Blood Gas Dynamics at the Onset of Exercise in Heart Transplant Recipients*

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One hypothesis to explain the rapid neural component of exercise hyperpnea contends that afferent stimuli originating in the ventricles of the heart act reflexly on the respiratory center at the onset of exercise, i.e., “cardiodynamic hyperpnea.” Orthotopic cardiac transplantation (Tx) results in the loss of afferent information from the ventricles. Thus, Tx possibly results in transient hypercapnia and hypoxemia in deafferented heart transplant recipients (HTR) at the onset of exercise due to hypoventilation. To examine the cardiodynamic hypothesis, we collected serial arterial blood gas (ABG) samples during both the transient and the steady-state responses to moderate cycle exercise in 5 HTRs (55±7 years) 14±7 months post-Tx and 5 control subjects matched with respect to gender, age, and body composition. Forced vital capacity, forced expiratory volume in 1s, total lung capacity, and diffusion capacity did not differ (p≥0.05) between groups. Resting arterial PaO2, PaCO2, and pH did not differ between groups (p≥0.05). The ABGs were drawn every 30s during the first 5 min and at 6, 8, and 10 min of constant load square wave cycle exercise at 40 percent of the peak power output (watts). Absolute and relative changes in arterial PaO2, PaCO2, and pH were similar (p≥0.05) between HTR and the control group at all measurement periods during exercise. Heart rate (%HRmax reserve), rating of perceived exertion, and reductions in plasma volume (%Δ from baseline) did not differ between HTR and control during exercise at 40 percent of peak power output (p≥0.05). Our results demonstrate that there is no discernible abnormality in ABG dynamics during the transient response to exercise at 40 percent of peak power output in patients with known cardiac denervation. These data do not support the cardiodynamic hyperpnea hypothesis of ventilatory control in humans. The absence of hypercapnia in HTRs is further evidence for the existence of redundant mechanisms capable of stimulating exercise hyperpnea. (Chest 1993; 103:1692-98)

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echanisms underlying the control of pulmonary ventilation at the onset of exercise have been studied extensively. Hypotheses involving neural,1-4 humoral,5-7 and combined neural-humoral8 mechanisms have been investigated and support for each has been found. Most investigators conclude that a rapid neurogenic stimulus to ventilation exists, producing a ventilatory response before humoral agents from the exercising muscle can reach central or peripheral chemoreceptors. However, there is disagreement on the site of origin and the magnitude of importance of the neurogenic component. Afferent stimuli originating from “proprioreceptors” or “mechanoreceptors” in exercising limbs (feedbackward)1-3 and efferent impulses originating in the motor cortex (feedforward)4 are neural stimuli that possibly control the rapid phase of exercise hyperpnea.

An alternative hypothesis to explain the rapid neural component of exercise hyperpnea contends that afferent stimuli from the heart act reflexly on the respiratory center immediately at the start of exercise. This phenomenon, which has been termed “cardiodynamic hyperpnea,” speculates that pressure information from cardiac ventricular stretch receptors stimulates ventilation.9-15 Wasserman and coworkers10,12 found that ventilation in the dog changed proportionally with acute increases and decreases in cardiac output induced by isoproterenol and propranolol, respectively. In subsequent experiments, Jones et al10 suggested that the signal linking blood flow changes to ventilation originated from “right ventricular strain” and reported a high correlation (r = 0.94) between minute ventilation (Ve) and changing right ventricular load in anesthetized dogs. Others have demonstrated afferent signals originating in the heart of cats and dogs that are capable of stimulating ventilation.10,11,14 In contrast, neither Adams et al16 nor Banner et al17 found support for a “cardiodynamic” drive to ventilation in humans during exercise.

The purpose of this study was to determine the importance of cardiodynamic mechanisms in arterial blood gas (ABG) dynamics during the transition from rest to exercise in man. Orthotopic cardiac transplantation results in ventricular deafferentation and provides a unique opportunity to study the cardiodynamic hypothesis. If the afferent neural component from
cardiac ventricles is an obligatory requirement in the control of ventilation, then the ABG responses to dynamic exercise would be characterized by transient hypercapnia and hypoxemia in cardiac deaferented patients due to hypoventilation. To examine the cardiodynamic hypothesis, we collected serial ABG samples during both the transient and the steady-state responses to moderate cycle exercise in heart transplant recipients (HTRs) and matched control subjects.

METHODS

Subjects

Eleven patients (n = 10 male; n = 1 female), 21 to 63 years of age, who underwent orthotopic cardiac transplantation at Shands Hospital at the University of Florida, Gainesville, volunteered to participate in the study. The indications for transplantation were idiopathic cardiomyopathy (seven HTRs), ischemic cardiomyopathy (three HTRs), and retransplantation for refractory rejection (one HTR).

All HTRs were clinically stable and free of significant rejection, infection, or other major illness. Nine HTRs received triple-drug immunosuppressive therapy with cyclosporine, prednisone, and azathioprine while two HTRs were treated with cyclosporine and prednisone. Four HTRs required furosemide for fluid retention and all required one or more antihypertensive drugs for mild-to-moderate hypertension: clonidine (three patients), nifedipine (six patients), captopril (three patients), and enalapril (eight patients). No β-blockers or other cardiac medications were used by HTRs at the time of the study. All HTRs followed their usual protocol of daily medications on the days of experiments.

Control subjects were selected to match the HTRs, as closely as possible with respect to age, gender, and body composition. They were sedentary, and had no clinical cardiac or pulmonary disease as determined by clinical examination, pulmonary screening, and graded exercise testing (GXT). None of the control subjects received prescription medication at the time of the study.

The subjects were tested on two different days separated by a minimum of 72 h. All subjects restricted strenuous physical activity for 24 h before experiments and reported to the laboratory 2 to 3 h postprandial. The protocol was approved by the Institutional Review Board of the University of Florida College of Medicine and all subjects provided their written informed consent to participate in the study.

Maximal Graded Exercise Test

During the first visit to the laboratory, subjects underwent a physical examination, resting 12-lead ECG, anthropometric body composition analysis, and pulmonary function test. Following initial screening, they underwent a GXT to symptom-limited maximum on an upright electromagnetically braked cycle ergometer. Initial power output was 20 W for HTRs and 40 W for control subjects. Power output increased every minute by 10 or 20 W for the transplant or control subjects, respectively, until the subject reached voluntary maximal exertion and could not maintain 60 rpm. Expired gas analysis was made continuously, breath-by-breath at rest, and during the GXT with a commercially available system (System 2001, Medical Graphics Corp). Ventilatory threshold was determined individually for each subject using the V-slope method described by Beaver et al. Peak oxygen consumption (VO2peak) and plasma levels of vasopressin, norepinephrine, atrial natriuretic peptide, angiotensin II, aldosterone, and renin activity were also measured during the GXT. Additional information concerning VO2peak and the neuroendocrine responses during exercise has been reported.

Submaximal Exercise Tests

Submaximal exercise tests on the second day of experiments were performed at the same time of day (12 to 3 pm) as the GXT on day 1 to control for a possible effect of circadian rhythms. Environmental conditions within the laboratory were maintained relatively constant at 22 to 23°C, 56 to 62 percent relative humidity, and 760 to 785 mm Hg barometric pressure.

To study transient and steady-state arterial PO2, PCO2, and pH dynamics during exercise of moderate intensity, each subject performed a 10-min bout of constant load square wave cycle exercise at 40 percent of the peak power output (watts) achieved during the maximal GXT. Relative ventilatory threshold occurred at 59 ± 3 percent of VO2peak in the heart transplant group. We elected to study our patients at 40 percent of peak power output because it represented a work intensity that was well below ventilatory threshold in all HTRs. Our aim was to study the patients during exercise at an intensity that would not result in a sustained or systematic rise in arterial blood lactate level. A 20-gauge catheter with a three-way stopcock and 7.5-cm T-connector was placed in the radial artery of the nondominant arm under local anesthesia. Before the submaximal exercise test, the subjects rested quietly for 10 min while seated on the cycle to allow stabilization of the recorded variables. Baseline arterial blood samples were collected for determination of hematocrit (Hct), hemoglobin (Hb), and ABGs.

Exercise was initiated from rest on verbal command without prior warning, although the subject was previously familiarized with the commands. The subject achieved a pedaling rate of 60 rpm as quickly as possible. Arterial blood gas samples were drawn every 30 s during the first 5 min of exercise and at 6, 8, and 10 min. The blood sampling periods were chosen to allow detection of blood gas alterations occurring during both the transition from rest to exercise and steady-state exercise.

Blood Gas Analysis

Blood samples were drawn after aspirating and discarding the contents of the catheter and T-connector dead space (~1 ml). Each ABG sample was uniformly drawn under anaerobic conditions over the last 15 s of each measurement period using a small (3 ml) heparinized plastic syringe. After blood removal (1.5 to 2 ml), the syringe was immediately capped and stored on ice until analysis. Blood gas determinations were performed within 60 min after sample removal. Blood gas and pH analysis were performed on a blood gas and acid-base analyzer (Nova Stat 5, Nova Biomedical, Waltham, Mass). The instrument autocalibrated after each sample was analyzed, using precision gases and buffers.

Pulmonary Function Tests

Pulmonary function tests were performed on the same day as the GXT. Pulmonary function reference values were calculated using gender-specific prediction equations with appropriate corrections for age, height, race, and smoking history. Repeated trials of all tests were performed until two trials were in close agreement (±5 percent). The mean of these trials served as the criterion value.

A flow-volume loop test was used to generate values for forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). Single-breath carbon monoxide transfer was used to measure total lung diffusion capacity (Dco) and the rate of diffusion per unit of lung volume (Kco). Dco and Kco were measured with appropriate correction for the subject's Hb level on the day of the pulmonary function tests. Alveolar volume (VA) was also estimated during the diffusion test by using inert and insoluble neon in the diffusion mix. VA values were considered estimates of total lung capacity (TLC) and they were subsequently used in all calculations requiring TLC values.

Hematocrit and Hemoglobin

The Hct and Hb determinations were made with a centrifugal
hematology system (QBC II Becton Dickinson, Franklin Lakes, NJ). Layer measurements were used to compute Hct. The Hb concentration was derived from the Hct and measurements of red blood cell density. The percentage of change in plasma volume during each exercise test was calculated from the preexercise and postexercise Hct values.

Statistical Analysis

Descriptive characteristics and pulmonary function test values were compared between groups using analysis of variance. Analysis of covariance for repeated measures was used to analyze the temporal pattern of PaO₂, Pco₂, and pH. When a statistically significant time effect or group by time interaction was observed, within-group comparisons between time points and/or among group comparisons at each time point were done using analysis of covariance with contrast analysis for obtaining appropriate post hoc custom hypotheses tests. All statistical analyses were completed using a statistical program (SAS). An α level of p≤0.05 was required for statistical significance.

RESULTS

Normal Dco values were observed in only five HTRs (Dco >70 percent of predicted). Using ABG data from HTRs with abnormal Dco would invalidate the comparisons with control subjects possessing normal pulmonary function. Therefore, we examined ABG responses to exercise at 40 percent of peak power output in five HTRs (men) and five matched control subjects. The ABG response of the complete group of HTRs during strenuous exercise has been presented previously.

Descriptive Characteristics

The physical characteristics of HTR and control groups are presented in Table 1. The two groups were closely matched and did not differ (p≥0.05) with respect to age, height, weight, and body composition.

Arterial Blood Gas

Both the pattern and the magnitude of the ABG responses to the exercise were similar for HTRs and control subjects. The dynamics of absolute arterial PaO₂ are presented in Figure 1. Baseline PaO₂ was not significantly different (p=0.05) between HTR and control groups. After 1 min of exercise, arterial PaO₂ decreased slightly but significantly (p≤0.05) below resting values in both groups. After the nadir, PaO₂ increased in both groups and reached values that were not significantly different (p≤0.05) from baseline at 2.5 min of exercise. PaO₂ remained stable throughout the remainder of exercise in both groups. The group by time interactions for both absolute and relative changes in arterial PaO₂ were not significant (p≥0.05).

Absolute changes in arterial PCO₂ are shown in Figure 2. Baseline PaCO₂ levels were not significantly different (p≥0.05) between HTR and control groups. Arterial PaCO₂ was well regulated in response to the exercise and was maintained within ~1 mm Hg of the resting value in both groups. PaCO₂ did not differ significantly from baseline levels at any measurement period in either HTR or control groups. The group by time interactions for both absolute and relative changes in arterial PaCO₂ were not significant (p≥0.05).

Arterial pH values are presented in Figure 3. Arterial pH was similar (p≥0.05) in both groups at rest and did not change significantly from baseline during exercise in either group.

Pulmonary Function Tests

Pulmonary function test data are shown in Table 2. None of the posttransplantation pulmonary function

| Table 1—Physical Characteristics of the Control and Heart Transplant Groups* |
|------------------|------------------|------------------|
| Variable        | Control (n = 5)  | Transplant (n = 5) |
| Age, yr         | 55.6 ± 6.8       | 55.6 ± 6.9       |
| VO₂, ml·kg⁻¹min⁻¹ | 31.1 ± 6.2       | 17.1 ± 3.8‡      |
| Height, cm      | 176.9 ± 4.7      | 179.9 ± 6.2      |
| Weight, kg      | 87.3 ± 14.1      | 90.9 ± 15.6      |
| Body fat, %     | 25.9 ± 3.7       | 27.7 ± 6.2       |
| Lean body mass, kg | 64.3 ± 8.1      | 65.2 ± 8.6       |
| Months post-Tx  | . . .             | 13.8 ± 6.7       |

*Values are mean ± standard deviation. Tx = transplantation.
†Peak systemic oxygen consumption.
‡p≤0.05, transplant vs control.

Figure 1. Temporal pattern of absolute arterial PaO₂ during 10 min of constant load cycle exercise at 40 percent of peak power output in the control and transplant groups. Values represent mean ± SEM.

Figure 2. Temporal pattern of absolute arterial PaCO₂ during 10 min of constant load cycle exercise at 40 percent of peak power output in the control and transplant groups. Values represent mean ± SEM.
test values for HTR were significantly (p≤0.05) different from the control group. Absolute and relative (percent of predicted) measures of FVC, FEV₁, TLC, Dco, and Kco were within a normal range in all subjects.

Relative Exercise Intensity

Physiologic variables that were considered valid indicators of differences in relative exercise intensity between the two groups are shown in Table 3. There were nonsignificant (p≥0.05) differences between HTR and control groups for heart rate (percent of heart rate reserve), rating of perceived exertion (RPE), and reductions in plasma volume (percent Δ from rest) at the conclusion of exercise in 40 percent of peak power output. These data indicate that the relative exercise stimulus during the submaximal exercise tests was comparable between groups.

Postural Influence on Heart Rate

We did not perform a definitive neurovegetative test to ascertain cardiac denervation in the HTR. However, as an index of "functional" denervation, we recorded heart rate responses during a postural shift from a supine to an erect seated position. The heart rate increased significantly (p≤0.05) from 60 to 65 beats/min during a postural shift from a supine to an erect seated position in the control group. There were no individual or group changes in heart rate during this orthostatic challenge in the transplant group. Resting heart rate in HTRs was 88 beats/min in the supine position and did not change (p≥0.05) during the postural shift. The tachycardic response to exercise was also blunted in all HTRs. These results suggest the absence of "functional" cardiac reinnervation in our HTR.

Discussion

Orthotopic cardiac transplantation severs all of the nerves projecting to and from the donor heart. Thus, ventricular deafferentation is a necessary consequence of the surgery which ablates all reflex stimuli originating from the right and left ventricles. We speculated that if ventilatory control is causally linked to cardiomediated reflexes originating in the ventricles, ABGs in HTRs at the onset of exercise would be characterized by transient hypercapnia and hypoxemia due to hypoventilation. Our blood gas data clearly demonstrate that there is no discernible abnormality in ABG dynamics during the transient response to exercise at 40 percent of peak power output in patients with known cardiac denervation. Although the results of the present study do not refute the possible existence of a cardiodynamic reflex, they may be interpreted as an indication that afferent ventricular stimuli are not essential in the maintenance of ABG dynamics during the onset of moderate exercise.

Our findings are consistent with recent studies that have reported Ve data in human heart or heart-lung transplant recipients during exercise. Theodore et al studied human heart-lung transplant patients during maximal incremental treadmill exercise and reported that the rise in Ve with exercise intensity was "appropriate" for the O₂ consumed. Normal arterial Pco₂ and Pao₂ values were found at rest and peak exercise. However, the dynamics of Ve and ABGs during the transition from rest to peak exercise were not reported. Thus, inferences regarding neural control of ventila-

![Figure 3. Temporal pattern of arterial pH during 10 min of constant load cycle exercise at 40 percent of peak power output in the control and transplant groups. Values represent mean ± SEM.](image-url)

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<th>Table 2—Pulmonary Function Values of the Control Group and the Transplant Group Following Cardiac Transplantation*</th>
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<td>Variable</td>
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<td>Kco, ml·min⁻¹·mm Hg</td>
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*Values are mean ± standard deviation. FVC = forced vital capacity; FEV₁ = volume expired in first second of FVC; TLC = total lung capacity; Dco = lung diffusion capacity; Kco = diffusion capacity per unit lung volume.

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<th>Table 3—Heart Rate,† Rating of Perceived Exertion,† and Plasma Volume Changes‡ During Exercise at 40 Percent of Peak Power Output‡‡</th>
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<td>Variable</td>
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<td>% Δ Plasma volume</td>
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†Heart rate expressed as percentage of heart rate reserve. †Borg (1962) scale. ‡Percentage loss in plasma volume (rest—exercise). ‡Values are mean ± standard deviation.
tion at the initiation of exercise cannot be made from their data. Banner et al.\textsuperscript{27} measured ventilatory and cardiovascular responses at the onset of leg pedaling exercise in HTRs, heart-lung transplant recipients, and normal control subjects. Cardiac output increases in the transplant recipients were attenuated compared with the normal control subjects. Nevertheless, $V_{E}$ and oxygen uptake increased immediately and with similar magnitude in all three groups. Although ABC data were not reported, their results indicate that it is possible to have an appropriate ventilatory response at the onset of exercise in the presumed absence of information from the heart and lungs, and in the absence of a normal cardiac output response to exercise. In contrast, Cerretelli et al.\textsuperscript{28} studied HTRs early after transplantation (1 to 8 months) and reported an attenuated ventilatory response in HTRs that the authors attributed to decreased cardiac output at the onset of exercise.

To date, however, our model is the first to examine more fully the transient effects of ventilation on ABG composition in human HTRs. Huszczuk and coworkers\textsuperscript{31} recently investigated both the transient and the steady-state ABC and ventilatory responses to treadmill exercise in calves with artificial hearts. The implanted animals experienced small reductions in arterial $Po_2$ (4 ± 3 mm Hg) but arterial $Pco_2$ and pH were well regulated despite the absence of increases in cardiac output. When cardiac output was experimentally increased in the implanted calves to a level commensurate with that spontaneously occurring in the control calves, ventilation was not affected. Their data indicate that neither cardiac nor hemodynamic effects of increased cardiac output constitute an obligatory cause of exercise hyperpnea in the calf. However, the authors were unable to conclude that transient ventilatory dynamics were unaltered by deaeration because the calves could only rarely be made to make a smooth transition from rest to the required walking speed without manual assistance from the investigators.

The technique used for orthotopic cardiac transplantation leaves undisturbed portions of the left and right atria and interatrial septum of the recipient's own heart.\textsuperscript{28} It also leaves intact the superior and inferior venae cavae and pulmonary veins at their junctions with the right and left atria. Most of the atrial mechanoreceptors are clustered in these areas\textsuperscript{28} and presumably are left intact after transplantation. Sensory endings in the lungs also remain undisturbed, thus making orthotopic cardiac transplantation a model mainly of ventricular deaeration. On this basis, we suggest that ventricular deaeration does not adversely effect blood gas dynamics during dynamic muscular exercise of moderate intensity. However, we cannot dismiss the possibility that atrial receptors or rapidly responding pulmonary chemoreceptors or mechanoreceptors are stimulated by increased cardiac output and that the increase in ventilation at the onset of exercise is proportional to either blood flow or $CO_2$ return to the lung.\textsuperscript{7,23}

Our finding of normal ABC dynamics at the onset of exercise should not be generalized to all HTRs, specifically those with pulmonary diffusion (Dco) abnormalities. Spirometric and diffusion abnormalities are frequently observed in heart failure patients awaiting cardiac transplantation.\textsuperscript{27,34-37} Following transplantation, FVC, FEV\textsubscript{1}, and TLC improve to normal values in most HTRs.\textsuperscript{27,34,35,37} However, impaired Dco persists posttransplantation in some HTRs without accompanying restrictive and obstructive ventilatory defects.\textsuperscript{27,34,37} We have previously reported that HTR experience exercise-induced hypoxemia during strenuous submaximal exercise when Dco is <70 percent of predicted values.\textsuperscript{27} In this respect, it is also appropriate to point out that the results of the present study should not be extrapolated to heavy exercise (ie, work intensities above anaerobic threshold). Ventilatory requirements during exercise are related to both the rate of metabolic gas exchange and acid-base status of the exercising subject or animal. Since heavy exercise results in greater production of lactic acid than exercise at moderate work rates, these two levels of exercise intensity should be considered separately when discussing ventilatory control. Thus, we focused on regulation of ABC during the transition from rest to exercise at 40 percent of peak power output, which was below ventilatory threshold in all HTRs. Although we did not measure plasma lactate levels, we assumed that 10 min of cycle exercise at 40 percent of peak power output would not be associated with a sustained or systematic rise in arterial blood lactate level considering the close coupling of ventilatory threshold and lactate threshold reported in HTRs.\textsuperscript{38}

The well-regulated Pa$CO_2$ observed at the onset of submaximal exercise in our HTRs and normal control subjects supports the contention by others that exercise hyperpnea is isocapnic in humans.\textsuperscript{36,39} However, not all investigators agree that Pa$CO_2$ remains unchanged from rest during moderate exercise. Powers et al.\textsuperscript{41} found that hyperventilation and hypocapnia occur in the pony during the onset of submaximal exercise. Flandrois et al.\textsuperscript{42} and Favier et al.\textsuperscript{43} reported that hyperventilation and hypocapnia also occur in the dog. The reasons for the divergent findings are not clear. One possible explanation is that a species difference exists in control of ventilation during exercise. It seems possible that humans regulate Pa$CO_2$ more tightly in the nonsteady state than do dogs or ponies. However, Pan et al.\textsuperscript{44} have suggested that the studies demonstrating exercise arterial isocapnia in humans have reported preexercise Pa$CO_2$ values that
are lower than typical resting values. Thus, hyperventilation at rest in these studies could have masked exercise-induced hypocapnia. In the present study, care was taken to avoid preexercise hyperventilation and our resting PaCO₂ data are consistent with normal resting values in humans.

In conclusion, our data demonstrate that ABG dynamics at the onset of moderate exercise are normal in HTRs with normal pulmonary function. These data do not support the cardiodynamic hyperpnea hypothesis of ventilatory control in humans. Arterial blood gas regulation in HTRs was normal during the transition from rest to exercise and during the steady state of dynamic exercise despite cardiac ventricular denervation. The absence of hypocapnia in HTRs suggests the existence of redundant mechanisms capable of stimulating exercise hyperpnea.

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