Increased Peripheral Chemoreceptors Sensitivity and Exercise Ventilation in Heart Transplant Recipients

Agnieszka Ciarka, MD; Nicolas Cuylits, MD; Jean-Luc Vachiery, MD; Michel Lamotte, BSc; Jean-Paul Degaute, MD, PhD; Robert Naeije, MD, PhD; Philippe van de Borne, MD, PhD

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; \( \text{P}<0.01 \)) and heart rates (83±3 versus 68±3 bpm; \( \text{P}<0.01 \)) during room air breathing. The ventilatory response to hypoxia was higher in HTRs than in referent subjects (\( \text{P}<0.01, \text{ANOVA} \)). The increase in MSNA also was more marked during hypoxia in the HTRs than in the referent group (\( \text{P}<0.05, \text{ANOVA} \)). 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 CO\(_2\) output, was steeper in HTRs than in referent subjects (38±2 versus 29±1 L/min Hg; \( \text{P}<0.01 \)). Exercise ventilation in HTRs was related to the ventilatory response to isocapnic hypoxia (\( r=0.57; n=16; \text{P}<0.05 \)) and to the ventilatory response to hyperoxic hypercapnia (\( r=0.50; n=16; \text{P}<0.05 \)).

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 (PaO\(_2\)). Peripheral chemoreceptors play an important modulatory role in the regulation of ventilation during exercise. 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 (PaCO\(_2\)). Their activation increases minute ventilation (V\(_{\text{E}}\)), heart rate (HR), blood pressure (BP), and sympathetic activity.9 In normal subjects and athletes, there is a positive relation between V\(_{\text{E}}\) and the rate of CO\(_2\) production (V\(_{\text{CO}}\)) 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 increased 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). Ve (pneumotacometer) and end-tidal carbon dioxide partial pressure (PetCO\(_2\); 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.\(^1\)\(^6\),\(^1\)\(^7\) After a 5-minute baseline period of stable ventilation, peripheral chemoreceptors were activated for 3 minutes by exposure to hypoxia (10% O\(_2\) in 90% N\(_2\)); 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% CO\(_2\) and 93% O\(_2\)) for 3 minutes, again after a 5-minute baseline period of stable ventilation; maintenance of hyperoxia 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 cardiopulmonary variables during central chemoreceptor testing are presented as means of the 3-minute exposures to hypercapnia. During peripheral chemoreceptor testing, changes in cardiopulmonary variables are presented minute 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 measured in the mixing chamber and sampled with an O\(_2\) and CO\(_2\) analyzer while Ve was also recorded (SensorMedics Corp). Ventilation and gas concentrations were averaged over 30 seconds, and from these values, Ve, the rate of oxygen uptake (Vo), the rate of carbon dioxide production (VCO\(_2\)), and the respiratory exchange ratio were derived. HR was recorded by a continuously monitored ECG, and systolic and diastolic BPs were determined at the end of each workload by an automatic sphygmomanometer. Peak Vo was defined as the Vo 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 (Vd/Vt) at the beginning of the exercise (while subjects were pedaling 20 W for 30 seconds) and at peak exercise. Vd/Vt was calculated from the Bohr equation. PetCO\(_2\) was used as an estimate of PaCO\(_2\).\(^1\)\(^8\)

**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,\(^2\)\(^,\)\(^2\)\(^0\),\(^2\)\(^1\) 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 CO\(_2\) output during exercise, Ve/VcO\(_2\), slope) through linear regression analysis.\(^1\)\(^1\)

Responses to hypercapnia were compared by a Mann-Whitney test. Ventilatory responses to hypercapnia at rest were related to the Ve/VcO\(_2\) slope during exercise with Spearman correlation coefficients. The level of statistical significance was fixed at P<0.05.

**Results**

**Subjects**

Nineteen (14 male) HTRs (age, 54±3 years; body mass index, 26±1 kg/m\(^2\)) and 11 (9 male) referent subjects (age, 50±4 years; body mass index, 25±1 kg/m\(^2\)) matched for age, gender, and body mass index took part in our study. The mean...
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), β-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). VE 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 VE 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 VE (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, VE, MSNA, Petco₂, and Arterial Blood Oxygen Saturation Between HTRs and the Referent Group During Hypercapnic Hypoxia**

<table>
<thead>
<tr>
<th></th>
<th>Referent Group (n=11)</th>
<th>HTR (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMean BP, mm Hg</td>
<td>11.2 (6.0)</td>
<td>8.1 (11.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>ΔHR, bpm</td>
<td>1 (11)</td>
<td>2 (5)</td>
<td>0.64</td>
</tr>
<tr>
<td>ΔVE, L/min</td>
<td>5.3 (3.5)</td>
<td>6.5 (4.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>ΔMSNA, % of baseline</td>
<td>33 (26)</td>
<td>35 (32)</td>
<td>0.11</td>
</tr>
<tr>
<td>ΔPetco₂, mm Hg</td>
<td>9 (2)</td>
<td>12 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>ΔSat, %</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
minutes of hypercapnia (RSpearman expressed as ventilation per saturation, normalized for body
surface area) in HTRs.

The V˙E/V˙CO2 slope during exercise in the HTR patients was
steeper V˙E/V˙CO2 slope (38 \pm 2 versus 29 \pm 1 L/mm Hg; P<0.01).
The V˙E/V˙O2 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 V˙E/V˙O ratio at peak load between
the 2 groups (0.22 versus 0.25; P=0.20).

Cardiopulmonary Exercise Testing
HTRs and referent subjects achieved the same respiratory
exchange ratio, but HTRs had lower peak Vo2, lower peak load
in Watts, lower anaerobic threshold, lower peak Ve, lower peak
oxygen pulse, higher peak V˙E/Vo, and higher peak V˙E/V˙CO2
(Table 2). HTRs compared with referent subjects presented with
a larger ventilatory response to exercise, as evidenced by a
steeper V˙E/V˙CO2 slope (38 \pm 2 versus 29 \pm 1 L/mm Hg; P<0.01).
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Chemosensitivity and the Ventilatory Response
to Exercise
The V˙E/V˙O2 slope during exercise in the HTR patients was
positively correlated to peripheral chemosensitivity at rest, ex-
pressed 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 V˙E/V˙CO2 slope during exercise in HTRs
was also directly related to central chemosensitivity at rest,
expressed as the ratio between V˙E and PetCO2 during the 3
minutes of hypercapnia (R_{spearman}=0.50, P<0.05).

The V˙E/V˙CO2 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 chemore-
ceptor sensitivity is increased in HTRs and may contribute to
abnormally increased Ve 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 V˙E/V˙CO2 ratio during exercise,11 and this is associated with a poor prognosis.22
The increase in the V˙E/V˙CO2 ratio during exercise in congestive
heart failure is explained by altered ventilation/perfusion matching23 and by early lactic acidosis,23 but also by in-
creased chemoreceptor gain for both PaO2 and PaCO2.12,22,24
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 Ve and lower PetCO2 in the
presence of identical oxygen saturations in HTRs suggests
that these patients also present with increased chemoreflex
sensitivity under resting normoxic conditions. These re-
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 normoxic conditions,26 which further
suggested altered chemoreflex control in HTRs. Hyperventi-
lation 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 Ve supports the impor-
tance 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, denerva-
tion of the transplanted heart and associated cardiopulmonary
baroreceptor dysfunction could increase peripheral chemoreces-
tor sensitivity by a mechanism similar to the cardiopulmonary
baroreceptor unloading by changes in body position in healthy
subjects.28 Second, impairment of arterial baroreceptor sensitiv-
ity 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

<table>
<thead>
<tr>
<th>Referent Group</th>
<th>HTRs</th>
<th>P value</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 Vo2, mL · kg⁻¹ · min⁻¹</td>
<td>31.1±2.7</td>
<td>17.8±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 Ve, 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 Ve/No₂</td>
<td>39.1±1.7</td>
<td>48.0±3.0</td>
</tr>
<tr>
<td>Peak Ve/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.

Figure 3. Linear regression between the ventilatory responses
to exercise expressed as the slope between V˙E and V˙CO2 during
exercise (slope V˙E/V˙CO2) and peripheral chemosensitivity at rest
(expressed as ventilation per saturation, normalized for body
surface area) in HTRs.
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 interaction 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: 

\[
Paco2 = 5.5 + (0.9 \times Petco2) - (0.0021 \times Vt)
\]

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 Vn/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 Ve/VO2 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/VO2 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/VO2 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
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**Clinical Perspective**

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