Increased Peripheral Chemoreceptors Sensitivity and Exercise Ventilation in Heart Transplant Recipients

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Background—Heart failure is characterized by increased ventilation during exercise, which is positively related to increased peripheral and central chemoreceptor sensitivity. Heart transplantation does not normalize the ventilatory response to exercise, and its effects on the chemoreflex control of ventilation remain unknown. We tested the hypothesis that chemoreceptor sensitivity is increased in heart transplant recipients (HTRs) and linked to exercise hyperpnea.

Methods and Results—We determined the ventilatory, muscle sympathetic nerve activity (MSNA), and circulatory responses to isocapnic hypoxia and hyperoxic hypercapnia 7±1 years after transplantation in 19 HTRs with a normal left ventricular ejection fraction of 60±2%. Results were compared with those of 11 closely matched referent subjects. Sixteen patients and 10 referent subjects also underwent cycle ergometer exercise tests. HTRs compared with referent subjects presented higher MSNA (52±4 versus 34±3 bursts/min; \(P<0.01\)) and heart rates (83±3 versus 68±3 bpm; \(P<0.01\)) during room air breathing. The ventilatory response to hypoxia was higher in HTRs than in referent subjects (\(P<0.01\), ANOVA). The increase in MSNA also was more marked during hypoxia in the HTRs than in the referent group (\(P<0.05\), ANOVA). Responses to hyperoxic hypercapnia did not differ between the HTRs and the referent group. The ventilatory response to exercise, characterized by the regression slope relating minute ventilation to CO2 output, was steeper in HTRs than in referent subjects (38±2 versus 29±1 L/min Hg; \(P<0.01\)). Exercise ventilation in HTRs was related to the ventilatory response to isocapnic hypoxia (\(r=0.57\); \(n=16\); \(P<0.05\)) and to the ventilatory response to hyperoxic hypercapnia (\(r=0.50\); \(n=16\); \(P<0.05\)).

Conclusions—Peripheral chemoreceptor sensitivity is increased in HTRs and is related to exercise hyperpnea after heart transplantation. (*Circulation. 2006;113:252-257.)*

Key Words: receptors ■ heart failure ■ transplantation

The peripheral chemoreflex, located in the carotid bodies, is the dominant reflex control mechanism regulating the ventilatory and muscle sympathetic nerve activity (MSNA) responses to reductions in partial pressure of oxygen (PaO2).1 Peripheral chemoreceptors also play an important modulatory role in the regulation of ventilation during exercise.2–5 This is evidenced by the observation that breathing oxygen decreases ventilation and increases arterial carbon dioxide to a greater extent during exercise than at rest.6,7

Central chemoreceptors are located in the brain stem and respond primarily to hypercapnia.8 These receptors exert important influences on the neural and circulatory responses to changes in arterial carbon dioxide content (Paco2).8 Their activation increases minute ventilation (VE), heart rate (HR), blood pressure (BP), and sympathetic activity.9 In normal subjects and athletes, there is a positive relation between VE and the rate of CO2 production (VCO2) during exercise and central chemoreceptor sensitivity at rest.2,5,10

Heart failure is accompanied by increased peripheral and central chemosensitivity,11,12 which correlates with an in-

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creased ventilatory response to exercise.11 The ventilatory response of heart transplant recipients (HTRs) during exercise is comparable to that of patients with moderate degrees of heart failure.13 Thus, although heart transplantation restores a close-to-normal cardiac function, it does not normalize the ventilatory response to exercise,14 and the mechanism of hyperpnea during exercise in HTRs remains incompletely understood.

On the basis of previous evidence that chemoreceptors are important regulators of the ventilatory response to exercise,1 that heart failure patients have increased peripheral and central chemoreflex sensitivity,12 and that HTRs have an increased ventilatory response to exercise,14 we decided to test the hypothesis that chemoreceptor sensitivity is increased in HTRs and that this mechanism is related to exercise hyperpnea after heart transplantation. For this purpose, we determined minute ventilation and MSNA in HTRs with...
normal left ventricular ejection fraction and in closely matched referent subjects.

Methods

Subjects

The study included 19 HTRs and 11 healthy referent subjects. Healthy referent subjects were recruited by panel advertisement in our hospital. The study protocol was approved by the ethics committee of Erasme Hospital. All patients and referent subjects agreed to participate in the study.

Measurements

Patients and referent subjects were studied in supine resting conditions in a quiet experimentation room. All were instrumented to measure HR by continuous ECG recording (Siemens). BP was determined every minute by an automatic sphygmomanometer (Physiocontrol Collin BP-880). VT (pneumotacometer) and end-tidal carbon dioxide partial pressure (PETCO2; M.E.C. capnometer) were assessed while subjects breathed through a mouthpiece with a nose clip, which guaranteed exclusive mouth breathing. Arterial blood oxygen was monitored continuously with a pulse oximeter (Nellcor). MSNA was recorded continuously with multiunit recordings of postganglionic sympathetic activity, measured from a nerve fascicle in the peroneal nerve posterior to the fibular head. Baseline recordings were obtained for 5 minutes once subjects had reached stable ventilation.

Chemoreflex Activation

The protocol used to test the chemoreceptor responses to isocapnic hypoxia and hyperoxic hypercapnia was the same as in previous studies. After a 5-minute baseline period of stable ventilation, peripheral chemoreceptors were activated for 3 minutes by exposure to hypoxia (10% O2 in 90% N2); activation of central chemoreceptors was prevented during these 3 minutes by adding carbon dioxide to the inspired gas mixture. Central chemoreceptors were activated by hyperoxic hypercapnia (7% CO2 and 93% O2) for 3 minutes, again after a 5-minute baseline period of stable ventilation; maintenance of hypoxia during central chemoreceptor stimulation minimized the activation of peripheral chemoreceptors. The sequence of central and peripheral chemoreflex activation was randomized in all subjects. A 15-minute rest period was ensured between the first intervention and the next 5-minute baseline period of stable ventilation.

Changes in the cardiorespiratory variables during central chemoreceptor testing were presented as means of the 3-minute exposures to hyperoxia and hyperoxic hypercapnia. During peripheral chemoreceptor testing, changes in cardiorespiratory variables are presented by minute during 3-minute exposure to hypoxia.

Cardiopulmonary Exercise Testing

Sixteen HTRs and 10 referent subjects underwent a maximum, symptom-limited exercise test on the cycle ergometer. They started with 1-minute unloaded pedaling; the load was subsequently increased by 10 W every minute.Expired gas was assessed in the mixing chamber and sampled with an O2 and CO2 analyzer while VT was also recorded (SensorMedics Corp). Ventilation and gas concentrations were averaged over 30 seconds, and from these values, VE, the rate of oxygen uptake (VO2), the rate of carbon dioxide production (VCO2), and the respiratory exchange ratio were derived. HR was recorded by a continuously monitored ECG, and systolic and diastolic BP were determined at the end of each workload by an automatic sphygmomanometer. Peak VO2 was defined as the VO2 during the last 30 seconds of peak exercise.

The adequacy of ventilation/perfusion matching was assessed by determining the ratio of physiological dead space to tidal volume ratio (VT/VT) at the beginning of the exercise (while subjects were pedaling 20 W for 30 seconds) and at peak exercise. VT/VT was calculated from the Bohr equation. PETCO2 was used as an estimate of PaCO2.

Statistical Analysis

All the data except variables during hyperoxic hypercapnia are presented as mean±SE. Variables during central chemoreceptor sensitivity testing were not distributed normally and are presented as medians (interquartile [IC]). Baseline quantitative variables were compared by unpaired t test. Responses to hypoxia were compared by ANOVA, with time (baseline versus intervention) and group as the factors. The group-by-time interaction was tested. Because the hypoxic ventilatory response correlates to the body surface area,2,20,21 changes in ventilation in response to hypoxia were normalized for body surface area and related to the ventilatory response to exercise (characterized by the regression slope relating ventilation to CO2 output during exercise, VE/VCO2 slope) through linear regression analysis.

Responses to hypercapnia were compared by a Mann-Whitney test. Ventilatory responses to hypercapnia at rest were related to the VE/VCO2 slope during exercise with Spearman correlation coefficients. The level of statistical significance was fixed at P<0.05.

Results

Subject

Nineteen (14 male) HTRs (age, 54±3 years; body mass index, 26±1 kg/m2) and 11 (9 male) referent subjects (age, 50±4 years; body mass index, 25±1 kg/m2) matched for age, gender, and body mass index took part in our study. The mean

Figure 1. Changes in VE (L/min), MSNA (percent baseline amplitude), and arterial blood oxygen saturation (Sat, %) in referent group (dotted line) and HTRs (straight line) during normoxia and 3 consecutive minutes of hypoxia. Comparisons by ANOVA repeated measurements with group and time as factors.
time from heart transplantation was 7.2±1.1 years (range, 1.0 to 16.5 years). HTRs had normal left ventricular ejection fraction estimated by echocardiography (60±2%; n=13) and/or by resting radionuclide ventriculography (59±3%; n=18). HTRs were on various combinations of immunosuppressive treatment and were receiving cyclosporine (n=17), azathioprine (n=6), tacrolimus (n=1), and mofetil mycophenolate (n=3). Some HTRs also were taking calcium channel blockers (n=9), angiotensin-converting enzyme inhibitors (n=11), ß-blockers (n=4), and diuretics (n=8). No patient suffered from acute allograft rejection at the time of the study. One patient was diabetic and was on oral antidiabetic treatment. For ethical reasons, medication was left unchanged in the HTRs. All referent subjects had a normal physical examination, and none was taking any medication.

**Baseline Room Air Breathing**
HTRs had higher MSNA (52±4 versus 34±3 bursts/min; P<0.01) and faster HRs (83±3 versus 68±3 bpm; P<0.01) than the referent subjects. Mean arterial BP of 107±3 mm Hg was higher in the HTRs than in the referent subjects (98±3 mm Hg), but the difference was not significant. Both groups had nearly identical arterial blood oxygen saturations (96.4±0.3% versus 96.2±0.4% in the HTRs and referent group, respectively; P=NS). V̇E was slightly larger (6.8±0.2 versus 6.5±0.2 L/min) in HTRs than in the referent subjects, but the difference was not significant (P=NS). PetCO₂ was lower (35±1 versus 39±1 mm Hg; P<0.01) in the HTRs than in the referent group.

**Isocapnic Hypoxia**
The increases in V̇E in response to the 3 minutes of hypoxia were more marked in the HTRs than in the referent subjects (P<0.01, ANOVA) despite identical reductions in arterial oxygen saturation (Figure 1 and Figure 2). The enhanced ventilatory response to hypoxia was also paralleled by a larger rise in MSNA in the HTRs (P<0.05, ANOVA) (Figure 1 and Figure 2). Mean BP and PetCO₂ changes were comparable in the 2 groups (P=NS, ANOVA), whereas the increase in HR was less marked in the HTRs (P<0.01, ANOVA).

**Hypercapnic Hypoxia**
Baseline values of V̇E (HTRs, 6.9 L/min [IC, 1.3 L/min]; referent group, 6.4 L/min [IC, 0.8 L/min]; P=NS) and oxygen saturation (HTRs, 97.0% [IC, 1.1%]; referent group, 98.3% [IC, 1.0%]; P=NS) were not different between HTRs and referent subjects before central chemoreceptor testing. Mean BP was higher in HTRs than in the referent group, but the difference did not reach significance (108 mm Hg [IC, 46 mm Hg] versus 96 mm Hg [IC, 15 mm Hg]; P=NS). PetCO₂ during room air breathing was lower in HTRs than in the referent subjects (36 mm Hg [IC, 4 mm Hg] versus 39 mm Hg [IC, 3 mm Hg]; P<0.001). Although the increase in PetCO₂ was larger in HTRs than in the referent group during hypercapnia, the increases in mean BP, HR, ventilation, MSNA, and oxygen saturation were similar in the 2 groups (Table 1).

**TABLE 1. Comparison of the Increases in Mean Arterial BP, HR, V̇E, MSNA, PetCO₂, and Arterial Blood Oxygen Saturation Between HTRs and the Referent Group During Hyperoxic Hypercapnia**

<table>
<thead>
<tr>
<th></th>
<th>Referent Group</th>
<th>HTR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=11)</td>
<td>(n=19)</td>
<td></td>
</tr>
<tr>
<td>∆Mean BP, mm Hg</td>
<td>11.2 (6.0)</td>
<td>8.1 (11.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>∆HR, bpm</td>
<td>1 (11)</td>
<td>2 (5)</td>
<td>0.64</td>
</tr>
<tr>
<td>∆V̇E, L/min</td>
<td>5.3 (3.5)</td>
<td>6.5 (4.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>∆MSNA, % of baseline</td>
<td>33 (26)</td>
<td>35 (32)</td>
<td>0.11</td>
</tr>
<tr>
<td>∆PetCO₂, mm Hg</td>
<td>9 (2)</td>
<td>12 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>∆Sat, %</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Sat indicates saturation. Values in parentheses are IC. Despite the larger increase in PetCO₂ in HTR, all other variables increase similarly in both groups.
The VD/VT ratio at the workload of 20 W did not differ between groups (0.22 versus 0.25; P=0.20). No difference was observed in the Vd/Vt ratio at peak load between the 2 groups (0.22 versus 0.25; P=0.20).

TABLE 2. Comparison of Exercise Test Variables in the Referent Group and HTRs

<table>
<thead>
<tr>
<th>Referent Group</th>
<th>HTRs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RER</td>
<td>1.4±0.3</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Peak load, W</td>
<td>195±19</td>
<td>89±7</td>
</tr>
<tr>
<td>Peak V̇O₂, mL·kg⁻¹·min⁻¹</td>
<td>31.1±2.7</td>
<td>17.7±1.1</td>
</tr>
<tr>
<td>AT, mL·kg⁻¹·min⁻¹</td>
<td>17.8±2.0</td>
<td>10.8±0.4</td>
</tr>
<tr>
<td>Peak V̇E, L/MIN</td>
<td>92±7</td>
<td>63±5</td>
</tr>
<tr>
<td>Peak oxygen pulse, mL/beat</td>
<td>14.5±1.1</td>
<td>10.2±0.7</td>
</tr>
<tr>
<td>Peak V̇E/No₂</td>
<td>39.1±1.7</td>
<td>48.0±3.0</td>
</tr>
<tr>
<td>Peak V̇E/No₂</td>
<td>30.2±1.2</td>
<td>36.7±1.6</td>
</tr>
</tbody>
</table>

RER indicates respiratory exchange ratio; AT, anaerobic threshold.

Cardiopulmonary Exercise Testing

HTRs and referent subjects achieved the same respiratory exchange ratio, but HTRs had lower peak V̇O₂, lower peak load in Watts, lower anaerobic threshold, lower peak V̇E, lower peak oxygen pulse, higher peak V̇E/V̇O₂, and higher peak V̇E/V̇CO₂ (Table 2). HTRs compared with referent subjects presented with a larger ventilatory response to exercise, as evidenced by a steeper V̇E/V̇CO₂ slope (38±2 versus 29±1 L/mm Hg; P<0.01). The Vd/Vt ratio at the workload of 20 W did not differ between referent subjects and HTRs (0.33 versus 0.31; P=0.66). No difference was observed in the Vd/Vt ratio at peak load between the 2 groups (0.22 versus 0.25; P=0.20).

Chemosensitivity and the Ventilatory Response to Exercise

The V̇E/V̇O₂ slope during exercise in the HTR patients was positively correlated to peripheral chemosensitivity at rest, expressed as the ratio between the rise in ventilation and the reduction in oxygen saturation during the 3 minutes of hypoxia normalized for body surface area, as shown in Figure 3 (r=0.57; n=16; P<0.05). The V̇E/V̇CO₂ slope during exercise in HTRs was also directly related to central chemosensitivity at rest, expressed as the ratio between V̇E and PetCO₂ during the 3 minutes of hypercarbia (R_{ppearance}=0.50, P<0.05).

Figure 3. Linear regression between the ventilatory responses to exercise expressed as the slope between V̇E and V̇CO₂ during exercise (slope V̇E/V̇CO₂) and peripheral chemosensitivity at rest (expressed as ventilation per saturation, normalized for body surface area) in HTRs.

The V̇E/V̇CO₂ slope in HTRs was related to peak PetCO₂ (r=0.67, P=0.0001), but it was not related to peak Vd/Vt (r=0.25, P=0.36).

Discussion

The original finding of this study is that peripheral chemoreceptor sensitivity is increased in HTRs and may contribute to abnormally increased V̇E during exercise in HTRs. To the best of our knowledge, this is the first study to assess chemoreflex control after cardiac transplantation.

Previous studies have shown that patients with congestive heart failure present with a high V̇E/V̇CO₂ ratio during exercise,11 and this is associated with a poor prognosis.22 The increase in the V̇E/V̇CO₂ ratio during exercise in congestive heart failure is explained by altered ventilation/perfusion matching23 and by early lactic acidosis,23 but also by increased chemoreceptor gain for both PaO₂ and PaCO₂.17,22,24 This augmented exercise-induced increase in ventilation in congestive heart failure is related to impaired autonomic and baroreceptor control as manifested by increased MSNA,17 decreased HR variability, and increased BP variability with predisposition to arrhythmia and sudden death.25 Our present study shows that heart transplantation does not restore normal peripheral chemoreceptor function.

Peripheral Chemoreflex Sensitivity

The increased peripheral chemoreflex sensitivity we observed in our HTRs cannot be explained by differences in resting oxygen saturation between the HTRs and referent subjects or by left ventricular systolic dysfunction in the patients. The trend toward a larger baseline V̇E and lower PetCO₂ in the presence of identical oxygen saturations in HTRs suggests that these patients also present with increased chemoreflex sensitivity under resting normoxemic conditions. These results are in keeping with our previous observation that HTRs compared with controls present with higher resting peripheral chemoreceptor drive with increased sympathetic nervous system tone under normoxemic conditions,26 which further suggested altered chemoreflex control in HTRs. Hyperventilation inhibits the sympathetic nerve response to chemoreflex activation through activation of pulmonary stretch afferents.27 Our observation of increased sympathetic nerve response to hypoxia in the presence of increased V̇E supports the importance of peripheral chemoreflex enhancement of MSNA after cardiac transplantation. It is unlikely that the lower PetCO₂ in the HTRs can explain our findings. If anything, the slightly lower PetCO₂ would have hampered the ventilatory and sympathetic response to hypoxia in the HTRs.

There are several possible explanations for the enhancement of peripheral chemoreceptor sensitivity in HTRs. First, denervation of the transplanted heart and associated cardiopulmonary baroreceptor dysfunction could increase peripheral chemoreceptor sensitivity by a mechanism similar to the cardiopulmonary baroreceptor unloading by changes in body position in healthy subjects.28 Second, impairment of arterial baroreceptor sensitivity by chronic cyclosporine intake29 may attenuate inhibitory stimuli toward peripheral chemoreceptors30 and result in a net increase in the sensitivity to hypoxia. Third, systemic arterial hypertension may enhance peripheral chemoreceptor sensitivity...
to an extent similar to that in patients with essential hypertension. Finally, mechanisms associated with increased peripheral chemoreceptor sensitivity in heart failure could have a lingering effect on chemoreceptor function in patients after cardiac transplantation.

Central Chemoreflex Sensitivity
This study also demonstrates that HTRs have a normal ventilatory and MSNA response to hypercapnia while maintaining an abnormal response to isocapnic hypoxia. It is interesting to speculate why central chemoreceptor sensitivity is normalized while peripheral chemosensitivity remains altered in this group of patients. One possible cause of this apparent discrepancy may relate to the inhibitory interaction between the arterial and cardiopulmonary baroreceptors and the peripheral chemoreceptors. In HTRs, cardiac baroreceptor afferents are cut and become dysfunctional. Arterial baroreceptor sensitivity is impaired because of chronic cyclosporine uptake. The close proximity of baroreceptor and chemoreceptor neurons in the solitary and paramedian reticular nuclei in the medulla could explain the interactions between these reflexes; however, such an interference between baroreceptors and central chemoreceptors has not been described. Thus, although the surgical procedure improves cardiac function, which may favor normalization of central chemoreceptor sensitivity, it also alters inhibitory loops and necessitates drug treatments, which may suppress baroreflex restraint on peripheral chemoreflex control. This issue requires further investigation.

Exercise Hyperpnea
Our results are consistent with observations that cardiac transplantation does not normalize exercise hyperpnea after cardiac transplantation. The exact mechanisms of the increased ventilatory response to exercise in HTRs remain unclear. Ventilation perfusion abnormalities resulting in increased dead space ventilation from an attenuated cardiac chronotropic response to exercise, respiratory muscle weakness, and hypoperfusion have been suggested to explain exercise hyperpnea in HTRs. Our HTRs disclosed a Vd/VT ratio similar to that of the referent group at the beginning and end of the ergospirometry. However, because the use of PetCO2 instead of PacO2 may lead to underestimation of Vd/VT, we cannot exclude that increased Vd/VT contributed to exercise hyperpnea in our HTRs. Nevertheless, we believe that the Vn/VT contribution to exercise hyperpnea is likely to be of minor importance in HTRs. This is based on the following observations. First, we estimated PacO2 in HTRs and control subjects using the following formula: PacO2 = 5.5 + (0.9 × PetCO2) − (0.0021 × Vt), as suggested by Jones et al. This method of PacO2 estimation is used in clinical studies on heart failure patients when only end-tidal PetCO2 is measured. Afterward, we recalculated Vd/VT using PacO2 in the Bohr equation. Although we observed a small difference between Vd/VT in the patients and control subjects at rest, we still could not find a significant difference between the 2 groups at peak exercise (P = 0.84). Second, the Vn/VCO2 slope correlated strongly with peak PetCO2, but it was not related to peak Vd/VT in HTRs. This further suggests that increased ventilation during exercise in HTRs is an integral part of deranged cardiorespiratory control rather than an impaired ventilation/perfusion matching in the lungs.

Another important finding of our study is that exercise hyperpnea, assessed by the Ve/VCO2 slope, is related to chemoreceptor sensitivity to hypoxia after transplantation. This is in accordance with previous observations that peripheral chemoreceptors, which sense the oscillations in H+–Paco2, K+–catecholamines, and body temperature, play an important modulatory role in the regulation of ventilation during exercise. The ventilatory response to exercise in normal humans, as well as in patients with heart failure, is positively related to chemosensitivity determined in resting conditions. Our study extends this observation to HTRs and suggests that increased peripheral chemoreflex sensitivity and exercise hyperpnea share common pathophysiological mechanisms in these patients.

The last interesting finding is that central chemosensitivity at rest is also related to ventilatory response to exercise in HTRs. The ventilatory response to hypercapnia correlates to the ventilatory response to exercise in normal subjects and athletes; we extend this observation to patients after heart transplantation. However, the ventilatory response from central chemoreceptors was strictly normal in these HTRs. Thus, central chemoreceptor sensitivity contributes to ventilation during exercise but cannot explain the exercise hyperpnea.

In conclusion, our study is the first to demonstrate increased peripheral chemoreceptor sensitivity in HTRs. The increased ventilatory response to exercise observed in HTRs is related to resting peripheral chemoreflex hypersensitivity.

Study Limitations
A positive correlation between the ventilatory response to hypoxia and exercise Ve/VCO2 does not necessarily imply a cause-effect relationship because of the complex pathophysiology that sustains exercise hyperpnea. Other potential limitations to our study are the fact that the data analysis was not performed in a blinded fashion; the possibility that hypertension, almost always accompanying heart transplantation, may have contributed to our findings; and, as discussed above, the absence of PacO2 measurements.

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Disclosures
None.

References
Clinical Perspective

Heart failure is characterized by decreased exercise capacity and abnormally increased ventilatory response to exercise. The ventilatory response to exercise, however, remains comparable to that of patients with moderate heart failure after successful heart transplantation. Several mechanisms such as chronotropic incompetence, increased dead space ventilation in the presence of ventilation-perfusion abnormalities, and abnormal muscle reflex regulation can account for this observation. Pulmonary function also can affect pulmonary gas exchange and increase ventilation once the critical value of lung diffusion capacities is attained. We tested the hypothesis that exercise hyperpnea is related to hypoxia in borderline hypertensive subjects. Hypertension. 1988;11:608–612.


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