Objective—During hypoxia, active substances released by the endothelium play a key role in the cardiovascular and respiratory responses elicited to optimize oxygen delivery. As hypercholesterolemia is a major cause of endothelial dysfunction, it may interfere with these responses.

Methods and Results—We studied cardiovascular and ventilatory responses to acute systemic hypoxia in 14 patients with hypercholesterolemia (HC) and 13 control (CO) subjects. Oxygen saturation decreased similarly in both groups. Diastolic blood pressure increased only in the HC group (P=0.0002) and, despite systolic blood pressure increases both in the HC group, 140±4 (95% confidence interval [CI],131 to 149 mm Hg) to 154±4 mm Hg (95% CI,145 to 164 mm Hg), and in the CO group, 133±3 (95% CI,126 to 140 mm Hg) to 140±4 mm Hg (95% CI,132 to 148 mm Hg), the HC group showed an enhanced pressor response (P=0.03, group comparison). Both groups had increased forearm blood flow, but the decrease in forearm vascular resistance in the CO group, 40±5 (95% CI, 30 to 51 UR) to 31±4 UR (95% CI,23 to 39 UR) (P=0.0001) was not seen in the HC group, 29±3 (95% CI, 22 to 37 UR) to 26±3 UR (95% CI, 20 to 33 UR), (P=0.03, group comparison).

Conclusions—Hypercholesterolemic patients demonstrate a hyperreactive pressor response and absence of forearm vasodilation during acute systemic hypoxia. (Arterioscler Thromb Vasc Biol. 2003;23:1660-1666.)

Key Words: lipids | endothelium | hypoxia | blood flow | blood pressure
TABLE 1. Study Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Control</th>
<th>HC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>37±2</td>
<td>39±3</td>
<td>0.60</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4±0.7</td>
<td>24.8±0.7</td>
<td>0.67</td>
</tr>
<tr>
<td>Men/Women</td>
<td>6/7</td>
<td>7/7</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118±2</td>
<td>120±2</td>
<td>0.63</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78±1</td>
<td>77±1</td>
<td>0.53</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>76±1</td>
<td>81±2</td>
<td>0.27</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>173±4</td>
<td>310±14</td>
<td>...</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>124±6</td>
<td>234±14</td>
<td>...</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>44±3</td>
<td>51±2</td>
<td>0.16</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>94±13</td>
<td>119±12</td>
<td>0.17</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>98±3</td>
<td>92±3</td>
<td>0.19</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14±0.3</td>
<td>14±0.4</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Blood pressure values represent the mean of two consecutive measurements obtained with a mercury manometer after the patients had been sitting for ~10 minutes in a calm room. Values are presented as mean±SE.

and 7 men; total cholesterol: 310±14 mg/dL, range: 250 to 445 mg/dL; LDL cholesterol: 234±14 mg/dL, range: 174 to 366 mg/dL; triglycerides: 119±12 mg/dL, range: 78 to 188 mg/dL) were studied. These patients had been referred to the Lipid Clinics of the Heart Institute of the University of São Paulo for evaluation of HC. Eleven were presented with a diagnosis of familial hypercholesterolemia. In the HC group, these differences were not statistically significant.

Experimental Protocol and Procedures

An established protocol currently used by Somers et al13 and our group was used. The individuals were not allowed to drink caffeinated products on the morning of the test. Studies were initiated after at least a 20-minute rest period in the supine position in a quiet room. Measurements were obtained for 2 minutes while the subjects breathed room air (baseline recording) and then for 5 minutes (analyzed using a minute-by-minute format) during isocapnic hypoxia. The latter was induced by administering 10% O₂ in N₂ with titrated CO₂ via a mouthpiece, using a noseclip to ensure exclusive mouthbreathing.

Statistical Analyses

Statistical analyses were performed with SAS software. Demographic and baseline measurements were compared using 2-tailed unpaired t test. The gender distribution was compared using Fisher’s exact test.

Responses to hypoxia were assessed by comparing baseline values with the mean values obtained during minutes 3, 4, and 5 of isocapnic hypoxia (ie, steady-state of the response to hypoxia); analysis of variance for repeated-measures was used for this comparison, with time (baseline versus intervention) as the within factor and group (CO versus CH) as the between factor. The key effect was the group-by-time interaction. Graphics show the changes in variables that occurred during minutes 3, 4, and 5 of hypoxia compared with baselines values. Data are presented as the mean±SEM. A probability value of <0.05 was considered significant.

Results

Subject Characteristics

The mean age, body mass index, sex distribution, arterial blood pressure, HDL cholesterol level, triglyceride level, fasting glucose level, and hemoglobin were similar between groups (Table 1).

Resting Values

At baseline, the mean oxygen saturation, end-tidal CO₂, minute ventilation, heart rate, and systolic, diastolic and mean arterial pressure in patients with HC were similar to values in CO subjects. Although a trend toward higher forearm blood flow and lower forearm vascular resistance was observed in the HC group, these differences were not statistically significant (P=0.09 and P=0.07, respectively). The baseline rate pressure product was higher in the HC group compared with the CO group (P=0.03) (Table 2).

Responses to Isocapnic Hypoxia

The magnitude of the hypoxia-induced decrease in oxygen saturation was similar in both groups (Table 3 and Figure 1), and the isocapnia was maintained (Table 3). Both groups had similar increases in minute ventilation during the hypoxia (Table 3 and Figure 1).
The marked increase in heart rate observed in the hypercholesterolemic patients was comparable to that in the CO subjects (Table 3 and Figure 2).

Diastolic blood pressure did not increase in the CO subjects (P=0.08) but increased in the hypercholesterolemic patients (P=0.0002). The mean arterial blood pressure increased in both groups but to a greater extent in the HC group (P=0.05). Moreover, despite the significant increase in systolic blood pressure in the HC group, 140±4 mm Hg (95% confidence interval [CI], 131 to 149 mm Hg) to 154±4 mm Hg (95% CI, 145 to 164 mm Hg) (P=0.0001), and in the CO group, 133±3 (95% CI, 126 to 140 mm Hg) to 140±4 mm Hg (95% CI, 132 to 148 mm Hg) (P=0.0017), hypercholesterolemic patients showed an enhanced pressor response (P=0.03, group comparison). In addition, the increase in the rate pressure product was significantly higher in patients with HC compared with CO subjects (P=0.02, group comparison) (Table 3 and Figures 2, 3, and 4). Whereas both groups demonstrated a similar increase in forearm blood flow, the decrease in forearm vascular resistance observed in the CO group (P=0.0001), 40±5 (95% CI, 30 to 51 UR) to 31±4 UR (95% CI, 23 to 39 UR), was not seen in the HC group (P=0.14), 29±3 (95% CI, 22 to 37 UR) to 26±3 UR (95% CI, 20 to 33 UR; P=0.03, group comparison) (Table 3 and Figures 2, 3, and 4).

**Discussion**

This is the first study to investigate integrated respiratory and cardiovascular responses to acute systemic hypoxia in humans with HC. The major findings are that, while the ventilatory response is not impaired, cardiovascular responses are altered. First, hypercholesterolemic patients demonstrate hyperreactivity of the pressor response. Second, patients with

**TABLE 3. Responses to Isocapnic Hypoxia**

<table>
<thead>
<tr>
<th></th>
<th>Normal Control Subjects (n=13)</th>
<th>HC Group (n=14)</th>
<th>Interaction, Group-by-Time, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Room Air</td>
<td>Hypoxia</td>
<td>Baseline Room Air</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>97±0.2</td>
<td>81±1.4*</td>
<td>97±0.3</td>
</tr>
<tr>
<td>End-tidal CO₂, mm Hg</td>
<td>39±1.1</td>
<td>39±1.0</td>
<td>39±0.7</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>6.9±0.7</td>
<td>12.5±1.3*</td>
<td>7.9±0.6</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>133±3</td>
<td>140±4*</td>
<td>140±4</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98±3</td>
<td>101±3*</td>
<td>99±4</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>78±3</td>
<td>81±3</td>
<td>79±4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±3</td>
<td>84±3*</td>
<td>77±3</td>
</tr>
<tr>
<td>Rate pressure product</td>
<td>9293±412</td>
<td>11 789±600*</td>
<td>10 672±571</td>
</tr>
<tr>
<td>Forearm blood flow, mL/100 mL per min</td>
<td>2.9±0.3</td>
<td>3.9±0.4*</td>
<td>4.4±0.8</td>
</tr>
<tr>
<td>Forearm vascular resistance, UR</td>
<td>40±5</td>
<td>31±4*</td>
<td>29±3</td>
</tr>
</tbody>
</table>

Baseline values were obtained immediately before hypoxia while subjects were breathing room air. Hypoxia values were the mean responses analyzed during minutes 3, 4, and 5 of hypoxia. Values are presented as mean±SE.

*P<0.05 vs baseline
†P<0.05 for the group-by-time interaction term
HC do not exhibit physiological forearm vasodilation during acute systemic isocapnic hypoxia.

The effects of systemic hypoxia on the cardiovascular system are complex and interdependent. They include the reflex effects of peripheral chemoreceptor stimulation, secondary effects of chemoreceptor-induced hyperventilation, effects arising from the influence of hypoxia on the central nervous system, effects of circulating hormones, and local effects on the heart and blood vessels.2

The first major finding in this study was the hyperreactive pressor response to the systemic hypoxia in the HC group. The overall systemic hemodynamic response during hypoxia reflects the increase in cardiac output and decrease in systemic vascular resistance.2,5 We found that only the hypercholesterolemic patients demonstrated an increase in diastolic blood pressure. Moreover, patients with severe HC exhibited greater systolic and mean blood pressure responses to isocapnic hypoxia. These findings reinforce the hypothesis that HC may interfere with blood pressure homeostasis14–16 and raise several important possibilities. First, the decrease in the systemic vascular resistance during hypoxia depends on the bioavailability of NO, which is decreased in patients with HC.5 Second, HC may be associated with a reduction in aortic compliance, which may disrupt acute modulation of the increase in cardiac output that occurs during hypoxia.17 Third, we observed a trend toward an enhanced heart rate response in the HC group; thus, an elevated cardiac output response cannot be ruled out.

The tendency toward a greater heart rate response in the patients with hypercholesterolemia, considering the greater increase in systolic blood pressure, was unexpected. The baroreflex modulates the cardiovascular responses during systemic hypoxia,18 and HC may be associated with depressed baroreflex function due to functional and/or structural factors.19–21 Thus, the heart rate response may occur partially, as a consequence of baroreflex impairment.

In normal humans, despite the increase in muscle sympathetic activity during systemic hypoxia,3 the net effect in territories of skeletal muscle vasculature is vasodilation.5–7,13 Evidence strongly suggests that the synthesis and release of vasoactive substances by the endothelium plays a key role.5–7

The second major finding was that, despite similar levels of hypoxia, the decrease in forearm vascular resistance normally observed was absent in our patients with HC. Several hypotheses may explain this finding. First, there is enhanced sympathetic activity to muscle vasculature during systemic hypoxia. Unfortunately, we did not measure sympathetic nerve activity to muscle in our patients to evaluate the neural component of this vascular response. Nevertheless, Narkiewicz et al22 and our group13 have previously demonstrated that the magnitude of these sympathetic changes parallels that of the ventilatory responses, and we observed no differences in the ventilatory responses between the HC and CO groups. Thus, it is tempting to propose that a selective potentiation of sympathetic nervous activity to muscle vasculature is not the sole explanation for the absence of vasorelaxation in our hypercholesterolemic patients.

Second, HC is characterized by coexisting endothelial dysfunction, the hallmark of which is altered vasodilation to endothelial-dependent vasodilators.10 Thus, endothelial dysfunction associated with severe HC may have led to the impaired forearm vascular response to hypoxia in the HC group. Taguchi et al23 demonstrated in vitro that relaxation of the carotid artery in response to mild and severe hypoxia is
impaired in Watanabe heritable hyperlipidemic rabbits and that the vascular response is mediated by activation of glibenclamide-sensitive potassium channels and by endothelial factors. In humans, NO released by the endothelium and adenosine acting at endothelial A1 receptors have been the most commonly implicated vasoactive substances in the forearm vasodilatory response to systemic hypoxia. Therefore, the abnormal vascular response we observed in the HC group during systemic hypoxia could, at least in part, reflect endothelial dysfunction associated with HC. Unfortunately, data correlating vasodilation elicited by acetylcholine and by systemic hypoxia are not available to permit evaluation of this maneuver (ie, induction of isocapnic hypoxia) as a surrogate test of endothelial function.

In vivo and in vitro studies indicate that NO modulates contractile responses to adrenergic stimulation. Moreover, there is evidence of β-adrenergic vasodilation in human forearm mediated through NO via β2 receptors, also attenuating the vasoconstriction to cathecolamines. Therefore, a more integrated hypothesis to explain our vascular finding is that, despite similar increases in sympathetic nervous system activity, the decreased bioavailability of NO associated with HC potentiated the neurogenic vascular response.
Our hypercholesterolemic patients demonstrated an intriguing finding: a tendency toward a greater heart rate, systolic blood pressure, and forearm blood flow associated with reduced forearm vascular resistance during baseline measurements but absence of forearm vasorelaxation during systemic isocapnic hypoxia. Similar findings of coronary microvascular dysregulation have been demonstrated in patients with type 2 diabetes mellitus and characterized by elevated baseline blood flow, reduced baseline microvascular resistance, and an abnormal increase in resistance during the cold pressor test. It was proposed that the degree of vasodilation at baseline limited the flow response to acute stress. In addition, despite the 20-minute rest period that preceded the cardiorespiratory measurements, elements of our experimental preparation (eg, mouthpiece, noseclip) may have already been eliciting a mild alert or stress response. Thus, the tendency toward differences in baseline values between the groups (ie, trend toward higher forearm blood flow and lower forearm vascular resistance in the HC group) may already reflect a dysregulation of cardiovascular adjustments during minimally stressful situations. In further support of this notion, we should emphasize that the baseline values in the present control group were similar to values observed in controls in our previous studies.

Clinical Implications
Acute episodes of systemic hypoxia may occur during critical phases of ischemic cardiomyopathy, and HC is a prevalent risk factor for this disease. HC is also a common metabolic finding in patients with sleep apnea syndrome. Therefore, one would expect to encounter hypercholesterolemic patients experiencing episodes of systemic hypoxia in clinical practice. The fact that the patients with HC demonstrated marked dysregulation of the cardiovascular responses to systemic hypoxia, characterized by the absence of forearm vasodilation associated with a hyperreactive pressor response, has several important clinical implications. The main one is that the skeletal muscle vascular response is an important adaptive response for optimizing oxygen delivery to vital territories during hypoxia. Therefore, the marked blunting of muscle vasodilation in the hypercholesterolemic patients, which may compromise delivery of oxygen, deserves further attention. The finding of an enhanced rate pressure product in the hypercholesterolemic patients indirectly suggests that HC is associated with a greater consumption of myocardial oxygen. In addition, it has been shown in an acetylcholine-induced vasodilation experiment that the coronary response correlates with flow-mediated brachial artery vasodilation in hypercholesterolemic patients. Therefore, if hypercholesterolemic patients also manifest the same dysregulation of the coronary response during acute oxygen desaturation, the reduced oxygen delivery to cardiac muscle combined with a greater increase in myocardial oxygen demand may be critical. The impaired vasoregulation associated with hypercholesterolemia may underlie poor oxygen delivery to organs and tissues and elicit an enhanced pressor response to increase blood flow, augmenting myocardial oxygen demand. Taken together, it is possible that blunted vasorelaxation associated with enhanced cardiovascular reactivity may impose additional risk of cardiovascular events in hypercholesterolemic patients during acute systemic hypoxia.

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References
Hypercholesterolemia Blunts Forearm Vasorelaxation and Enhances the Pressor Response During Acute Systemic Hypoxia

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