Paradoxic Action of Amyl Nitrite in Coronary Patients

By Stephen Contro, M.D., Olga M. Haring, M.D., and Walter Goldstein

Amyl nitrite inhalation in patients with sclerotic coronary vessels is followed by electrocardiographic changes typical of temporary coronary insufficiency. It is suggested that, in such cases, a slight increase of cardiac work (tachycardia) together with a decrease of blood supply (fall in blood pressure), leads to myocardial ischemia. Comparison between an exercise test and amyl nitrite inhalation in the same patients indicates similar results. Amyl nitrite inhalation may be used as a simple functional test in borderline or questionable cases of coronary heart disease.

Amyl nitrite was discovered by Balard and further investigated by Guthrie and Gamgee. Brunton observed that patients suffering from angina pectoris were promptly relieved by inhalation of the drug. In the following decades, the beneficial effects of several nitrous products were reported; some of them still represent the most used medication for angina pectoris. Nitrites, nitrous esters, and organic nitrates (which are reduced in the body to nitrites) cause a prompt drop of blood pressure. Their action is exerted directly on the smooth muscle of the arteries and is antagonistic to that of epinephrine.

Angina pectoris is due to absolute or relative insufficiency of the coronary circulation, followed by myocardial anoxia. The nitrites act both on the coronary vessels, increasing the blood flow, and on other arteries. The peripheral effect consists of vasodilation followed by decreased work of the myocardium and decreased blood demand.

The beneficial effect of these drugs in most patients is an established fact. However, clinical experience has proved that, in certain patients, the use of nitrites is not followed by clinical improvement and may even cause untoward effects.

Electrocardiographic changes after inhalation of amyl nitrite have been reported in the literature by various authors (Nagl, Goepfert and co-workers, Nordenfelt, Langeron and associates, Goldberger, Ashman and Bayer). Goldberger attributes them to positional changes caused by deep inspiration; Nordenfelt compares them to those occurring in the change from the supine to the erect position.

The present study was prompted by the observation of paradoxical changes of the electrocardiogram suggesting ischemia of the myocardium after amyl nitrite inhalation.

Material and Method

Fifty-nine adults of both sexes, ranging in age from 25 to 75 years, were studied. Ten were healthy young men and constituted a control group; 49 were ambulatory patients from the Cardiac Clinic of Mount Sinai Hospital and were divided into three groups. Group 1 included patients with angina pectoris and normal or borderline resting electrocardiogram; group 2 included patients with angina pectoris and an abnormal resting electrocardiogram; group 3 included patients with atypical anginal pain (four of them were patients with rheumatic heart disease with valvular deformities, three had no evidence of organic heart disease).

After a short period of rest in recumbent position, an electrocardiogram was recorded, using a direct writing Sanborn Poly-Viso. Standard leads, unipolar limb leads, and three chest leads (V1, V4, V6) were recorded. At the same time, the blood pressure was taken. A brief explanation of the immediate subjective effects of amyl nitrite was given in order to avoid undue alarm of the patient. A peak of 0.18 c.c. of amyl nitrite (Lilly) was used in each test. A team of three took part in the study. One administered the drug, one took the blood pressure, the third recorded the tracings. An electrocardiogram was taken as soon as flushing of the face occurred. Unipolar limb leads and the three chest leads were recorded alternately until the tracing showed stabilization. Taking of the standard limb leads was omitted in subsequent tracings in
order to save time, as they can be calculated from the unipolar limb leads. In several instances, changes of the tracing persisted after the blood pressure had returned to the previous level. The study was continued for about 10 minutes.

The following data were correlated: age and sex; clinical and electrocardiographic diagnosis; use of digitalis; systolic and diastolic blood pressures; heart rate; duration of the electrical systole (Q-T) ratio of the electrical systole to electrical diastole (Q-T/T-Q) ratio; S-T segment and T-wave changes; possible occurrence of premature ectopic beats. In evaluating the electrocardiographic changes, Master's criteria were employed.19, 20

The following data were accepted as evidence of abnormal response (ischemic reaction): displacement of the S-T segment of more than 1 mm. above or below the isoelectric line*; flattening or inversion of the T wave in any lead; premature ectopic beats, not present in the control tracing.

Twenty patients who had received amyl nitrite inhalation were also submitted to Master's "two-step test." Twelve of these had normal or borderline resting electrocardiogram (group 1), six had slightly abnormal electrocardiogram (group 2) and two others had a normal tracing and a history of atypical anginal pain (group 3). Patients with definite abnormalities of the resting electrocardiogram were not submitted to the Master test because of the danger represented by this procedure. The Master test was performed at least 24 hours after the inhalation of amyl nitrite and according to the original description of the author.19

RESULTS

In 27 cases out of 59, the first electrocardiogram recorded after amyl nitrite administration showed definite changes from the control tracing. Within 10 minutes, the electrocardiograms of 17 cases reverted to the initial pattern while the changes persisted in 10. The pattern of these changes corresponded to that usually seen in myocardial ischemia, consisting of displacement of the S-T segment, inversion of the T wave not associated with changes of the electrical position, or both (figs. 1 through 5). Fifteen of the 27 cases had clinical and electrocardiographic evidence of coronary heart disease (group 2). Nine of these cases presented alterations which persisted till the end of the experiment. Nine cases had a history of angina pectoris with a normal or borderline resting electrocardiogram (group 1). Two had rheumatic heart disease; one of them was receiving digitalis and had auricular fibrillation, while the other had a normal tracing at

* The P-Q level was considered as the isoelectric line because it does not change with an increased heart rate. In severe tachycardia, the T-P segment may not represent the isoelectric line because atrial depolarization may start before cessation of the ventricular repolarization.31

![Graph](Fig. 1. Paradoxic action of amyl nitrite in a 28 year old normal subject.)

rest (group 3). One case belonged to the supposedly normal control group. In two instances (group 2), appearance of ventricular premature beats was noted beside the S-T and T changes. Case 7 of group 1 did not show S-T or T changes. However, it was classified among those with an abnormal response because of the onset of nodal premature beats with aberrant con-
duction and abnormal prolongation of electrical systole.

Blood pressures dropped in all cases during inhalation of the drug and usually returned to the control level within one minute. In several cases, however, blood pressure rose above control level before stabilizing. The drops of mean systolic and diastolic pressures were calculated in each case. An increase of the heart rate following the drop of blood pressure was noted in all cases but two. In the great majority of cases (40 out of 59), the rate was still slightly elevated after 10 minutes.

Among the 20 patients in whom both Master's and the amyl nitrite test were performed, six showed a positive and eight a negative response to both procedures; one presented a positive response to the Master test only, and another a positive response to amyl nitrite inhalation only. The results in the various groups are presented in table 2.
DISCUSSION

Our study revealed that in 27 out of 59 subjects (45 per cent), amyl nitrite inhalation was followed by electrocardiographic changes similar to those usually seen in myocardial ischemia. A possible relationship of these changes with either the modification of the heart rate or that of the blood pressure was considered.

Heart Rate. In several instances, the tracing showed electrocardiographic modifications when the heart rate increased and these changes disappeared with the return of the heart rate to previous values (four cases in group 2; one among the controls; one in group 3) (fig. 1). This would suggest a connection between electrocardiographic modifications and tachycardia. However, the electrocardiographic changes were observed even when the cardiac rate increased but slightly (one case in group 1). In other cases, no abnormal response was observed when the rate became very rapid (seven cases in the control group; one in group 1), or the electrocardiographic changes were still present when the rate had returned to normal or had fallen below the control values (two cases of group 2).*

Blood Pressures. A slightly greater mean fall in blood pressure was presented by subjects showing the "ischemic" type of reaction in comparison with the others (table 1). The highest percentage of "ischemic" changes (60 per cent) occurred in patients having a history of angina pectoris but no definite electrocardiographic evidence of coronary heart disease. The changes were more permanent among cases having an abnormal electrocardiogram before the test (55.5 per cent).

In the patients subjected to both the Master test and amyl nitrite inhalation, the results of the two procedures were similar with the exception of two cases. In the first, amyl nitrite caused an "ischemic" reaction while Master's test did not modify the tracing. In the second, the opposite was true. However, while performing the Master test the patient experienced an attack of angina pectoris; amyl nitrite was immediately administered and was followed by increased severity of the electrocardiographic changes (fig. 5).

Coronary insufficiency is caused by a disproportion between blood supply and blood demand. The use of amyl nitrite, as well as that of other powerful vasodilators, is open to question. The increase of coronary flow may not be equivalent to the increased work (or

* Nordenfelt observed electrocardiographic changes after amyl nitrite in a case of complete A-V block. This further indicates the lack of connection between electrocardiographic changes and modifications of the ventricular rate.
PARADOXIC ACTION OF AMYL NITRITE IN CORONARY PATIENTS

Fig. 5. Fifty-nine year old patient with hypertension and angina pectoris. (A) Control. (B) After Master's test (anginal pain). (C) After inhalation of amyl nitrite immediately following Master's test.

Table 1.—Results Following Amyl Nitrite Test

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Controls</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No evidence of cardiac disease</td>
<td>Angina pectoris</td>
<td>Coronary heart disease</td>
<td>Atypical angina pectoris</td>
</tr>
<tr>
<td>Resting ECG</td>
<td>Normal</td>
<td>Normal or borderline</td>
<td>Abnormal</td>
<td>Either normal or abnormal</td>
</tr>
<tr>
<td>Total cases</td>
<td>10</td>
<td>15</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Reaction to amyl nitrite</td>
<td>Paradoxical</td>
<td>No reaction</td>
<td>Paradoxical</td>
<td>No reaction</td>
</tr>
<tr>
<td>Mean BP drop in mm. Hg</td>
<td>22/44</td>
<td>25/24</td>
<td>48/17</td>
<td>25/20</td>
</tr>
<tr>
<td>Mean heart rate increase (per minute)</td>
<td>36</td>
<td>36</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Average cycle</td>
<td>28.00</td>
<td>28.00</td>
<td>61.46</td>
<td>46.66</td>
</tr>
</tbody>
</table>

Table 2.—Comparison of Results Following the Master Test and Amyl Nitrite Inhalation

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>Coronary heart disease</td>
<td>Atypical angina pectoris</td>
</tr>
<tr>
<td>Resting ECG</td>
<td>Normal or Borderline</td>
<td>Abnormal</td>
<td>Either normal or abnormal</td>
</tr>
<tr>
<td>Total cases</td>
<td>12</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Reaction To:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Master's test</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Amyl nitrite</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Positive To Only:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Master's test</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Amyl nitrite</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>
the increased oxygen consumption) of the heart. Moreover, coronary dilatation may be counteracted by a sudden and dramatic drop of the aortic pressure to the point at which coronary flow may actually decrease. It is true that the low blood pressure is followed by decreased cardiac work if the rate of the heart fails to increase beyond certain limits. However, the reduction of the coronary flow caused by low aortic pressure may be greater than the reduction of work.

Our observations suggest that, if the coronary arteries are sclerotic and narrowed, a slight increase of cardiac work (increase of rate) together with a decrease of blood supply (fall in blood pressure) may lead to coronary insufficiency. Therefore, vasodilators should not be given in too large a dose or too rapidly, whenever coronary pathology is suspected.

It is suggested that amyl nitrite inhalation represents a new and simple test for borderline or questionable cases of coronary heart disease.

**Summary**

Electrocardiographic studies were made in 49 cardiac patients and 10 control subjects after inhalation of amyl nitrite.

In 27 cases out of 59, the first tracing recorded after amyl nitrite inhalation showed a pattern of ischemia; for example, displacement of S-T and flattening or inversion of T in one or more leads. Fifteen of these cases had clinical and electrocardiographic evidence of coronary heart disease, while nine had only a history of angina pectoris. Only one case of the control group showed similar changes.

While the increase of cardiac rate did not seem related to the observed changes, the drop in blood pressure was always definitely connected with them.

In 20 cases, comparison was made between the results of the Master test and those of amyl nitrite inhalation. These results were similar in 18 of them.

It is suggested that, whenever the coronary arteries are sclerotic, the sudden blood pressure drop caused by amyl nitrite may be followed by coronary insufficiency.

Amyl nitrite inhalation may be used as a functional test in borderline or questionable cases of coronary heart disease.

**References**

1 Quoted by Brunton (reference 4).
2 Quoted by Brunton (reference 4).


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