Carboxyhemoglobin Caused by Smoking Nonnicotine Cigarettes

Effects in Angina Pectoris

By Wilbert S. Aronow, M.D., and Stanley N. Rokaw, M.D.

SUMMARY
The effects of increased carboxyhemoglobin levels caused by smoking nonnicotine cigarettes upon exercise-induced angina were investigated in 10 patients. The mean carboxyhemoglobin level after smoking eight nonnicotine cigarettes, one every 30 minutes, rose from 1.58 to 7.79%. Smoking significantly decreased the mean exercise time from the onset of exercise until the onset of angina from 109.8 to 83.5 seconds. There was significantly less of an increase in systolic blood pressure, heart rate, and product of systolic blood pressure times heart rate after exercise-induced angina after smoking compared to the nonsmoking state. Smoking nonnicotine cigarettes increased the carboxyhemoglobin level, decreasing the rate of oxygen deliverability to the myocardium, with angina developing sooner, following less cardiac work.

Additional Indexing Words:
Nicotine  Coronary heart disease  Exercise

SMOKING one high-nicotine or one low-nicotine cigarette caused patients with angina pectoris due to coronary heart disease to have a significant decrease in exercise performance before the onset of angina. Smoking one nonnicotine lettuce-leaf cigarette did not cause any significant change in exercise performance in these patients before the onset of angina.

Smoking high-nicotine, low-nicotine, or nonnicotine lettuce-leaf cigarettes caused a significant similar increase in carboxyhemoglobin levels in normal subjects and in patients with angina pectoris due to coronary heart disease. The presence of increased carboxyhemoglobin probably reduces the amount of oxygen deliverable to the myocardium. Therefore, this study was performed to determine whether patients with angina pectoris would have any significant difference in exercise performance after serial smoking of nonnicotine lettuce-leaf cigarettes, compared to the nonsmoking state.

Materials and Methods
Ten men, all of whom had smoked at least 20 cigarettes daily for at least 19 years, were subjects. Each subject had a classical history of exertional angina pectoris. Five patients had a previously documented transmural myocardial infarction, at least 2 years old. The other five subjects had coronary artery disease documented by previous coronary angiography, with 50% or greater narrowing of the lumen of at least one major vessel.

The subjects were familiarized with the equipment and the procedure and had practiced exercising on the bicycle ergometer before the study was begun. The studies were performed on four consecutive mornings. Smoking was performed on two mornings. The order of the two smoking and the two nonsmoking mornings was randomized. Smoking was not permitted for at least 12 hours prior to the onset of the study each morning and was not permitted during the study.
periods except by protocol. The subjects remained in the same area during the study periods and were carefully observed to make sure they did not smoke outside the protocol.

At 8:00 a.m. each morning, the resting blood pressure was recorded with a mercury sphygmomanometer and the resting heart rate with an electrocardiograph with the patient sitting upright on a bicycle ergometer. Then, venous blood was drawn and analyzed immediately for carboxyhemoglobin and hemoglobin levels with a 182 Co-Oximeter.* All determinations were made in duplicate.

If the morning was a smoking morning, the subject smoked eight nonnicotine lettuce-leaf cigarettes, one every 30 minutes, at his normal pace, inhaling the smoke. The last cigarette was smoked while the subject was sitting on the bicycle ergometer. The blood pressure and heart rate were measured immediately after the last cigarette was smoked. The subject then performed upright exercise at a load of 60 watts until he experienced and reported the onset of angina pectoris. Immediately after the onset of angina, the blood pressure and heart rate were again measured.

If the morning was a nonsmoking morning, the blood pressure and heart rate were measured at 8:00 a.m. as above. Then, venous blood was drawn and analyzed immediately for carboxyhemoglobin and hemoglobin levels as above. On the first nonsmoking morning, at 9:00 a.m., a measurement of the 1-sec forced expiratory volume (FEV₁₀sec) and the forced vital capacity (FVC) was obtained in each patient by a Model 170 Wedge Spirometer.† At 11:35 a.m., the blood pressure and heart rate were measured. Then, venous blood was drawn and analyzed immediately for carboxyhemoglobin and hemoglobin levels. At 11:40 a.m., the patient performed upright exercise on the bicycle ergometer at a load of 60 watts until he experienced and reported the onset of angina pectoris. Immediately after the onset of angina, the blood pressure and heart rate were again measured.

Electrocardiograms, using lead II, were obtained at rest, immediately before exercise, and immediately after the onset of angina pectoris on the smoking and nonsmoking mornings.

**Results**

Table 1 shows the age and the spirometric observations for each subject. The patients (all male) were between the ages of 41 and 56 years, with a mean age of 51.3 years. The observed FEV₁₀sec/observed FVC ranged from 75 to 86% in our patients, indicating the absence of significant airway obstruction at the time of study. Similarly, the normal FVC values suggest that no significant restrictive disease (pulmonary congestion, fibrosis, etc.) was present at the time of study.

Table 2 reveals the blood pressure and heart rate measurements at rest, immediately before exercise, and immediately after the onset of angina; the carboxyhemoglobin measurements at rest and immediately before exercise; and the exercise time before the development of

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*Manufactured by Instrumentation Laboratory, Inc.

†Manufactured by Med-Science Electronics, Inc.
Table 2

Blood Pressure and Heart Rate at Rest, before Exercise, and after Exercise, Carboxyhemoglobin Level at Rest and before Exercise, and Exercise Performance until Onset of Angina in Smoking and Nonsmoking States*

<table>
<thead>
<tr>
<th>Pt.</th>
<th>S or NS</th>
<th>Resting state</th>
<th>Before exercise</th>
<th>After exercise</th>
<th>Exercise time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood pressure (mm Hg)</td>
<td>Heart rate (beats/min)</td>
<td>Blood pressure (mm Hg)</td>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>1.</td>
<td>S (1)</td>
<td>160/98</td>
<td>82 1.3</td>
<td>162/96</td>
<td>84 9.3</td>
</tr>
<tr>
<td></td>
<td>NS (1)</td>
<td>162/100</td>
<td>74 0.5</td>
<td>158/98</td>
<td>74 0.3</td>
</tr>
<tr>
<td></td>
<td>S (2)</td>
<td>158/98</td>
<td>72 0.8</td>
<td>156/98</td>
<td>72 0.6</td>
</tr>
<tr>
<td></td>
<td>S (2)</td>
<td>156/92</td>
<td>72 0.5</td>
<td>158/90</td>
<td>72 6.1</td>
</tr>
<tr>
<td>2.</td>
<td>NS (1)</td>
<td>136/80</td>
<td>72 0.7</td>
<td>138/80</td>
<td>68 0.6</td>
</tr>
<tr>
<td></td>
<td>S (1)</td>
<td>128/76</td>
<td>76 0.4</td>
<td>130/76</td>
<td>84 6.6</td>
</tr>
<tr>
<td></td>
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<td>132/80</td>
<td>84 0.8</td>
<td>126/76</td>
<td>80 6.4</td>
</tr>
<tr>
<td></td>
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<td>72 0.5</td>
<td>130/76</td>
<td>80 0.2</td>
</tr>
<tr>
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<td>106/66</td>
<td>68 2.0</td>
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<td>72 2.9</td>
<td>104/68</td>
<td>76 9.5</td>
</tr>
<tr>
<td></td>
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<td>84 3.1</td>
<td>102/64</td>
<td>76 8.9</td>
</tr>
<tr>
<td></td>
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<td>100/62</td>
<td>60 1.7</td>
<td>106/68</td>
<td>66 1.3</td>
</tr>
<tr>
<td>4.</td>
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<td>96 2.0</td>
<td>128/88</td>
<td>88 6.9</td>
</tr>
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<tr>
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<td>88 0.6</td>
</tr>
<tr>
<td></td>
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<td>94 1.7</td>
<td>138/100</td>
<td>88 5.8</td>
</tr>
<tr>
<td>5.</td>
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<td>138/98</td>
<td>82 6.2</td>
</tr>
<tr>
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<td>74 0.7</td>
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<td>88 0.7</td>
<td>132/94</td>
<td>72 0.1</td>
</tr>
<tr>
<td></td>
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<td>86 0.6</td>
<td>136/98</td>
<td>88 5.5</td>
</tr>
<tr>
<td>6.</td>
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<td>76 1.3</td>
<td>104/68</td>
<td>74 1.0</td>
</tr>
<tr>
<td></td>
<td>S (1)</td>
<td>104/68</td>
<td>74 0.8</td>
<td>104/66</td>
<td>76 8.3</td>
</tr>
<tr>
<td></td>
<td>S (2)</td>
<td>102/66</td>
<td>71 1.0</td>
<td>104/66</td>
<td>76 9.6</td>
</tr>
<tr>
<td></td>
<td>NS (2)</td>
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<td>74 0.6</td>
<td>106/68</td>
<td>72 0.2</td>
</tr>
<tr>
<td>7.</td>
<td>S (1)</td>
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<td>78 2.0</td>
<td>122/74</td>
<td>82 6.7</td>
</tr>
<tr>
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<td>118/72</td>
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</tr>
<tr>
<td></td>
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<td>114/72</td>
<td>74 0.2</td>
</tr>
<tr>
<td></td>
<td>S (2)</td>
<td>114/72</td>
<td>84 0.3</td>
<td>112/74</td>
<td>82 5.4</td>
</tr>
<tr>
<td>8.</td>
<td>NS (1)</td>
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<td>86 2.0</td>
<td>142/78</td>
<td>82 1.6</td>
</tr>
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<td>S (1)</td>
<td>148/82</td>
<td>90 1.0</td>
<td>150/80</td>
<td>90 9.8</td>
</tr>
<tr>
<td></td>
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<td>86 2.5</td>
<td>142/80</td>
<td>88 12.2</td>
</tr>
<tr>
<td></td>
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<td>74 1.7</td>
<td>138/78</td>
<td>76 1.1</td>
</tr>
<tr>
<td>9.</td>
<td>NS (1)</td>
<td>132/92</td>
<td>72 3.3</td>
<td>138/94</td>
<td>78 2.8</td>
</tr>
<tr>
<td></td>
<td>S (1)</td>
<td>136/88</td>
<td>82 3.0</td>
<td>134/86</td>
<td>80 9.7</td>
</tr>
<tr>
<td></td>
<td>S (2)</td>
<td>136/86</td>
<td>80 3.9</td>
<td>132/82</td>
<td>78 9.6</td>
</tr>
<tr>
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<td>132/86</td>
<td>80 2.6</td>
</tr>
<tr>
<td>10.</td>
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<td>110/66</td>
<td>78 7.3</td>
</tr>
<tr>
<td></td>
<td>NS (1)</td>
<td>112/70</td>
<td>80 0.8</td>
<td>114/72</td>
<td>76 0.5</td>
</tr>
<tr>
<td></td>
<td>NS (2)</td>
<td>114/68</td>
<td>84 1.2</td>
<td>116/70</td>
<td>88 0.7</td>
</tr>
<tr>
<td></td>
<td>S (2)</td>
<td>114/72</td>
<td>86 0.5</td>
<td>112/70</td>
<td>84 5.9</td>
</tr>
</tbody>
</table>

*Each observation period is numerically delineated in parentheses in the order in which it was performed.

Abbreviations: S = smoking state; NS = nonsmoking state; COHb = carboxyhemoglobin.

Angina on all of the smoking and nonsmoking mornings. All the hemoglobin values were within normal limits.

Table 3 indicates the mean carboxyhemoglobin levels ± 1 SD at rest and immediately before exercise on the two smoking and two nonsmoking mornings. An analysis of variance tests was performed. The carboxyhemoglobin...
level after smoking compared to the baseline level was significantly increased (F 206.7, P < 0.01).

Table 4 reveals the mean exercise performance ± 1 std from the onset of exercise until the onset of angina pectoris on the two smoking and two nonsmoking mornings. An analysis of variance tests was performed. There was a significant decrease in exercise performance after smoking compared to the nonsmoking state (F 22.4, P < 0.01). There was no significant difference in exercise performance on the second smoking day compared to the first smoking day. There was a significant improvement in exercise performance on the second nonsmoking day compared to the first nonsmoking day (F 6.89, P < 0.05).

Figure 1 reveals the mean exercise time in seconds until the onset of angina pectoris in the smoking and in the nonsmoking states for each individual patient.

Table 5 indicates the mean systolic and diastolic blood pressure, heart rate, and product of systolic blood pressure times heart rate ± 1 std at rest, immediately before exercise, and immediately after the onset of angina pectoris on the two smoking and two nonsmoking mornings. An analysis of variance tests was performed.

There was no significant difference in either the mean systolic and diastolic blood pressures, heart rate, or product of systolic blood pressure times heart rate at rest and immediately before exercise, in the smoking compared to the nonsmoking state.

There was significantly less increase in the systolic blood pressure immediately after the onset of angina in the smoking compared to the nonsmoking state (F 42.3, P < 0.01).

There was significantly more increase in the diastolic blood pressure immediately after the onset of angina in the smoking compared to the nonsmoking state (F 7.6, P < 0.05).

Table 3

<table>
<thead>
<tr>
<th>Mean Carboxyhemoglobin Levels ± 1 Standard Deviation at Rest and before Exercise on the Two Smoking and Two Nonsmoking Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Mean carboxyhemoglobin level at rest (%)</td>
</tr>
<tr>
<td>Mean carboxyhemoglobin level before exercise (%)</td>
</tr>
<tr>
<td>Mean carboxyhemoglobin level at rest (%)</td>
</tr>
<tr>
<td>Mean carboxyhemoglobin level before exercise (%)</td>
</tr>
</tbody>
</table>

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Table 4

Mean Exercise Performance ±1 Standard Deviation until Onset of Angina on the Two Smoking and Two Nonsmoking Days

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking</td>
<td>Nonsmoking</td>
</tr>
<tr>
<td>Mean exercise performance (sec)</td>
<td>86.2 ±104.9</td>
<td>80.8 ±114.6</td>
</tr>
</tbody>
</table>

Table 5

Mean Systolic and Diastolic Blood Pressure, Heart Rate, and Product of Systolic Blood Pressure and Heart Rate ±1 Standard Deviation at Rest, before Exercise, and after Exercise on the Two Smoking and Two Nonsmoking Days

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking</td>
<td>Nonsmoking</td>
</tr>
<tr>
<td>At rest BP in mm Hg</td>
<td>127.6/81.0 ±127.2/82.0</td>
<td>127.0/80.2 ±124.6/79.6</td>
</tr>
<tr>
<td>HR in beats/min</td>
<td>81.8 ±82.8</td>
<td>75.6 ±7.9</td>
</tr>
<tr>
<td>SBP X HR</td>
<td>10,494 ±9,887</td>
<td>10,516 ±9,458</td>
</tr>
<tr>
<td>Before exercise BP in mm Hg</td>
<td>132.2/79.8 ±132.2/82.0</td>
<td>126.2/80.0 ±126.8/80.8</td>
</tr>
<tr>
<td>HR in beats/min</td>
<td>82.0 ±82.8</td>
<td>75.6 ±7.9</td>
</tr>
<tr>
<td>SBP X HR</td>
<td>10,572 ±9,674</td>
<td>10,260 ±9,760</td>
</tr>
<tr>
<td>Immediately after exercise BP in mm Hg</td>
<td>149.4/88.2 ±157.4/88.6</td>
<td>147.0/87.8 ±159.8/87.2</td>
</tr>
<tr>
<td>HR in beats/min</td>
<td>113.7 ±119.0</td>
<td>110.2 ±120.4</td>
</tr>
<tr>
<td>SBP X HR</td>
<td>16,992 ±18,759</td>
<td>16,248 ±19,237</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; HR = heart rate; SBP X HR = systolic blood pressure times heart rate.

There was significantly less increase in the heart rate immediately after the onset of angina in the smoking compared to the nonsmoking state (F 52.8, P < 0.01).

There was significantly less increase in the product of systolic blood pressure times heart rate immediately after the onset of angina in the smoking compared to the nonsmoking state (F 86.3, P < 0.01).

No ischemic S-T-segment depression was precipitated after smoking the nonnicotine cigarettes in any of the 10 patients. The
electrocardiographic changes from preexer-
cise to onset of angina did not differ
significantly in the smoking compared to the
nonsmoking state.

Discussion

The results of the present study and of our
previous ones\textsuperscript{3,}\textsuperscript{5} indicate that smoking non-
nicotine lettuce-leaf cigarettes does not signifi-
cantly affect the resting systolic or diastolic
blood pressure or the resting heart rate. There
is, however, a significant increase in the
carboxyhemoglobin level.

Smoking high-nicotine, low-nicotine, or non-
nicotine cigarettes adversely affected the mean
A-wave ratio in the apexcardiogram in patients
with coronary heart disease.\textsuperscript{8} This adverse
effect on the apexcardiogram was most marked
after smoking high-nicotine cigarettes and
least marked after smoking nonnicotine ciga-
rettes.\textsuperscript{8}

Chevalier and associates\textsuperscript{9} have reported that
nonsmokers who inhaled carbon monoxide to
raise their carboxyhemoglobin level to the
range seen in a control group of smokers
developed an increased oxygen debt with
exercise. Ayres and associates\textsuperscript{10} have reported
that carbon monoxide decreases myocardial
oxygen tension by three mechanisms: (1)
decreased oxygen extraction, (2) decreased
capillary oxygen tension because of the
leftward shift of the oxyhemoglobin dissocia-
tion curve, and (3) increased ventricular work
and oxygen demand due to stimulation of the
adrenergic system. These investigators\textsuperscript{10} have
also shown that elevated levels of carboxy-
hemoglobin cause an increase in coronary
blood flow to prevent a decrease in coronary
sinus and myocardial oxygen tension.

Patients with coronary heart disease have
an increased myocardial demand for oxygen
when they exercise. When their myocardial
oxygen demand exceeds their myocardial
oxygen supply, angina pectoris develops. The
presence of carboxyhemoglobin caused by
smoking or other inhalation sources makes less
oxygen deliverable to the myocardium. The
significant decrease in exercise performance to
the development of angina pectoris after
smoking the nonnicotine cigarettes compared
to the nonsmoking state is probably related to
this disturbance in oxygen transport.

There are theoretical grounds for concern
that other inhaled gaseous pollutants, such as
oxides of nitrogen, may also act to impair the
hemoglobin-oxygen transport and delivery
system. Further investigation of these mecha-
nisms is clearly indicated.

Sarnoff and coworkers\textsuperscript{11} have found the
primary hemodynamic determinant of myoc-
ardial oxygen consumption to be the total
tension developed by the myocardium (heart
time times the area under the systolic portion
of the aortic pressure curve). The present
study shows that the product of systolic blood
pressure times heart rate after exercise-in-
duced angina was significantly less after
smoking the nonnicotine cigarettes than in
the nonsmoking state. This suggests strongly
that less myocardial work can be performed
before the onset of angina in the presence of
elevated carboxyhemoglobin levels, related to
lessened oxygen available for the myocardium.

Smoking high-nicotine\textsuperscript{1,}\textsuperscript{5} or low-nicotine\textsuperscript{2,}\textsuperscript{5}
cigarettes causes an increase in systolic blood
pressure and in heart rate, thereby increasing
the myocardial oxygen demand, but this is not
found after smoking of nonnicotine ciga-
rettes.\textsuperscript{3,}\textsuperscript{5} However, smoking high-nicotine, low-
nicotine, or nonnicotine cigarettes does cause
increased carboxyhemoglobin levels,\textsuperscript{4,}\textsuperscript{5}
decreasing the amount of oxygen available to
the myocardium. Therefore, patients with historic
angina pectoris develop pain sooner after
exercise following smoking either high-nico-
tine cigarettes,\textsuperscript{1} low-nicotine cigarettes,\textsuperscript{2} or
nonnicotine cigarettes, in relation to at least
two factors: increased myocardial oxygen
demand in the presence of nicotine, and
impaired oxygen delivery, whether or not
nicotine is present.

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References

Carboxyhemoglobin Caused by Smoking Nonnicotine Cigarettes: Effects in Angina Pectoris

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