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

José Augusto S. Barreto-Filho, Fernanda Marciano Consolim-Colombo, Grazia Maria Guerra-Riccio, Raul D. Santos, Ana Paula Chacra, Heno Ferreira Lopes, Sandra H. Teixeira, Tânia Martinez, José Eduardo Krieger, Eduardo Moacyr Krieger

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 HC groups, 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 ± 3 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:lll–lll.)

Key Words: lipids ▪ endothelium ▪ hypoxia ▪ blood flow ▪ blood pressure

Acute systemic hypoxia is a very common clinical manifestation of several cardiovascular syndromes such as heart failure, shock, and pulmonary edema. Intermittent acute episodes of systemic hypoxia are also the most important pathophysiological event in sleep apnea syndrome, which is frequently associated with cardiovascular disease. During hypoxia, integrated cardiovascular and respiratory responses critical for maintaining life are activated to compensate for the decrease in oxygen delivery.1,2 Cardiovascular adjustments to systemic hypoxia depend not only on neural mechanisms but also on endothelium, which synthesizes and releases vasoactive substances.3–6 It has been demonstrated that during acute hypoxia in humans, the increase in sympathetic nerve activity to muscle evaluated by microneurography1 is associated with a decrease in muscular vascular resistance.6 It has been proposed that the endothelial release of nitric oxide (NO) and adenosine plays a role in this vasorelaxation.6,7 Moreover, endothelium-derived NO and adenosine produced within the carotid body may modulate ventilatory responses to acute hypoxia.8

Hypercholesterolemia (HC) is a major risk factor for ischemic cardiomyopathy and is frequently associated with hypertensive heart disease. There is also evidence that patients with sleep apnea syndrome often have hypercholesterolemia.9 Consequently, HC is associated with several syndromes that may involve episodes of acute hypoxia. HC is also an important cause of endothelial dysfunction, the hallmark of which is altered vasorelaxation in response to endothelial-dependent vasodilators.10 Moreover, a study in vitro demonstrated that HC impairs the relaxation of the carotid artery to hypoxia.11 Thus, it is reasonable to hypothesize that endothelial dysfunction associated with HC may impair compensatory vascular and also the ventilatory responses during systemic hypoxia in humans. To our best knowledge, the actual consequences of this combination of conditions in humans are unknown. Therefore, we investigated and compared cardiovascular and respiratory responses to acute systemic hypoxia between patients with isolated HC and healthy control subjects.

Methods

Subjects
A carefully selected population of 14 consecutive patients with isolated HC (mean age: 39 ± 3 years, range: 18 to 55 years; 7 women

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From The Hypertension Unit, Heart Institute (InCor), University of São Paulo Medical School, Brazil.
Address correspondence to José Augusto S. Barreto-Filho, MD, Hypertension Unit, Heart Institute–InCor–HCFMUSP, Av.Dr.Eneas de Carvalho Aguiar, 44, 05403-000 São Paulo, Brazil. E-mail jose.barreto@incor.usp.br
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TABLE 1. Study Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Control Subjects (n=13)</th>
<th>HC Group (n=14)</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 mol/L/7W</td>
<td>7 mol/L/7W</td>
<td>0.84</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 patients had been referred to the Lipid Clinics of the Heart Institute of the University of São Paulo for evaluation of HC.12 Exclusion criteria were: hypertension, sleep apnea syndrome, diabetes, smoking, or a family history of cardiovascular disease. The latter was defined as a history of myocardial infarction in a first-degree relative. In addition, patients older than 40 years underwent a treadmill stress test to rule out silent myocardial ischemia.

The control (CO) group consisted of 13 normal volunteers (age: 37±2.2 years, range: 22 to 46 years; 7 women and 6 men) who were matched to patients in the HC group in regard to age, sex, body mass index, and office blood pressure measurements (Table 1). Individuals in the CO group had a normal total cholesterol concentration (173±4 mg/dL, range: 149 to 192 mg/dL). Only 2 subjects had an LDL cholesterol level >130 mg/dL (mean LDL cholesterol: 124±5.6 mg/dL, range: 92 to 144 mg/dL), and all subjects had a triglyceride level <200 mg/dL (triglycerides: 94±13, range: 49 to 182 mg/dL).

All patients provided informed, written consent to participate, and the study was approved by the Ethics Committee of the Heart Institute of the University of São Paulo. All procedures followed were in accordance with institutional guidelines.

Cardiovascular Monitoring
Arterial pressure was continuously monitored by the volume clamp method (Finapress Ohmeda 2300-Ohmeda Monitoring Systems). The heart rate was monitored by electrocardiography. As an indirect estimate of myocardial oxygen uptake, the rate pressure product was calculated as the product of the systolic arterial pressure and heart rate. Forearm blood flow was measured in the right arm by venous occlusion plethysmography (D.E. Hokansen, Model EC-4). Forearm flow measurements were recorded for intervals of approximately 10 seconds every 20 seconds. Three readings were obtained for each mean minute value. Forearm vascular resistance was calculated as the mean arterial pressure during a one-minute record divided by the mean minute forearm blood flow.

Respiratory Monitoring
The end-tidal carbon dioxide (CO₂) and oxygen saturation were monitored with a capnograph and pulse oximeter (Novametrix model 7100 CO₂SMO ETCO₂/SpO Monitor, Novametrix Medical Systems Inc), respectively. Minute ventilation was monitored with a pneumotachograph (Heated Pneumotachometer, Hans-Rudolph, Inc) and a differential pressure transducer (MP 45 to 871 Validyne, Engineering Corporation) linked to a signal integrator amplifier (Gould Instruments Systems, Inc).

All signals were recorded simultaneously on a Gould strip-chart recorder (RS 3800, Gould Instruments Systems, Inc) and on a computer using customized CODAS software (Computer Operated Data Acquisition Software; AT-CODAS; DATAQ Instruments).

Experimental Protocol and Procedures
An established protocol currently used by Somers et al13 and by our group was used.11 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 a humidification chamber (Baking Soda 8.5% NaHCO₃, Aduarte, Brazil) via a mouthpiece, using a noseclip to ensure exclusive mouth breathing.

Statistical Analyses
Statistical analyses were performed with SAS software. Demographic data 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).
TABLE 2. Baseline Measurements

<table>
<thead>
<tr>
<th></th>
<th>Normal Control Subjects (n=13)</th>
<th>HC Group (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>97±0.2</td>
<td>97±0.3</td>
<td>0.82</td>
</tr>
<tr>
<td>End-tidal CO₂, mm Hg</td>
<td>39±1.1</td>
<td>39±0.7</td>
<td>0.75</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>6.9±0.7</td>
<td>7.9±0.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>133±3</td>
<td>140±4</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98±3</td>
<td>99±4</td>
<td>0.77</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>78±3</td>
<td>79±4</td>
<td>0.96</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±3</td>
<td>77±3</td>
<td>0.08</td>
</tr>
<tr>
<td>Rate pressure product</td>
<td>9294±412</td>
<td>10872±571*</td>
<td>0.03</td>
</tr>
<tr>
<td>Forearm blood flow, mL/100 mL per min</td>
<td>2.9±0.3</td>
<td>4.4±0.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Forearm vascular resistance, UR</td>
<td>40±5</td>
<td>29±3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Baseline measurements obtained while subjects were breathing room air. Values are presented as mean±SEM.

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 HC 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

Table 3. Responses to Isocapnic Hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Baseline Room Air</th>
<th>Hypoxia</th>
<th>Interaction, Group-by-Time, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen saturation, %</td>
<td>97±0.2</td>
<td>81±1.4*</td>
<td></td>
</tr>
<tr>
<td>End-tidal CO₂, mm Hg</td>
<td>39±1.1</td>
<td>39±1.0</td>
<td>0.94</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>6.9±0.7</td>
<td>12.5±1.3*</td>
<td></td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>133±3</td>
<td>140±4*</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98±3</td>
<td>101±3*</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>78±3</td>
<td>81±3</td>
<td>0.08</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70±3</td>
<td>84±3.1*</td>
<td>0.1</td>
</tr>
<tr>
<td>Rate pressure product</td>
<td>9293±412</td>
<td>11 789±600*</td>
<td></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></td>
</tr>
<tr>
<td>Forearm vascular resistance, UR</td>
<td>40±5</td>
<td>31±4*</td>
<td>0.03†</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.
group \( (P=0.14), 29\pm 3 \) (95\% CI, 22 to 37 UR) to 26\pm 3 \) (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 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.

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. We found that only the hypercho-
Lesterolemic 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 homeostasis and raise several important possibilities. First, the decrease in the systemic vascular resistance depends on the bioavailability of NO, which is decreased in patients with HC. 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. 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, and HC may be associated with depressed baroreflex function due to functional and/or structural factors. 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, the net effect in territories of skeletal muscle vasculature is vasodilation. Evidence strongly suggests that the synthesis and release of vasoactive substances by the endothelium plays a key role.

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 al and our group 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. Thus, endothelial dysfunction associated with severe HC may have led to the impaired forearm vascular response to hypoxia in the HC group. Taguchi et al 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,

![Figure 3](http://atvb.ahajournals.org/)

**Figure 3.** Experimental recordings showing the cardiovascular response during systemic isocapnic hypoxia in a patient with isolated HC (total cholesterol = 387 mg/dL, LDL-C = 296 mg/dL). The baseline values (2 minutes of room air) are compared with the mean of values obtained during minutes 3, 4 and 5 of hypoxia. The forearm vascular resistance decreased in the normal control subject (see Figure 3) but paradoxically increased in the patient with HC. Moreover, in the normal control subject, the increase in BP observed during the third minute was followed by normalization of the BP and even a small decrease (see arrow). Conversely, the increase in BP initiated during the first minute in the patient with HC was sustained throughout the stimulus.
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.24

In vivo and in vitro studies indicate that NO modulates contractile responses to adrenergic stimulation.25–27 Moreover, there is evidence of β-adrenergic vasodilation in human forearm mediated through NO via β2 receptors, also attenuating the vasoconstriction to catecholamines.28 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.29 It was proposed that the degree of vasodilation at baseline limited the flow response to acute stress.29 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.14 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.13,30

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.9 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.2 Therefore, the marked blunting of muscle vasodilation in the hypercholesterolemic patients, which may compromise delivery of oxygen, deserves further attention.

Figure 4. Experimental recordings showing the cardiovascular response during systemic isocapnic hypoxia in a normal control subject (total cholesterol=192 mg/dL; LDL-cholesterol=144 mg/dL). The baseline values (2 minutes of room air) are compared with the mean of values obtained during minutes 3, 4 and 5 of hypoxia. The forearm vascular resistance decreased in the normal control subject but paradoxically increased in the patient with HC (see Figure 4). Moreover, in the normal control subject, the increase in BP observed during the third minute was followed by normalization of the BP and even a small decrease (see arrow). Conversely, the increase in BP initiated during the first minute in the patient with HC was sustained throughout the stimulus. O2 Sat indicates oxygen saturation; ETCO2, end-tidal CO2; V̇e, minute ventilation; FBF, forearm blood flow; FVR, forearm vascular resistance; BP, blood pressure; HR, heart rate.
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.\(^1\) 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 HC may underlie poor oxygen delivery to organs and tissues and elicit an enhanced pressor response to increase blood flow, augmenting the 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.

**Acknowledgments**

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**References**

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