Augmented Ventilatory Response to Exercise in Pulmonary Hypertension*

James Theodore, M.D.;† Eugene D. Robin, M.D.;‡
Adrian J. R. Morris, M.B.;§ Conor M. Burke, M.B.;§
Stuart W. Jamieson, M.B., F.C.C.P.;¶ Antonius Van Kessel;¶
Edward B. Stinson, M.D.;** and Norman E. Shumway, M.D., F.C.C.P.**

The ventilatory response to submaximal exercise, defined as the slope of minute ventilation over carbon dioxide production (VE/VCO₂), was determined in 12 normal subjects, ten patients with pulmonary hypertension before and after heart-lung transplantation, and eight patients following heart transplantation. Patients with pulmonary hypertension show an augmented ventilatory response compared to normal subjects (pulmonary hypertension mean, 57.7 ± 6.8 (SE) ml/ml VCO₂; normal subjects, 22.3 ± 1.4 ml/ml VCO₂; p < 0.001). Following heart-lung transplantation, VE/VCO₂ slope fell to 24.7 ± 1.6 ml/ml VCO₂, a value which is not significantly different than the value in normal subjects. Patients after heart transplantation show a mean slope value of 25.3 ± 1.3 ml/ml VCO₂, which is not significantly different than the normal value or the value found after heart-lung transplantation. The augmented ventilatory response to exercise did not correlate with the usual chemical modulators of ventilation (arterial pH, arterial carbon dioxide tension, or arterial oxygen tension). These results suggest the following: (a) the existence of a neural system in patients with pulmonary hypertension which results in an augmentation of ventilatory drive in response to exercise; (b) the augmented ventilatory response reflects excessive neural activity of pulmonary afferents during exercise; (c) narrow regulation of the ventilatory response to exercise in normal subjects which is preserved in the denervated lung, indicating that pulmonary afferents are not critical to ventilatory control during exercise in the normal subject; and (d) the possible use of measurements of the ventilatory response to exercise as a noninvasive screening test for pulmonary hypertension.

Patients with pulmonary hypertension usually manifest both resting hyperventilation and also excessive ventilation for any given exercise load. The mechanisms for both phenomena are obscure.

The availability of human heart-lung transplantation has provided an opportunity to study the latter phenomenon. Following heart-lung transplantation, the lung and pulmonary vasculature are totally and perhaps irreversibly denervated (unpublished data). The heart is irreversibly denervated. In addition, pulmonary hypertension is no longer present. By studying these patients before and after heart-lung transplantation, the role of peripheral control mechanisms for the regulation of ventilation operating in the lungs or heart could be assessed. We studied the ventilatory response to submaximal exercise in pulmonary hypertension before and after heart-lung transplantation. Before transplantation, all subjects showed a marked augmentation of the ventilatory response to exercise. Following transplantation, the augmented ventilatory response during exercise was abolished. In addition, the ventilatory response to exercise became narrowly regulated and indistinguishable from the response in normal subjects. The magnitude of exercise hyperventilation associated with pulmonary hypertension did not correlate with arterial pH, arterial carbon dioxide tension (PaCO₂), or arterial oxygen tension (PaO₂), the known chemical mediators of ventilation. This suggests that the excitatory mechanism is neural in nature and could involve baroreceptors located in the walls of the pulmonary vasculature as the source of pulmonary afferent activity.

**Materials and Methods**

Four groups of subjects were studied. Group 1 consisted of 12 normal subjects (ten men and two women, aged 20 to 65 years) who were free of cardiac and pulmonary disease. Group 2 consisted of ten patients (seven men and three women, aged 20 to 41 years) with a diagnosis of pulmonary hypertension established by clinical criteria as well as cardiac catheterization. Eisenmenger's syndrome had been established as the cause of pulmonary hypertension in five (all men), and five patients (two men and three women) were regarded as showing primary pulmonary hypertension. Hemodynamic measurements of the pulmonary circulation were not obtained immediately before surgery because of the risks to the patients, but mean pulmonary arterial pressures obtained weeks to months before surgery ranged from 32 to 87 mm Hg, with nine of the ten pressures greater than 60 mm Hg.

Group 3 consisted of the same ten subjects studied four to six weeks after heart-lung transplantation. At least one measurement of right-sided hemodynamics was obtained after transplantation in

*From the Departments of Medicine and Cardiovascular Surgery, Stanford University School of Medicine, Stanford, Calif.
Supported by a program grant HL 13108 from the National Heart, Lung, and Blood Institute and by the Samuel and Leah Osher Medical Education Fund.
† Professor of Medicine.
‡ Professor of Medicine and Physiology.
§ Postdoctoral Scholar.
¶ Associate Professor of Cardiovascular Surgery.
¶ Technical Director, Pulmonary Physiology Laboratory.
**Professor of Cardiovascular Surgery.
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Reprint requests: Dr. Theodore, Division of Respiratory Medicine, Stanford School of Medicine, Stanford 94305."
each of the ten subjects, and the values were found to be normal.

Group 4 consisted of eight patients (five men and three women, aged 22 to 57 years) who had undergone heart transplantation without lung transplantation for either advanced coronary artery disease or for cardiomyopathy. Candidates for heart transplantation are class 4 cardiac patients, and many, if not most, present with pulmonary edema and elevated pulmonary arterial pressure associated with elevated pulmonary capillary pressures, pulmonary venous pressures, and pulmonary vascular resistance (PVR). The PVR must be below 6 to 8 Wood units, either before or following infusion with vasodilators (sodium nitroprusside [sodium nitroprusside]), in order to be acceptable for heart transplantation. Hemodynamic measurements after transplantation showed normal pulmonary arterial pressures in each, and there was no clinical evidence to suggest the existence of pulmonary hypertension at the time of study. This group provided a control group who had undergone a similar surgical experience as group 3 with reversible increases in pulmonary arterial pressure, as well as providing data on the effects of cardiac denervation alone on the ventilatory response to exercise.

The ventilatory response to exercise was quantitated as the slope of the line for minute ventilation over carbon dioxide production (VE/VCO2). Each individual point on these response curves represents the ventilatory equivalent for carbon dioxide; however, the slope of the line represents a stimulus-response curve in which the stimulus is increasing levels of exercise quantitated as increased carbon dioxide production and the response is increasing levels of ventilation. These curves are conceptually equivalent to the better known PaCO2 vs VE or PaO2 vs VE curves.

The VE/C02 during exercise shows a linear relation with increasing work during submaximal exercise and is an acceptable index of increasing work.1,4,8 Each individual slope was calculated by linear regression using the least-squares method.

Physiologic responses during exercise6 were measured at rest in the standing position and during increasing levels of treadmill exercise at a constant work rate (Quinton treadmill model 18-49-CI) for periods of seven minutes at each level before and following heart-lung transplantation in patients with pulmonary hypertension. Parameters measured included VE, respiratory rate, physiologic dead space (Vd/Vt), respiratory exchange ratio, heart rate, blood pressure, VCO2, oxygen consumption, ventilatory equivalents for carbon dioxide and oxygen, arterial blood gas levels, and lactate levels. Data unrelated to the ventilatory response to submaximal exercise will be presented in a separate report.

Measurements were made with the patients either standing or walking on the treadmill and breathing room air through a standard mouthpiece (Collins) attached to a modified Otis McKerrou low-resistance valve (dead space, 35 ml) with nose clip in place. The expiratory port was connected with ribbed tubing (1/4 inches in inner diameter) to a T-shaped stopcock for diverting expired gases either into the room or for collection into a 120-L Neoprene Latex meteorologic balloon (Collins). Continuous monitoring of end-tidal carbon dioxide fractions for each breath was obtained through a needle tap in the mouthpiece attached via 1/4-inch inner-diameter polyethylene tubing to an infrared carbon dioxide analyzer (Godart Mark II capnograph) with a kymograph for permanent records. Flow rates of sample gas flow into the analyzer were 500 ml/min. The electrocardiogram was monitored throughout with both oscillographic observation and permanent recordings (Quinton ECG monitor 622). Blood pressures were monitored with multiple measurements with a sphygmomanometer.

The time periods for sampling varied somewhat for measurements during rest and exercise. During standing rest, expired gases over the first two minutes were diverted into the room while flushing the system and were then collected for five minutes. End-tidal carbon dioxide was monitored breath by breath over the last five minutes, and the ECG and blood pressure were followed over the entire period. During exercise, expired gases were collected over the final minute and the end-tidal carbon dioxide monitored over the last three minutes.

Collected expired gas volumes were measured by Wet Test Meter (Precision Scientific Products). End-tidal carbon dioxide pressure was computed from the kymographic tracings of the infrared analyzer. The fraction of carbon dioxide in the collected expired gases (FE CO2) was measured by the infrared carbon dioxide analyzer. The gas analyzer was calibrated prior to each study with appropriate test gas mixtures and, in addition, was repeatedly checked with electrical calibrations during the course of each study.

Minute ventilation was computed from the measured expired gas volume and corrected for volumes lost (tidal sampling of carbon dioxide and analysis of FE CO2), and the volumes were corrected to standard temperature and pressure, dry (STPD), for the purposes of this study.

Carbon dioxide production (STPD) was calculated from

VE (STPD) x FE CO2

Arterial catheters were inserted only in the patients undergoing heart-lung transplantation, and arterial blood was obtained for measurements of PaO2, PaCO2, arterial pH and lactate level by standard methods.

Patients with pulmonary hypertension were exercised on the treadmill before and after heart-lung transplantation at rates between 1.0 and 3.5 mph at varying degrees of slope. The VE during submaximal exercise was defined by measurements obtained prior to the onset of metabolic acidosis (determined by arterial pH, PaCO2, bicarbonate level, and blood lactate levels). Measurements of VE beyond 1.0 mph on the treadmill could only be obtained in half of the patients prior to heart-lung transplantation. Thus, in five patients the VE/VCO2 slope was computed from the resting and a single exercise point.

Normal control subjects and patients with heart transplants were exercised at treadmill speeds of 1, 2, and 3 mph at zero percent slope.

![Figure 1. Relationship between VE and VCO2 during submaximal exercise for four groups. Shaded areas represent standard error of mean slope for normal group and groups with pulmonary hypertension.](http://coil.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21502/ on 04/03/2017)
The respiratory exchange ratios were less than 1.0, with the end-tidal carbon dioxide fractions remaining essentially constant over the course of the respective level of exercise. These levels of exercise in the normal subjects were consistent with mild to moderate workloads, as judged by carbon dioxide outputs of less than 1 L/min, and were within the range of work required for submaximal exercise in the patients.

The resting VE and VCO2 values were included in determining the VE to VCO2 relationship during exercise by linear regression. The slopes of the responses before and after heart-lung transplantation were directly compared statistically by the paired Student's t-test. All statistical comparisons between the respective groups used the unpaired t-test.

### RESULTS

Figure 1 and Table 1 summarize the data in the four groups of subjects. In the normal group, the VE/VCO2 slope showed a mean value of 22.3 ± 1.4 (SE) ml/ml VCO2. There is a highly reproducible ventilatory response to increasing workloads in a normal population. The small standard error is consistent with a highly regulated process. Repeat measurements on different days in normal subjects showed a mean variability within normal individuals of 11 percent for the VE/VCO2 slope. The values obtained by us do not differ substantially from those previously reported by Wasserman et al.7 by Jones and Campbell,8 and by Astrand et al.9 which were obtained under somewhat different conditions of submaximal exercise. The ventilatory response to submaximal exercise as measured by the slope of the VE/VCO2 appears to be a highly reproducible value in normal subjects.

In the period before transplantation (group 2), the

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**Table 1—Slopes and Y Intercepts as Determined by Linear Regression for VE/VCO2 during Submaximal Exercise**

<table>
<thead>
<tr>
<th>Group</th>
<th>Slope</th>
<th>Y Intercept</th>
<th>r</th>
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<tbody>
<tr>
<td>1. Normal controls</td>
<td>22.3 ± 1.4</td>
<td>+2.8 ± 0.5</td>
<td>0.99 ± 0.005</td>
</tr>
<tr>
<td>2. Pulmonary hypertension</td>
<td>57.7 ± 6.8</td>
<td>-3.5 ± 2.1</td>
<td>0.97 ± 0.019</td>
</tr>
<tr>
<td>before heart-lung transplant</td>
<td>24.7 ± 1.6</td>
<td>+3.5 ± 0.8</td>
<td>0.99 ± 0.003</td>
</tr>
<tr>
<td>3. After heart-lung transplant</td>
<td>25.3 ± 1.3</td>
<td>+2.7 ± 0.8</td>
<td>0.99 ± 0.003</td>
</tr>
</tbody>
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*Values represent means (± SE) of linear regressions obtained for each individual subject within respective group.*
Venous gas exchange during exercise appears to be dependent upon high pressures in the pulmonary arterial/arteriolar portions of the circulation. Although usually present in all forms of pulmonary hypertension, low cardiac output per se does not appear to account for the increased ventilation, since previous studies showed no significant correlation between the two.11

The precise cause of the increased ventilatory drive to exercise is not clear. It does not appear to be related to hypoxemia, changes in PaCO2, or changes in arterial pH, as there is no correlation between changes in these variables and the ventilatory response to exercise. Similar conclusions were drawn previously by Gazetopoulos et al.13 Humoral agents generated by the pulmonary hypertensive lung seem unlikely as the cause of the augmented ventilatory drive. It is, of course, possible that some unknown humoral agent is synthesized in the lung of patients with pulmonary hypertension and released to increase ventilatory drive. The most probable stimulus is neural, arising from afferents in either the pulmonary parenchyma, the pleura, the pulmonary vasculature, or the heart, both because the increased ventilation of exercise ultimately reflects neuromuscular regulation, but also because both the lung and heart were denervated after heart-lung transplantation in the patients with pulmonary hypertension.

It seems unlikely that either the pulmonary parenchyma or pleura is the primary site of origin of the stimulus to augmented ventilation. Although there are definite abnormalities of the mechanical properties of the lung in patients with pulmonary hypertension, these tend to be minor, and their nature is variable.1 The most attractive possibility is that the site of the stimulus is either the pulmonary vasculature or the heart. In the former case, altered mechanical properties of the pulmonary vasculature might excite appropriate mechanoreceptors located in the walls. In the latter case, direct alterations of right ventricular pressure might similarly stimulate appropriate cardiac receptors. In either case the afferents could result in hyperactivity directly, either by affecting central respiratory drive or by affecting some other portion of the neural loop which ultimately controls the motor neurons of respiratory muscle.

While these possibilities are admittedly speculative, they serve to emphasize the point that neurophysiologic and not respiratory or cardiac physiologic studies will be required to determine the precise nature of the control system which is involved.

The fact that after transplantation the ventilatory response to submaximal exercise is normal provides insight into another physiologic process. Substantial emphasis has been placed on the possibility of carbon dioxide receptors within the lungs as a mechanism for regulating ventilation during exercise in the normal
subject. We have preliminary evidence that the lungs are irreversibly denervated following exercise (unpublished data). The present studies suggest that a normal ventilatory response to exercise does not require the existence of functioning carbon dioxide receptors.

Another issue which is raised by the present results is whether the resting hyperventilation observed in patients with pulmonary hypertension is related to the same control system responsible for augmenting the ventilatory response during exercise. The lack of correlation between resting $\dot{V}E$ and the slope of the $\dot{V}E/VCO_2$ plot suggests that the two control systems may be independent.

Moreover, in the period after transplantation, resting hyperventilation continues despite a normal $PaO_2$, 27 despite relatively normal mechanical properties of the lung, despite normal pulmonary hemodynamics, and despite a denervated lung and heart.1 It is obvious that our knowledge of the regulation of ventilation during both rest and exercise in pulmonary hypertension is rudimentary and that additional (neurophysiologic) studies will be required to determine specific mechanisms.

Another interesting aspect of the present results is the narrow limits within which the $\dot{V}E/VCO_2$ relation operates in the normal subject and following transplantation of lungs and heart or heart. Given these narrow limits of response, it is possible that measurements of the slope of $\dot{V}E/VCO_2$ during submaximal exercise could be used to detect pulmonary hypertension clinically by a noninvasive approach, although separation of left-sided cardiac causes from primary pulmonary hypertension may require additional study. Sensitivity would be determined as the lowest level of pulmonary arterial mean pressure associated with a significant increase in the slope of the curve. The determination of specificity would require a demonstration that parenchymal pulmonary disease, hypoxemia, and hypercapnia did not influence the slope of the $\dot{V}E$ work curve. There is evidence suggesting that interstitial pulmonary disease16 and hypercapnia17 do not increase the slope of $\dot{V}E/VCO_2$. Whether, in fact, such an approach will be feasible and whether, if feasible, such a diagnostic approach can be translated into more effective management of patients will require additional studies.18

The similar nature of the $\dot{V}E/VCO_2$ relationship found in normal subjects and after heart-lung transplantation alike strongly suggests a relatively minor role for pulmonary afferents in the overall regulation of ventilation during exercise under normal conditions. Denervation of the lung appears to be of little consequence to these patients in carrying out their normal daily activities. Ventilation has never been limiting, even under conditions of maximum exercise in these patients, providing the lungs remain uncomplicated.19 Additional studies will be required to determine if pulmonary afferents play a more important role in subtle modulation of neural regulation normally.

The present studies have important limitations. The use of $VCO_2$ as an index of exercise intensity is not optimal. Since the calculation of $VCO_2$ is influenced by $\dot{V}E$ directly, the linearity of the calculated relationship could be influenced artifically. Optimally, for studies of this type, a direct estimate of work during progressive exercise would be preferable. Preliminary work in our laboratory indicates that direct measurement of work, rather than $VCO_2$, does not alter the nature of the present findings. As previously indicated, studies of neurophysiologic mechanisms require the use of neurophysiologic methods, and these will ultimately be required in pulmonary hypertension. Simple studies of ventilatory control of exercise, focusing on non-specific output such as $\dot{V}E$, are not likely to uncover neurophysiologic mechanisms.

After transplantation, pulmonary arterial pressures became normal. In the absence of patients with pulmonary hypertension after transplantation, it cannot be determined at present whether normalization of the ventilatory response to exercise results from a normalization of pulmonary hemodynamics or from denervation of the lung. No patients have become available for study with isolated heart transplantation and pulmonary hypertension. It is therefore not possible to determine the impact of cardiac regulation on the augmented ventilatory response to exercise in pulmonary hypertension; however, it is clear that a new and previously undescribed mechanism has been uncovered for the control of ventilation in pulmonary hypertension and that knowledge of this mechanism should provide new insight into the pathophysiology of pulmonary hypertension, as well as possibly provide a test of clinical utility in patients.

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Sarasota National Conference on Pediatric Lung Disease

The University of Buffalo, State University of New York will present this program March 14-16 at the Sarasota (Florida) Hyatt House. For information, please contact: Ms. Rayna Saville, Coordinator, Pediatric Continuing Medical Education, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo 14222 (716:878-7630).

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