Cardiopulmonary Function at Maximum Tolerable Constant Work Rate Exercise Following Human Heart-Lung Transplantation*

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Studies were performed measuring parameters of respiratory and circulatory function at rest and during maximum tolerable constant work rate treadmill exercise in 16 clinically well patients who had undergone heart-lung transplantation for end stage pulmonary hypertension. Ten patients were studied before and within eight weeks following transplantation. Long-term function with exercise was further evaluated with follow up studies at one year (n = 10) and two years (n = 6), posttransplantation. Posttransplant gas exchange and ventilation during exercise are essentially normal with neither being limiting to maximal exercise. Exercise capacity is significantly improved posttransplant,primarily as a result of improvement in the circulation over cardiopulmonary function during maximum constant work rate exercise in 16 clinically well patients who had undergone heart-lung transplantation.

The ability of the transplanted lung to maintain function during rest and exercise with the passage of time has a direct bearing on the clinical usefulness of heart-lung transplantation.

Standard measurements of pulmonary function indicate that the long-term function of the transplanted lung is well maintained for periods of time measurable in years, providing no complications arise.1,2 Gas exchange at rest remains essentially normal despite the persistence of a mild restrictive abnormality.

Pretransplant and posttransplant studies performed during exercise provide a more rigorous assessment of function in heart-lung transplant patients than is possible from standard pulmonary function measurements alone.

We report studies evaluating exercise capacity and that found pretransplant in uncorrected pulmonary hypertension. Although improved, circulatory limitations of maximal exercise may still persist. Cardiorespiratory function at maximum tolerable exercise is well maintained following heart-lung transplantation for at least two years, providing no complications occur. This suggests that denervation of the heart and lungs, disruption of the bronchial circulation and pulmonary lymphatics, and the graft ischemia encountered at the time of transplantation impose no serious limitations on long-term cardiopulmonary function. The overall functional capacities of the transplanted heart and lungs are more than adequate for meeting the activities of normal life.

METHODS

Exercise studies were performed in 16 patients (12 men, four women, ages 22 to 45) who had undergone heart-lung transplantation for endstage pulmonary hypertension (eight with primary pulmonary hypertension and eight with congenital heart disease and Eisenmenger's physiology). Ten patients (seven men, three women) were studied both before and within eight weeks following transplantation. The remaining patients were included in the long-term follow-up studies which were subdivided and grouped according to time intervals posttransplant, of less than six months and one year for one patient group, and less than six months, one year, and two years for the other. Project approval was granted by Human Subjects Committee review and informed consent was given by the patients prior to the study.

Pretransplant, all patients were clinically stable at the time of study although exercise tolerance was markedly compromised. All posttransplant studies were conducted after recovery from surgery, and at times thereafter, when the patients were without clinical complications and were physically well. No training sessions were conducted prior to study.

Standard physiologic parameters monitoring respiratory and circulatory responses during exercise were measured.3,4 Measurements were made at rest, in the standing position, and during increasing levels of constant work rate treadmill exercise to patient tolerance or termination by the physician in attendance as a result of complications (chest pain, ECG changes, hypotension, near syncope). Patients exercised for seven minutes at each work level with ten minute

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rest periods in between. Work rate was varied on the treadmill as a function of speed (MPH) and slope (percent grade).

The predicted values for VO2 max and maximum heart rate were derived from equations recommended by Jones and Campbell, and predicted O2 pulse was derived as predicted VO2 max/predicted maximum heart rate.4

Exercise results are expressed as those that were obtained during constant work rate exercise that was the maximum achievable by the individual patients. Although not directly established, a steady state or near steady state was assumed to be present when the end tidal CO2 was constant.

Pretransplant and posttransplant results in the ten patients were directly compared statistically by the paired Student’s t-test. In the long-term follow-up studies, the results between the respective time intervals are also statistically analyzed by the paired Student’s t-test since the results obtained compare each individual patient to himself/herself with respect to time.

RESULTS

Arterial Blood Gases

Table 1 shows the results (means ± SE) of arterial blood gas measurements obtained at rest and during maximum exercise before and within eight weeks following transplantation.

Pretransplant (pulmonary hypertension) blood gas values reveal marked impairment of gas exchange with hypoxemia (PaO2: 59.1 ± 5.4 mm Hg) and an increased P(A-a)O2 difference of 53.8 ± 5.6 mm Hg at rest, which become significantly worse during exercise. In contrast, posttransplant blood gases show normal oxygenation of arterial blood during both rest and exercise with the maintenance of a mean arterial PaO2 of 98.9 ± 1.5 mm Hg at maximum exercise in association with a P(A-a)O2 difference of 18.3 ± 1.7 mm Hg.

Alveolar hyperventilation, as reflected by the reduction in arterial PaCO2, persists following transplantation with no significant differences found for PaCO2 in comparing rest and exercise, and in comparing pretransplant with posttransplant values.

The significant falls in arterial pH and HCO3− concentrations occurring with posttransplant maximum exercise, in comparison to pretransplant values, primarily reflect a greater rise in posttransplant blood lactate.

Ventilation

Pretransplant and posttransplant results obtained during rest and maximum exercise for minute ventilation (Ve), the ventilatory equivalents for CO2 (Ve/VCO2) and O2 (Ve/VNO2), dead space ventilation (Vd/VT), and the minute ventilation to maximum voluntary ventilation ratio (Ve/MVV) are given as the means (± SE) in Table 2.
Posttransplant resting ventilation appears to be excessive as reflected by the mean resting VE of 15.0±2.0 L/min and the high ventilatory equivalents for CO₂ and O₂. Similarly, the resting Vd/VT is mildly elevated. At maximum exercise, the ventilatory equivalents for CO₂ and O₂ and Vd/VT rise significantly above resting values and are well above the expected normal values. Although VE may also be excessive at maximum exercise, in particular with respect to the O₂ consumption (Table 3), the mean VE/MVV ratio of 0.327±0.059 is still well below the upper limit of 0.7.

Posttransplant resting values for all of the ventilatory parameters are not significantly different from those found pretransplant, indicating that resting VE and dead space ventilation remain elevated following transplantation despite their somewhat lower values.

The posttransplant VE/VCO₂ and VE/V0₂ values at maximum exercise are not significantly different from the resting values. Thus, posttransplant, the rise in VE with maximum exercise over resting VE is appropriate for the O₂ consumed and the increased work performed (Table 3). The posttransplant mean VE/MVV ratio during maximum exercise is 0.342±0.044.

In comparing pretransplant with posttransplant ventilation during maximum exercise, the only parameters showing significant changes are the reductions in posttransplant Vd/VT, VE/VCO₂ and VE/V0₂ towards normal values. The VE and the VE/MVV ratio are not significantly different.

Circulatory Capacity

Mean data (±SE) for oxygen consumption (V0₂), heart rate, oxygen pulse, and blood lactates are shown in Table 3. Table 3 also shows mean values for the treadmill speed (MPH) and percentage of slope that was attained at maximum exercise.

Pretransplant, the mean level of maximum exercise achieved by the group is considered to be mild, as judged by treadmill speed (1.3±0.1 mph) and slope (0.9±0.4 percent). The changes seen from rest to maximum exercise reveal a twofold increase in VO₂ in association with relatively modest increases in heart rate, O₂-pulse, and blood lactates. The percentages of maximum predicted values are quite reduced at maximum exercise with VO₂, 24.2±2.0 percent, heart rate, 61.7±3.4 percent, and O₂-pulse, 41.3±5.3 percent.

Posttransplant exercise is significantly improved over pretransplant exercise. Changes from resting to maximum exercise reveal mean increases of 3.5-fold for VO₂, threefold for O₂-pulse, and sixfold for lactate concentrations, with only modest increases in heart rate. Posttransplant resting heart rate is significantly greater than the pretransplant value as a result of cardiac denervation. This increase in resting heart rate may also account, in part, for the modest increases in rates found between rest and maximum exercise, posttransplant.

At maximum exercise posttransplant, VO₂ is 39.3±2.6 percent, heart rate, 68.1±2.5 percent, and O₂-pulse, 57.4±2.5 percent of the maximum predicted values, with VO₂ and O₂-pulse being significantly greater than the pretransplant values and maximum heart rate remaining unchanged statistically.

<table>
<thead>
<tr>
<th>Table 3—Oxygen Consumption (V O₂), Heart Rate, Oxygen Pulse, and Lactates Before and Within Eight Weeks After Heart-Lung Transplant</th>
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<tr>
<td>VO₂ (ml/min/kg)</td>
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<td>VO₂ (% of Max Predicted)</td>
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<td>Heart Rate (beats/min)</td>
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<td>Heart Rate, % of Max Predicted</td>
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<td>O₂-Pulse, (ml/kg/beat)</td>
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<td>O₂-Pulse, % of Max Predicted</td>
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<td>Lactate (mM/L)</td>
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<td>Treadmill:</td>
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<td>Max Speed (MPH)</td>
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<td>Max Slope (% slope)</td>
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<td>(Mean ± SE)</td>
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<td>(n = 10)</td>
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Table 4—$\dot{V}O_2$, Heart Rate, $O_2$ Pulse, Ventilation and Blood Gases Obtained at Maximum Tolerable Constant Work Rate Exercise as Function of Time For One Year Posttransplant (N = 10)

<table>
<thead>
<tr>
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<th>Within Six Months</th>
<th>One Year (Paired Student's <em>t</em>-Test)</th>
<th>&quot;p&quot;</th>
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<tbody>
<tr>
<td>$\dot{V}O_2$ (ml/min/kg)</td>
<td>18.6 ± 1.8</td>
<td>19.4 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>$\dot{V}O_2$, % of max predicted</td>
<td>46.6 ± 4.1</td>
<td>49.3 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>136.8 ± 3.3</td>
<td>149.4 ± 4.1</td>
<td>&lt;0.05</td>
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<tr>
<td>Heart rate, % of max predicted</td>
<td>73.0 ± 1.7</td>
<td>79.8 ± 1.7</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>$O_2$ Pulse (ml/kg/beat)</td>
<td>.134 ± .010</td>
<td>.130 ± .009</td>
<td>NS</td>
</tr>
<tr>
<td>$O_2$ Pulse, % of max predicted</td>
<td>63.4 ± 4.5</td>
<td>62.2 ± 4.4</td>
<td>NS</td>
</tr>
<tr>
<td>$\dot{V}E$ (L/min)</td>
<td>44.8 ± 5.9</td>
<td>46.7 ± 5.2</td>
<td>NS</td>
</tr>
<tr>
<td>$\dot{V}O_2/VT$</td>
<td>.32 ± .03</td>
<td>.27 ± .05</td>
<td>NS</td>
</tr>
<tr>
<td>$PaO_2$ (mm Hg)</td>
<td>95.7 ± 3.5</td>
<td>92.0 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>$PaCO_2$ (mm Hg)</td>
<td>30.4 ± 1.4</td>
<td>30.1 ± 0.9</td>
<td>NS</td>
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<td>(mean ± SE)</td>
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Long-Term Follow-Up Studies

Tables 4 and 5 present mean data obtained from follow-up studies posttransplantation which compare the effects of time on maximal $\dot{V}O_2$, heart rate, $O_2$ pulse, ventilation, and blood gas levels for periods of up to two years.

In the group of ten patients studied at one year posttransplant (Table 4), maximal heart rate increases significantly at one year over heart rate values found at less than six months. All other parameters do not change significantly at one year in comparison to earlier values.

In the group of six patients studied over the two-year period (Table 5), the maximal values obtained are not significantly different for any of the time periods following transplantation.

Table 5—$\dot{V}O_2$, Heart Rate, $O_2$ Pulse, Ventilation and Blood Gases Obtained at Maximum Tolerable Constant Work Rate Exercise as a Function of Time For Two Years Posttransplant (N = 6)

<table>
<thead>
<tr>
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<th>Within Six Months*</th>
<th>One Year*</th>
<th>Two Years*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2$ (ml/min/kg)</td>
<td>18.9 ± 2.8</td>
<td>19.6 ± 2.2</td>
<td>20.2 ± 2.3</td>
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<tr>
<td>$\dot{V}O_2$, % of max predicted</td>
<td>50.3 ± 5.6</td>
<td>52.8 ± 4.0</td>
<td>55.2 ± 5.2</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>134.3 ± 4.7</td>
<td>145.0 ± 5.6</td>
<td>142.0 ± 6.0</td>
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<tr>
<td>Heart rate, % of max predicted</td>
<td>72.7 ± 2.2</td>
<td>78.6 ± 2.7</td>
<td>77.4 ± 3.7</td>
</tr>
<tr>
<td>$O_2$ Pulse (ml/kg/beat)</td>
<td>.139 ± .015</td>
<td>.134 ± .011</td>
<td>.142 ± .014</td>
</tr>
<tr>
<td>$O_2$ Pulse, % of max predicted</td>
<td>68.6 ± 5.7</td>
<td>67.3 ± 4.5</td>
<td>71.0 ± 5.1</td>
</tr>
<tr>
<td>$\dot{V}E$ (L/min)</td>
<td>44.2 ± 7.8</td>
<td>46.0 ± 5.2</td>
<td>46.7 ± 6.1</td>
</tr>
<tr>
<td>$\dot{V}O_2/VT$</td>
<td>.34 ± .05</td>
<td>.25 ± .06</td>
<td>.32 ± .05</td>
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<tr>
<td>$PaO_2$ (mm Hg)</td>
<td>93.6 ± 6.0</td>
<td>97.2 ± 3.5</td>
<td>92.8 ± 6.3</td>
</tr>
<tr>
<td>$PaCO_2$ (mm Hg)</td>
<td>30.4 ± 1.9</td>
<td>29.2 ± 1.4</td>
<td>29.6 ± 0.9</td>
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<tr>
<td>(mean ± SE)</td>
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The results in each time period are not significantly different when statistically compared to each other.

DISCUSSION

As an introduction to the main discussion, some comment regarding methodology is required in order to provide a proper perspective for the interpretation of results. The exercise protocol used best addressed the aims of our studies which were to determine if heart-lung transplantation improves exercise capacity in patients previously severely limited with pulmonary hypertension; and to define cardiac-respiratory function at the greatest level of sustainable exercise. In the latter, it was particularly important to determine if abnormalities of either the respiratory or circulatory systems were limiting exercise.

The seven-minute constant work rate protocol was used in order to obtain the most accurate data on gas exchange during exercise. Under these conditions, gas exchange should be less variable and more in phase with the level of exercise performed since the key variables $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ should be relatively constant, that is, until very heavy work loads are reached.7,8

In view of the repetitive nature of the protocol which required multiple runs of increasing levels of exercise to tolerance, fatigue may have become a critical factor. Therefore, maximum exercise in our studies probably more accurately represents maximum exercise tolerance. Endurance becomes more critical for sustaining exercise at the highest levels, which is quite different from that of peak exercise of short duration. We use exercise capacity and exercise tolerance interchangeably although there may be semantic differences. Since the same conditions existed for all studies, differences in exercise found should be valid for the comparison of pre-with posttransplant results.

Composition of the arterial blood gases during maximum exercise can be used as an index for determining the efficiency of pulmonary gas exchange. Under these conditions, the transplanted lungs are capable of essentially normal gas exchange. This would indicate that the integrating function required for matching ventilation and perfusion (ie, maintenance of proper $V/Q$ relations) is intrapulmonary and auto-regulatory in nature, and that an external nerve supply is not a crucial requirement for regulating gas exchange within the lung. Although independent validation of denervation is not available, eight weeks posttransplantation is too short a period for reinnervation to occur.9

Posttransplant ventilation appears to remain functionally normal without imposing limitations on exercise capacity. Although limitations of this nature may have been a concern prior to human heart-lung transplantation,10 our results indicate that this is not the case. At maximum constant work rate exercise and in the presence of alveolar hyperventilation, the $\dot{V}E$/MVV ratio remains well below 0.7, indicating that a
sufficient ventilatory reserve remains and that ventilation is not a factor in limiting exercise.

Ventilatory control during exercise also appears to be normal following transplantation. The slope of the \( V_{E}/V_{CO2} \) response relationship during submaximal exercise is not significantly different in heart-lung transplanted patients from that present in normal subjects and in heart transplanted patients with intact pulmonary nerve supplies. Since heart-lung transplantation results in denervation of the cardiopulmonary axis, the normal nature of posttransplant ventilation also suggests that pulmonary neural reflexes play a relatively minor role in the control of ventilation with exercise in normals as well.

Posttransplant, the proportion of wasted ventilation \( (VD/VTr) \) falls in a normal fashion during the transition from rest to maximum exercise. Despite the normal response, \( VD/VTr \) still remains mildly elevated with respect to the predicted values given for maximal exercise. The reason for this is not clear. Since, in uncomplicated cases, gas exchange at rest and exercise, pulmonary hemodynamics (at rest), and the distribution of ventilation, and airway dynamics are essentially normal, the mild elevation of \( VD/VTr \) does not appear to be of pathophysiologic significance.

The immediate (within eight weeks) and long-term (at least two years) improvement in posttransplant exercise is primarily the result of an improved circulation in comparison to that present with pulmonary hypertension preoperatively. This is evident from the increases in posttransplant \( VO_2 \), heart rate, and \( O_2 \)-pulse during exercise over that present pretransplant.

The greater lactate levels with posttransplant exercise are also consistent with a greater maximum exercise tolerance, if indeed, it be different from exercise capacity. In either case, increases should parallel increases in posttransplant circulatory capacity over that present prior to surgery. Our lactate results with maximum exercise posttransplant are in keeping with those reported in normal subjects by Wasserman et al., during the performance of moderate to heavy exercise under similar conditions and with comparable \( VO_2 \) values. In terms of maximum exercise tolerance, it may reflect an endurance level of exercise closer to the "physiologic limits" in the posttransplants than is possible for those with pulmonary hypertension. Hence, the higher lactate levels in the former.

Although significantly improved, circulatory limitations may still persist posttransplant, as judged by \( VO_2 \), heart rate, and the \( O_2 \)-pulse attainable at maximum levels of exercise. These limitations of exercise present in patients with heart-lung transplants are in keeping with previous observations made in subjects with heart transplants who were studied hemodynamically by cardiac catheterization during supine exercise, and also by progressive incremental exercise to exhaustion on a bicycle. In the absence of complications producing intrinsic graft injury, long-term dynamic cardiopulmonary function during exercise is well maintained, for at least two years, following heart-lung transplantation. Gas exchange and ventilation at maximum exercise are maintained at essentially normal levels. Circulatory limitations persist, but without any significant trends in either direction (ie, worsening or improving). However, a greater number of patients studied over longer periods of time would be required to finalize this conclusion.

A number of factors are present in postoperative patients which can limit exercise capacity and maximum \( VO_2 \), and as a result, directly influence qualitative estimates of circulatory capacity and lead to underestimates of "true" circulatory capacity by limiting exercise performance.

Factors potentially limiting posttransplant exercise include cardiac denervation, chronic anemia, physical deconditioning, and in a significant number of cases, systemic hypertension as a result of cyclosporine drug treatment. Cardiac denervation reduces peak heart rate, and possibly, maximal contractility. Chronic anemia reduces exercise capacity and \( VO_2 \) max directly. Thus, the combination of cardiac denervation and chronic anemia, the latter being frequently present posttransplant, would be expected to reduce maximum \( VO_2 \) and exercise capacity.

Physical conditioning and motivation have major effects on exercise performance. In sedentary and deconditioned normal subjects, exercise and circulatory capacities are reduced. Posttransplant, following a lifelong history of limited activity for many of these patients, it is difficult for them to adjust to the act of maximally exerting themselves "to the limit" without fear of harm. All patients are not equally motivated to engage in strenuous exercise for the purpose of maximizing physical conditioning. Peak exercise requires both physical fitness and strong motivation, and anything less results in suboptimal exercise performance. It is difficult to determine how much these factors influenced the results.

The imposition of limits on exercise from increases in peripheral vascular resistance, as a result of systemic hypertension, is of substantial concern since it may produce a reduction in the systemic vascular bed. The long-term effects of hypertension associated with cyclosporine drug therapy, however, remain unclear.

As a consequence of some of the limiting factors noted above, it is possible that our subjects never achieved their actual maximum exercise capacity. If this is so, then our results could represent an underestimation of circulatory capacity in the post heart-lung transplant state. Since endurance was a require-
ment of our method of study to some degree, it is also possible that fatigue could have had a greater effect than limitations of circulatory capacity on our results. On the other hand, Sietsma et al. using a progressive incremental exercise protocol, demonstrated a maximal \( \dot{V}O_2 \) of 49 ± 2 percent of predicted in four patients with heart-lung transplants. Although their results show a greater \( \dot{V}O_2 \) than ours in the immediate posttransplant period, there are no differences in \( \dot{V}O_2 \) when compared with our long-term follow-up results. Despite any differences in absolute \( \dot{V}O_2 \) values that may arise as a result of differences in technique, their results support our supposition of posttransplant limitations of circulatory capacity with exercise.

In pulmonary hypertension (pretransplant), our studies reaffirm previous work indicating that exercise is primarily limited by a markedly impaired circulation. The high pulmonary vascular resistance results in an inadequate cardiac output which, in turn, serves as the principal source of impairment of the circulation.  

Respiratory factors, independent of the high pulmonary vascular resistance, appear to be less critical in limiting exercise in pulmonary hypertension. With the possible exception of severe hypoxemia, there are no discernible limitations of exercise which can be directly attributed to the respiratory process per se.

Although ventilation is excessive during rest and exercise, a sufficient ventilatory reserve is still available at maximum exercise. The excessive nature of the ventilatory response to graded exercise appears to be unique to pulmonary hypertension. This response appears to be independent of the usual chemical modulators of ventilation and also of factors controlling ventilation at rest.

The excessive ventilation may have been an effect of instrumentation to some extent (i.e., nose clip, mouthpiece, etc.), particularly at rest. In this context, arterial PaCO\(_2\) values, measured with the patients instrumented during the resting period of the exercise protocol, were not significantly different from those obtained during normal breathing. During exercise, \( \dot{V}E \) increased appropriately above resting \( \dot{V}E \) with each increasing level of exercise. Although some effect is possible, it is unlikely that the excessive ventilation present in our studies is predominantly an effect of instrumentation.

It is difficult to exclude hypoxemia as a possible cause of exercise limitation by virtue of its effects on the circulation and/or exercising skeletal muscle. On the other hand, patients with relatively mild hypoxemia and pulmonary hypertension show the same degree of limited exercise as their counterparts with severe hypoxemia. This suggests that, in general, circulatory factors are more critical in limiting exercise than the level of arterial oxygenation per se.

In summary, the results of these studies indicate that the integrated functions of the transplanted heart and lungs are well maintained with exercise. The dramatic clinical improvement seen in patients with heart-lung transplant is further substantiated by the increases in posttransplant exercise capacity. Although circulatory limitations of maximal exercise may persist, it is evident that the transplanted heart and lungs perform sufficiently well to sustain normal life.

It should again be emphasized that the results reported herein represent posttransplant function at its best when the transplanted heart and lungs were free of any complications or disease. Late complications have occurred in approximately 40 percent of the long-term survivors, with obliterative bronchiolitis the complication of greatest concern. In general, however, in the absence of such complications, the overall function of the respiratory system does not appear to be dramatically altered by the extensive nature of combined heart-lung transplant surgery. The long-term function of the transplanted lung remains intact despite the acute transient ischemia and disruption of its nerve, lymphatic, and bronchial arterial supplies at the time of transplantation.

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References

Second Annual National Conference: Cardiopulmonary Rehabilitation; The Ideal, The Real

The American Association of Cardiovascular and Pulmonary Rehabilitation will present this conference at the Newport Beach Marriott Hotel, Newport Beach, California, November 14-15. For information, contact Barry Franklin, Ph. D., AACVPR, 53 Park Place, New York City 10007.

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