ ratios. Maximal ventilation was very closely related to the FEV_1 (Wehr and Johnson):

$$\dot{V}_E(L/min) = 35.5\ FEV_1(L) - 2.7;\ (r = 0.871)$$

Thus, these patients at maximal exercise, are ventilating at their maximal breathing capacity. This is in contrast to normal individuals who only utilize only about 60% of their maximal breathing capactiy.

As opposed to studies in patients with COPD, patients with ILD retained CO_2 only slightly at maximum exercise (35 mmHg at rest vs 37 mmHg at maximum exercise; Wehr and Johnson). This is indicative of a normal neural response, and further underscores the abnormal control exemplified in patients with COPD, who on the average, retained 20 mmHg CO_2.

This has prompted a more intense exploration of the factors regulating $\dot{V}_E$ including the pattern and timing of breathing. Tidal volume at any designated work load or level of ventilation is reduced in patients with ILD, compared to normals (Burdon et al., 1983).

Frequency of breathing was elevated at rest and at designated work loads in patients with ILD compared to normals. Frequency (f) of breathing is also expressed as the reciprocal of f; i.e., the time of one respiratory cycle, which is termed T_{TOT} for the total time of the respiratory cycle. The fraction of time spent in inspiration, termed T_I, is a function of the force developed by the inspiratory muscles. T_I is reduced, as well as tidal volume, even before maximal ventilation and tidal volume are attained, and the fractional time spent in inspiration, which is often expressed as the ratio , T_I/T_{TOT} , is shortened.

These findings have been interpreted as adaptive by Burdon et al. (1983). The increased elastance associated with pulmonary fibrosis imposes an impedance to the action of the inspiratory muscles. The peak force is the product of the tidal volume and the elastance of the respiratory system. The maintenance of a given tidal volume in the face of high elastance requires a large peak intensity of inspiratory muscles, which could result in diaphragmatic fatigue in spite of normal respiratory muscle power. Thus, this pattern of reduced tidal volume that was adapted by patients with ILD would be expected to delay the onset of respiratory muscle fatigue.

Reduction in peak force was accompanied by an increase in the frequency of force development (i.e., f of breathing) which increases the total force developed. However, a shortening of the duration of force development in each breath (i.e., a reduction in T_I/T_{TOT}) serves to minimize the total force generated by the inspiratory muscles over a period of time. This maximizes their ability to maintain force development without fatigue.

Keogh et al. (1984) also found that patients with idiopathic pulmonary fibrosis (107 patients), and sarcoidosis (42 patients), who might be supposed to have increased elastic loads imposed on the respiratory muscles, also minimized the force development of the inspiratory muscles needed to increase ventilation by increasing tidal volume by 100% and by increasing f of breathing by over 200%.

3. Diffusing capacity

The extent to which D_{LCO} may be reduced is a variable function of the specific disease and the extent of involvement. Diffusing capacity varies with lung volume. In normal subjects without lung disease, this is such a constant relationship that the ratio of diffusing capacity per unit lung volume, D_L/V_A, is reasonably constant among individuals of varying sizes. However, diffusing capacity tends to decrease less than proportionately as lung volume is reduced from total lung capacity (TLC) within each individual (Rose et al., 1979). Thus, if lung volume is reduced without a concomitant loss of capillary bed or change in the structure of the membrane, then the constant, D_L/V_A, rises. A reduction of lung volume from TLC to approx. half way between TLC and functional residual capacity (FRC) raised D_L/V_A about 10-15% and by about 20-25% when lung volume was reduced to near FRC. There is substantial variability in this relationship, and some investigators had reported that diffusing capacity does not vary at all as lung volume varies above tidal volume. However, several years ago this variance was found to result from hysteresis of the alveolar surface area (Cassidy et al., 1980). If lung volumes are reached by expanding from FRC, the D_L will be lower than if the lung is expanded to TLC and then deflated to a comparable lung volume. D_L actually decreases very little as lung volume decreases from TLC. This hysteresis effect is desirable when exercising because keeping the alveolar-capillary membrane expanded will increase D_L and enhance diffusion

related oxygen transport.

This is relevant when intrepreting the significance of a reduced D_{LCO} in the setting of restricted lung volumes in order to establish whether the disease process has altered the alveolar capillary membrane independently of fibrosing and restricting the expansion of the lung.

From a functional point of view it is the total diffusing capacity of the lung, not D_L/V_A, that will determine the rate at which oxygen can be transfered from alveolar air to the blood in the capillaries.

In 31 patients with sarcoidosis reported by Matthews and Hooper (1983), D_{LCO} was 75.8% predicted (not a value we usually consider abnormal). When their patients were grouped according to radiological criteria, eight out of 18 patients with parenchyma disease, as well as hilar adenopathy, had a D_{LCO} < 70% of predicted. Whereas, two out of nine patients had reduced D_{LCO} in the group with adenopathy alone, and the D_{LCO} in both these patients was 68% of predicted. He found only an occasional patient who desaturated on exercise. Thus, radiological criteria do not necessarily correlate with functional derangements that would limit exercise performance.

Wehr and Johnson (1979), nine patients, and Baughman et al. (1984), 14 patients, reported sarcoid patients that had more severe reductions in diffusing capacity (< 50%), and their $\dot{V}O_2$ was reduced by 48% correspondingly.

In addition to the restrictive and elastic loads that these interstitial lung diseases impart on their hosts, diffusing capacity may be sufficiently reduced to cause end-capillary blood to leave the lung during exercise before equilibration with alveolar air is complete. This causes exercise-induced desaturation which is usually severe. In the patients with ILD (including the eight sarcoid patients reported by Wehr and Johnson), Pa_{O_2} fell from 76 mmHg at rest to 56 mmHg with maximal exercise. Saturation fell from 93% at rest to 82% with exercise. Thus, in patients with ILD in contrast to COPD, hypoventilation can account for practically none of the exercise-induced hypoxemia, which occurs primarily as the result of a decreased diffusing capacity.

4. Cardiac Output

The relationship between cardiac output and $\dot{V}_{O_2}$ was found to be normal in patients with ILD reported by Wehr and Johnson and many others.

Pulmonary hypertension is variably present, but studies of the responses of PA pressures to exercise in patients with ILD are rare. An exception is in patients with ILD who are in cor pulmonale. Three such patients were reported in Rubin and Peter's series (1981). In these patients, whose PA pressures were 56 mmHg rising to 79 mmHg with exercise, $\dot{V}_{O_2}$ increased from 410 to 705 ml. Cardiac output rose minimally from 4.5 to 5.1 L/min. This small increase in $\dot{V}_{O_2}$ caused the A-V O_2 difference to widen from 9.1 to 14.0 ml/100 ml blood. This contrasts with an A-V O_2 difference of 6.5 ml that would be expected in a normal suppine-exercising subject (Ekelund and Holmgren; 1967). Thus, the response to exercise in patients with ILD and cor pulmonale is characteristic of patients with cardiac disease.

Baughman et al. (1984) studied right and left ventricular function in 14 patients with sarcoidosis. LV function was normal (LVEF rose by > 5% with exercise) in all but two patients. RV function was abnormal at rest in three patients and responded to exercise abnormally by falling in all but two patients. The RVEF at exercise correlated positively with TLC, r = .83; with D_{LCO}, r = .58; and with exercise Sa_{O_2}, r = .74. Although sarcoidosis may involve the heart in as many as 10% of the cases, RV lesions are rare with respect to LV lesions. Thus, the isolated abnormalities in RV function probably reflects pulmonary hypertension.

Cardiac function is also abnormal in progressive systemic sclerosis. Follansbee et al. (1984) found that 20 out of 26 patients had abnormal redistribution of thallium scans. Coronary artery disease was excluded by coronary angiography, thus indicating abnormalities in microcirculation. This was associated with impaired RV and LV function. These findings occur less often in patients with CREST syndrome (Follansbee, 1984). Thus, in patients with ILD, cardiac output responses to exercise are normal in the absence of severe cor pulmonale unless there is primary involvement of the myocardium, as seen in certain patients with scleroderma.

5. $\dot{V}_A/\dot{Q}$

A large proportion of the lung is relatively over-ventilated (i.e., contains regions with high $\dot{V}_A/\dot{Q}$ ratios > 3.0), which accounts for the high $\dot{V}_E$ relative to the $\dot{V}_{O_2}$. There is mild hypoxemia at rest, which is entirely accounted for (West, 1977) by the profusion of regions with mildly reduced $\dot{V}_A/\dot{Q}$ ratios. These are not as prominent a feature as in patients with chronic bronchitis. During exercise, the hypoxemia cannot be accounted for by the perfusion of low $\dot{V}_A/\dot{Q}$ regions, indicating the failure of end-capillary blood to equilibrate with alveolar air.

In summary

Patients with interstitial lung disease have the following responses to exercise:

1. Work load or power output are reduced.

2. Exercise is limited by the maximal breathing capacity.
   a) Tidal volume is reduced relative to the $\dot{V}_{O_2}$ and the level of ventilation.
   b) Frequency of breathing is elevated relative to the $\dot{V}_{O_2}$ and $\dot{V}_E$.
   c) T_I/T_{TOT} is reduced to minimize force development.
   d) Severe CO_2 retention does not occur, indicating intact neural control.

3. Diffusing capacity is usually severely reduced, but this is not invariable, and is responsible for arterial desaturation with exercise when present.

4. $\dot{V}_A/\dot{Q}$ disturbances are characterized by both moderate high $\dot{V}_A/\dot{Q}$ and mild low $\dot{V}_A/\dot{Q}$. This gives rise to mild hypoxemia at rest and increased physiological dead space with high $\dot{V}_E/\dot{V}_{O_2}$ responses to exercise.

5. Pulmonary hypertension is quite variable. If cor pulmonale is present, exercise will be limited out of proportion to the reduction in vital capacity and diffusing capacity.

IV. Prediction of $\dot{V}max O_2$ in patients with lung diseases

We have learned that each component of lung function when sufficiently impaired can reduce exercise or work performance. In other words, we can in a general sense predict that exercise performance or oxygen consumption would be reduced in the presence of an impairment in pulmonary function. There are many reasons why it might be practical to be able to quantify our prediction of the $\dot{V}max O_2$ that would be achieved in a patient with impairment of pulmonary function caused by lung disease.

To this end, Wehr and Johnson (1979) developed a nomogram to predict maximum oxygen consumption that could be attained in patients with normal cardiac reserve and various types of lung impairment.

This nomogram was based on the theoretical capacities to transport oxygen through the steps in the oxygen transport chain that are related to the lung, as were detailed earlier.

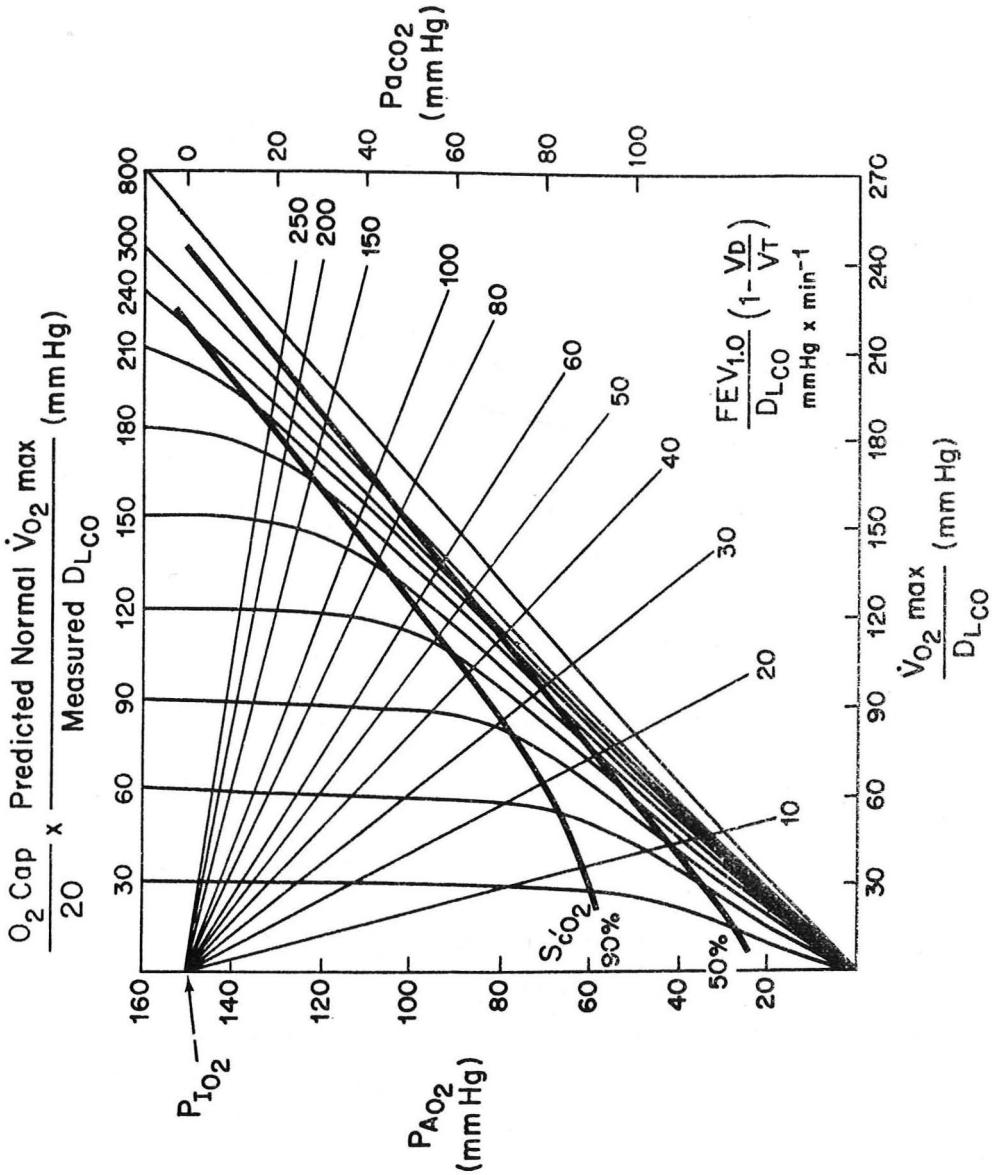
The nomogram appears complicated at first glance, but it is simple to use. The information needed is:

1. The patient's measured $FEV_{1.0}$.

2. The patient's measured D_{LCO}.

3. The patient's measured V_D/V_T.

4. The normal predicted maximal oxygen consumption (Table 2).



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If V_D/V_T measurements are not available, the error made by estimating V_D/V_T to be 50% will not be large.

Steps involved to obtain predicted $\dot{V}_{O_2}$ and alveolar gas tensions are:

1. Calculate and select the appropriate curvilinear isopleth along the top horizontal axis.

$$\frac{O_2\ Cap}{20} \times \frac{\text{Predicted Normal } \dot{V}maxO_2}{\text{Measured } D_{LCO}} \text{ (mmHg)}$$

2. Calculate and select the appropriate linear isopleth originating at the $P_{I_{O_2}}$ on the left vertical axis.

$$\frac{FEV_1}{D_{LCO}} (1 - V_D/V_T)$$

This set of isopleths is displaced downward when inspired oxygen tension ($P_{I_{O_2}}$) is lowered (i.e., at higher altitudes; Denver $P_{I_{O_2}}$ = 125 mmHg and Leadville, Colorado $P_{I_{O_2}}$ = 100 mmHg).

3. Read the predicted alveolar P_{O_2} off the left vertical scale.

4. Read the predicted arterial P_{CO_2} off the right vertical scale.

5. Read the $\dot{V}maxO_2/D_{LCO}$ off the bottom horizontal scale, and multiply this ratio by the D_{LCO} to obtain the $\dot{V}maxO_2$.

Patient I.M. (age 51 yr.; wt. 47.2 kg) exemplifies the use of the nomogram. His measured values are (Wehr and Johnson; 1979):

$$FEV_1 = 650 \text{ ml.}$$

$$V_D/V_T = 0.52$$

$$D_{LCO} = 19.2 \text{ (ml/min)/mmHg}$$

$$O_2 \text{ capacity} = 19.9 \text{ ml/100 ml}$$

$$\text{Predicted } \dot{V}_{O_2} \text{ max without lung disease} = 1{,}562 \text{ ml/min}$$

Calculate isopleths as follows:

1. Select appropriate curvilinear isopleth.

$$\frac{19.9}{20} \times \frac{1{,}562}{19.2} = 81$$

2. Select appropriate linear isopleth

$$\frac{650}{19.2} \times (1 - 0.52) = 16$$

3. These two isopleths intersect at 58, along the bottom horizontal axis.

4. Calculate $\dot{V}maxO_2$ based on the limitation in pulmonary function.

$$58 \times 19.2 = 1{,}114 \text{ ml/min}$$

I.M.'s measured $\dot{V}maxO_2$ was 910 ml.

The correlation between predicted and measured $\dot{V}maxO_2$ in these patients was very good ($r = 0.946$).

There is, however, a systematic error between the measured and the predicted $\dot{V}maxO_2$. Predicted $\dot{V}maxO_2$ overestimates actual $\dot{V}maxO_2$. The cause for this might be speculated as being due to our not incorporating measures of low $\dot{V}_A/\dot{Q}$ inequalities, or due to a degree of pulmonary hypertension, or due to incorrect estimates of peripheral oxygen extraction (est. 75%). Whatever the cause, it is not random and is an improvement over the wide variability of using single measures (such as the FEV_1) to predict maximal performance. The actual $\dot{V}maxO_2$ will be 70-80% lower than predicted.

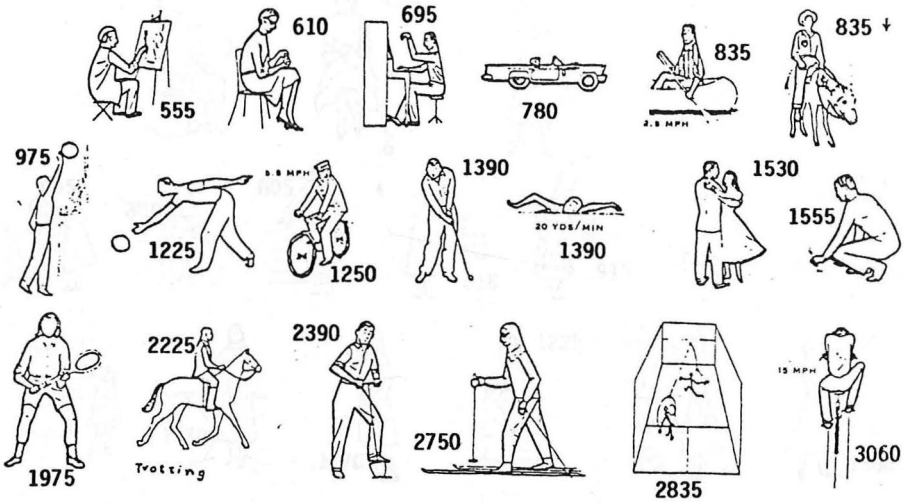
Having predicted the maximal oxygen consumption; and therefore, work capacity, the next step in using this information is to associate the individual's capacity to perform work with the oxygen or caloric requirements of individual tasks.

Attached is a pictorial table illustrating the oxygen costs of various recreational and occupational activities. It is taken from an article by E.E. Gordon, M.D.: "The Use of Energy Costs in Regulating Physical Activity in Chronic Diseases," A.M.A. Archives of Industrial Health, November, 1957.

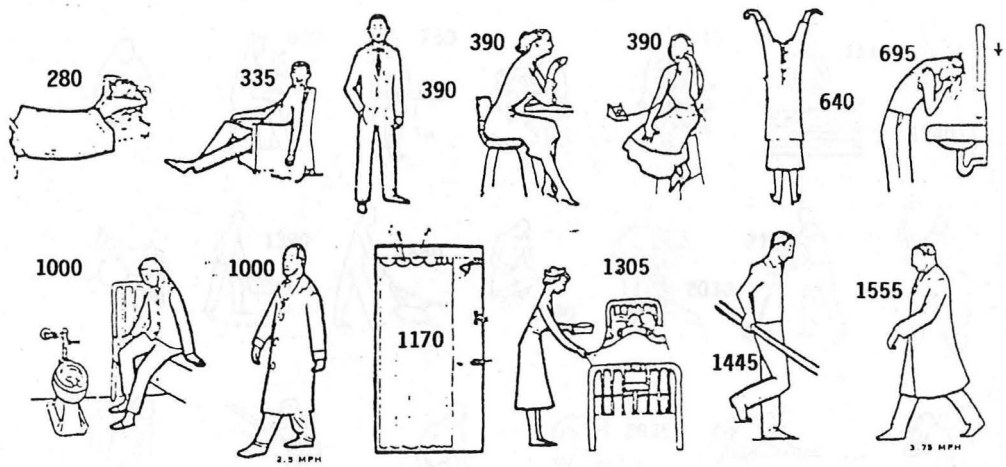
In normal individuals who are limited by their cardiovascular system, we know that $\dot{V}maxO_2$ can be sustained for only a few minutes, but that individuals can perform at 75% of their $\dot{V}maxO_2$ for hours. We do not know, however, the relationship between $\dot{V}maxO_2$ and endurance capacity in patients who have pulmonary limitations to oxygen transport. Thus, our patient I.M. with a measured $\dot{V}maxO_2$ of about 900 ml/min, 75% of which is 675 ml, would be limited to sedentary activities (those activities to the left of the arrow), and these may have to be interrupted for periods of rest. The patient could perform light housework but nothing as strenuous as scrubbing floors, washing windows, or making beds. We expect our patient could hold down a sedentary position that requires only fine motor skills, such as computer operator or an assembler in the construction of semi-conductors, but would be prevented from doing farm labor or heavy construction work. Even walking at 2.5 mph requires a higher level of $\dot{V}O_2$ than he can achieve. So, we expect he can walk only a few paces, then rest. It is of interest that showering would be prohibitive, and faintness when attempting to shower, is a frequent complaint of patients who are severely limited.

Up to this point these patients with lung diseases have been described and characterized in terms of their functional capacities and limitations. Disability is the term used to relate an impairment to its effect on a person's life. It is dependent on the energy requirements of the occupation or other

RECREATION



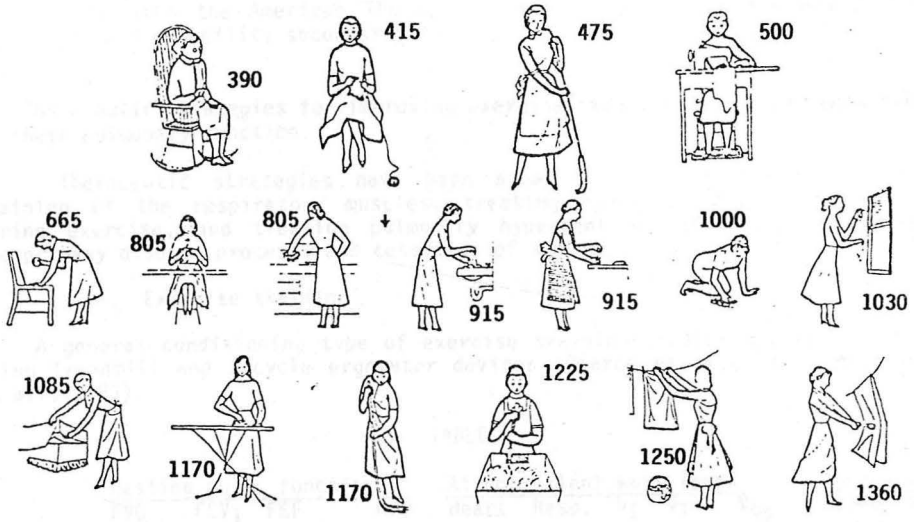
SELF CARE



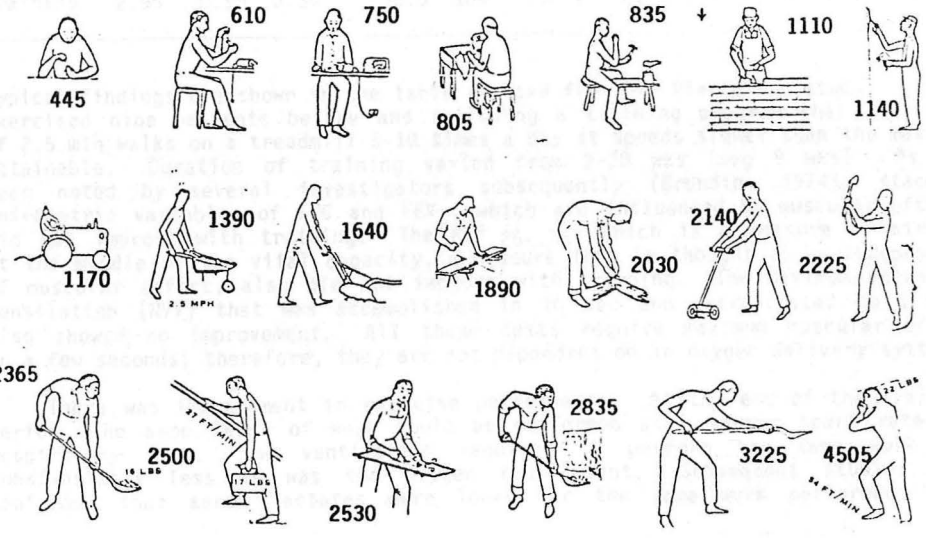
These illustrations indicate energy costs in ml O_2/min.

ENERGY COSTS OF VARIOUS ACTIVITIES

HOUSEWORK



OCCUPATION



These illustrations indicate energy costs in ml O_2/min.

activity in question and is influenced by such diverse factors as the person's age, gender, educational level, social and economic factors. Various social and political organizations have developed schemes to affix disability ratings to patients with lung diseases in the population with which the particular organization is concerned. Additional reading regarding disability ratings could begin with the American Thoracic Society statement on the evaluation of impairment and disability secondaray to respiraatory disease (1982).

V. Therapeutic strategies for improving exercise capabilities in patients limited by their pulmonary function.

Therapeutic strategies have been aimed at exercise training, exercise training of the respiratory muscles, treating hypoxemia with supplemental O_2 during exercise, and treating pulmonary hypertension, altering the course of the primary disease process, and cessation of smoking.

A. Exercise training

A general conditioning type of exercise training studies has been performed using treadmill and bicycle ergometer devices (Pierce et al., 1964; Mohsensifar et al., 1983).

TABLE 6

	Resting pulm. function				At equivalent work loads					At max work	
	FVC	FEV_1	FEF	MVV	Heart	Resp.	$\dot{V}_E$	V_T	$\dot{V}_{O_2}$	Speed	$\dot{V}_{O_2}$
Before Training	2.99	0.93	0.32	37.0	137	325	37	1.14	1,064	3.5	1,090
After Training	2.95	0.95	0.30	38.5	104	18.7	22	1.18	761	5.5	1,336

Typical findings are shown in the table adapted from Dr. Pierce's study. They exercised nine patients before and following a training program that consisted of 2.5 min walks on a treadmill 5-10 times a day at speeds slower than the maximum attainable. Duration of training varied from 2-20 wks (avg 8 wks). As has been noted by several investigators subsequently (Brundin, 1974), standard spirometric variables of FVC and FEV_1, which are influenced by muscular effort, did not improve with training. The $FEF_{.25-.75}$, which is a measure of airflow at the middle of the vital capacity, a measure that is thought to be independent of muscular effort, also did not improve with training. The maximum voluntary ventilation (MVV) that was accomplished in 10 sec and extrapolated to 1 min, also showed no improvement. All these tests require maximum muscular effort in a few seconds; therefore, they are not dependent on an oxygen delivery system.

There was improvement in exercise performance. At the end of the training period, the same level of work could be performed at a slower heart rate and respiratory rate. The ventilation required to perform the same work was substantially less as was the oxygen requirement. Subsequent studies have confirmed that serum lactates were lower for the same work performed, also

(Mohsenifar, 1983). Before training, ventilation approaches the maximum ventilation estimated from the MVV test (37 L/min vs 37 L/min); whereas, after training, they were not limited by ventilation at that work load. In addition to being able to perform work at a lower ventilatory cost and energy expenditures, they also found that maximum work performance, as measured by $\dot{V}O_2$, was increased by about 25%. Subsequently, Alpert et al. (1974) showed that cardiac output, left and right ventricular pressures, and stroke work were not influenced by physical training in these patients with lung disease.

Data such as these are interpreted as showing that, as a consequence of physical training, performance of physical work becomes more efficient. This improved efficiency may be the result of improved performance of the peripheral muscles and an increased extraction of the oxygen delivered. Work of breathing probably decreased since frequency of breathing decreased without a change in tidal volume, and the total inspiratory muscle force development was likely reduced. Thus, the improved efficiency also may be the result of increased efficiency of the respiratory muscles in which less oxygen is needed by the respiratory muscles for a given level of ventilation. Thus, patients with COPD benefit from an exercise training program. In the few studies that have addressed the question of the safety of patients with COPD undergoing an exercise training program, the presence of respiratory failure and/or cor pulmonale have not precluded a beneficial response to exercise. Thus, the potential hazards of respiratory failure and cor pulmonale have to be weighed against these potential benefit of improved exercise capacity. In all circumstances, the usual precautions to scrutinize for coronary artery disease and arrhythmias, as outlined by the A.H.A., should be judiciously adhered to.

B. Inspiratory muscle training

Inspiratory muscle training has been proposed for years to aid ventilatory performance in patients with lung diseases, especially COPD. This area has received renewed interest since Leith and Bradley (1976) demonstrated that respiratory muscle strength and endurance could be improved in normal subjects.

A group of subjects that underwent static respiratory muscle training by inspiring or expiring maximally against obstructed airways for 45 min/day were found to increase the maximum pressures generated by about 55%. Endurance estimated as the maximum voluntary ventilation that could be sustained for 15 min did not improve with this static training. Subjects that undertook an endurance training program of isocarbic hyperventilation to exhaustion daily did not alter the maximal static inspiratory and expiratory pressures they could generate, but were able to increase maximal ventilation that could be sustained for 15 min from 81% of the 15 sec MVV to 96%. Similar studies have been reported in patients with COPD. Belman and Mittman found that an isocapneic hyperventilation training program (15 min BID for 6 wks) in patients with severe COPD (FEV_1 = 0.85) improved their subsequent endurance time of submaximal treadmill exercise tests.

Static inspiratory muscle training programs do not seem to improve overall endurance, but recently there has been an interest in flow resistive training. Because a training program using flow resistive loading could be made to be simple and inexpensive and could be self-administered away from a laboratory setting, such devices would have great practical benefit. These devices are

simple mouthpieces with variable orifices. The benefit of respiratory muscle training using flow resistive devices is not clear, however. Sonne et al. (1982) demonstrated improved exercise performance following a flow resistive training program. Flow resistive training is associated with CO_2 retention, and Jederlinic has raised the possibility that the effect of training may not be to improve ventilatory muscle function, but to train the patient to accommodate to CO_2 retention. Asher et al. (1982) found that exercise endurance only slightly improved in a group of patients with cystic fibrosis following flow resistive training.

At best, ventilatory muscle training appears to achieve the same benefit on endurance exercise that general endurance training does. Thus, it appears that a general endurance exercise program, such as walking on a level grade at tolerable speeds to near exhaustion, which can be carried out in the patient's home environment, cannot be improved upon by ventilatory muscle training. The field of respiratory muscle performance is currently receiving a great deal of attention in many areas (acute and chronic respiratory failure, paraplegic victims, nutrition) as well as in exercise performance. Studies to better understand respiratory muscle fatigue, its causes, and how to measure it, and how to prevent or treat it are being investigated extensively in many centers including here.

C. Oxygen supplementation

The potential for improvement of exercise endurance in patients with exercise-induced hypoxemia is obvious. Even in normal subjects, oxygen supplementation increases endurance time and delays accumulation of lactate in the blood. Patients with interstitial lung diseases who have exercise induced hypoxemia have universally improved their endurance time when breathing supplemental oxygen (Bye et al., 1982; Todisco et al., 1977). Bye found that the degree of improvement in endurance time was proportional to the fall in oxygen saturation during exercise while breathing room air. The mechanism responsible for this improvement is not clear. It may improve systemic and respiratory muscle O_2 delivery and delay respiratory muscle fatigue. Pulmonary vascular resistance may be lowered also (Todisco et al., 1977).

It is of interest that $\dot{V}maxO_2$ did not improve with oxygen breathing. This suggests that the limitation to incremental maximal work performance might be tied to a different component of the oxygen transport system than is sub-maximal endurance time.

In patients with COPD , oxygen breathing improved endurance time, also (Bradley et al., 1978), but a correlation with either CO_2 retention, or the degree that oxygen saturation fell when breathing room air cannot always be found.

It would appear that oxygen supplementation would be an adjunct to general exercise conditioning in the attempt to improve exercise endurance in patients with lung disease, but when to use supplemental oxygen is not clear. Whether supplemental oxygen should be used to prolong endurance time beyond that which can be achieved with exercise training, or whether supplemental oxygen used concommitantly with an exercise training program would further lengthen endurance time is not yet known.

D. Pulmonary Vasodilators

Treatment of patients with cor pulmonale, whether caused by idiopathic pulmonary hypertension or by chronic interstitial or airway lung diseases, with vasodilators has been the subject of a recent Grand Rounds by Lewis Rubin. Improvement of exercise performance ($\dot{V}maxO_2$ or endurance time) has not been clear to date because resting values of cardiac output and $\dot{V}_{O_2}$ are usually altered, and because often these patients are not exercised to $\dot{V}maxO_2$ or to exhaustion at a submaximal work load. The reasons for the cautiousness in exercise testing of patients with severe pulmonary hypertension is their propensity to arrhythmias and sudden death. Keller et al. (1984) recently reported improvement in $\dot{V}maxO_2$, following hydralazine in four out of eleven patients with pulmonary hypertension secondary to COPD. The majority could not tolerate the combination of exercise and hydralazine because of arrhythmias, which illustrates the extreme caution that must be undertaken with the patients with severe pulmonary hypertension and vasodilator therapy and exercise. Dr. Rubin will soon be reporting their experiences with the effects of vasodilator therapy on exercise endurance time in patients with cor pulmonale.

E. Specific Therapy

Specific therapy for the individual diseases is beyond the scope of this discussion. Bronchodilators are employed in patients with bronchitis and emphysema. Anti-inflammatory and immunosuppressive drugs are used in patients with selected interstitial lung diseases.

The objectives in the treatment of interstitial lung disease are usually to prevent or to delay a premature death. Using a quantitative assessment of impairment, such as presented earlier, it is reasonable to propose that therapy could be directed also toward prevention or reversal of a designated degree of pulmonary disability in patients whose diseases might be disabling but not imminently fatal.

F. Smoking Cessation

Individuals with impairment in lung function can delay the progression of disability by ceasing to smoke.

Summary of Therapeutic Strategies

1. General exercise conditioning improves exercise performance and efficiency in patients with lung disease as well as in normal persons.

2. Specific training to improve inspiratory muscle strength and endurance can be accomplished by high ventilation and low load or a low-ventilation high load (flow resistive devices) as well as by general body conditioning exercises. The latter two can be accomplished in the patient's home environment.

3. Exercise endurance time can be prolonged with supplemental oxygen.

4. Vasodilators may improve exercise ability in selected patients with severe pulmonary hypertension, but exercise testing and exercise training

programs in these patients still should be approached with extreme caution.

5. Specific therapy is directed toward the individual diseases.

6. Recommend that the patient stop smoking.

When is exercise testing appropriate in patients with lung disease?

Reasons to subject patients with lung diseases to exercise testing come under two categories:

1. Exercise testing may be warranted in patients in whom symptoms indicate that they are limited in performing tasks out of proportion to that which would be predicted based on the abnormalities in pulmonary function tests (FVC, FEV_1, D_{LCO}, and $\dot{V}_D/V_T$). The Wehr/Johnson nomogram and E. E. Gordon's or other tables relating the energy (or O_2) requirements to various activities may be beneficial in assessing the appropriateness of the symptoms and the associated pulmonary functional impairment. If the work load performed or the $\dot{V}maxO_2$ are substantially less than predicted based on the respiratory impairment, other causes of reduced work performance or $\dot{V}maxO_2$, such as muscular weakness or cardiac disease, should be explored.

2. Exercise testing can be employed in patients with lung disease to answer specific questions related to their exercise performance. Effectiveness of the therapeutic strategies can be monitored. In this regard, the exercise test could be a simple test such as monitoring the distance that the patient can walk in 12 min (O'Reilly et al., 1982).

The question is often asked as to the appropriateness of exercise testing in determining the cause of dyspnea or limited endurance because of the differences in the pattern of responses of the various cardiac and respiratory diseases. The cause of the dyspnea usually is suspected or revealed upon taking a thorough history and performing a careful physical examination. If lung disease is suspected on the basis of the history and physical examination, confirmation should be sought with radiographs of the chest, pulmonary function tests (including spirometry, diffusing capacity and fractional physiological dead space), arterial blood gases, and electrocardiogram. Some or all of these tests should suffice to establish a diagnosis of chronic lung disease. If respiratory, cardiac, or muscle disease can not be substantiated, it may be desirable to document symptom limited reduction in exercise capacity with exercise testing.

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