Studies of the Central and Peripheral Hemodynamic Effects of Amyl Nitrite in Patients with Aortic Insufficiency

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SUMMARY
The cardiovascular reaction induced by amyl nitrite was studied in a main group of 11 patients with pronounced and isolated aortic insufficiency, and in an additional and more heterogeneous group of seven patients with moderate aortic insufficiency combined with other lesions, by measuring left ventricular end-diastolic pressure, systemic and peripheral arterial pressures, cardiac output, peripheral blood flow, and venous tone.

Total peripheral resistance decreased, but local vascular resistance differed significantly between the upper and the lower extremities. In most cases arterial dilatation in the forearm (mainly muscle) was found. Simultaneously, there was uniform vasoconstriction in the calf (mainly muscle) which was interpreted to be secondary (baroreceptor reflex). This regional difference in circulatory reaction was also manifested in a pronounced change of the contour of the brachial arterial pulse, while the femoral arterial pulse was practically unchanged. The hand blood flow (skin) decreased while the foot blood flow did not change significantly.

A marked fall in systemic arterial pressure and in left ventricular end-diastolic pressure was clearly demonstrated, and secondarily there was a rise in heart rate as well as a pronounced venoconstriction in both the upper and lower extremities, also interpreted to be secondary (a baroreceptor reflex). There was good correlation between maximal increase in heart rate and maximal increase in venous tone and also between the augmentation in heart rate and cardiac output. An elevation in stroke volume was noted in most cases. The reaction to amyl nitrite was not significantly different in the two groups of patients.

Additional Indexing Words: Cardiac output Intracardiac pressures Peripheral blood flow Peripheral vascular resistance Venous tone

More than a century ago, Brunton\(^1\) introduced amyl nitrite for relieving the pain of angina pectoris. In recent years this nitrite has been utilized as a diagnostic tool in the evaluation of different cardiac murmurs.\(^2\)\(^-\)\(^9\) The hemodynamic effects, especially the systemic circulatory effects, of amyl nitrite are well known and attributed to a marked fall in systemic arterial pressure, tachycardia, and an increased cardiac output.\(^10\)\(^-\)\(^12\) The primary pharmacologic action of nitrites, however, is on the peripheral vessels. Most authors have concluded that the observed central hemodynamic effects of amyl nitrite are due to arterial dilatation and venous constriction, but few quantitative measurements have been made.

Amyl nitrite is well suited for studying the regulation of the cardiovascular system as this drug induces pronounced circulatory reaction and the inhalation test has good reproducibility. The simultaneous investigation of both the central and the peripheral reactions seems to be essential for a better differentiation between the direct action of amyl nitrite and the secondary counter effects. As far as we

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know such a study has not been previously performed.

Methods

Our investigations were performed on two groups of patients. The main group consisted of 11 adult patients (10 males and one female), ranging in age from 18 to 49 years. All of them had pronounced and isolated aortic insufficiency classified as grade IV on the basis of thoracic aortography, and they were in functional classes I to III, according to the criteria of the New York Heart Association. No one was in frank heart failure. The additional group was more heterogeneous and consisted of seven patients (five males and two females) between 46 and 58 years of age. Two of the latter patients had isolated aortic insufficiency of a moderate degree, and five had aortic stenosis and regurgitation; in two of these five mitral stenosis of a slight degree was present also. The studies were all made as part of a clinical evaluation of the patients before cardiac surgery. The patients were informed about the aim of the investigation and gave their free consent.

A complete hemodynamic study was obtained in all patients by means of a routine cardiac catheterization including right heart catheterization, transeptal left heart catheterization, and angiography. Approximately 1 hour before the catheterization was started in the morning, the patients, who were fasting, were given a small dose of a barbiturate (amobarbital, 0.1 g). The patients were studied in the supine position throughout the whole procedure. A polyethylene catheter (PE 160) 75 cm long was introduced percutaneously via the brachial artery to the arch of the aorta. Right heart catheterization was performed in the usual manner via an exposed superficial cubital vein, followed by transeptal left heart catheterization. The transeptal catheter, a radiopaque Teflon catheter, was introduced into the right femoral vein by the percutaneous technic of Seldinger. For the interatrial septal puncture we used the modified instrument of Bevgård’s group. The tip of the right heart catheter was placed in the pulmonary artery, and the transeptal catheter was in the left ventricle. Pressure measurements were made with pressure transducers EMT 34 or 35 and electromanometer EMT 31.* The pressure curves and ECG were recorded on a direct-writing six-channel ECG apparatus (Mingograf 81*).

Owing to the short duration of the effects of amyl nitrite, the dye-dilution method was used for determination of cardiac output: 5 mg of indocyanine green (Cardio-Green) was injected into the pulmonary artery and dye-dilution curves were recorded by drawing blood at a constant rate from the arterial catheter through a Gilford cuvette densitometer. A five-point calibration curve was constructed from known concentrations of dye in blood samples from the patient. The dye-dilution curves were calculated according to the conventional method of Kinsman and associates* including semi-logarithmic plotting, extrapolation, and planimetry of the curve area. During a control period ECG, systemic arterial pressures, or left ventricular pressures or both were recorded simultaneously prior to the administration of amyl nitrite. In 14 of 18 patients, cardiac output was determined during simultaneous recordings of ECG and of systemic or left ventricular pressures. After the control period amyl nitrite was inhaled for about 60 sec from two broken ampules (0.1 g each) held lightly over the nose with a small cloth. ECG and pressures were recorded continuously. At the height of the amyl nitrite effect (30 to 40 sec after the inhalation had started) indocyanine green was injected and the dye-dilution curve was recorded. Because we could not study the action of the drug on both the systemic and the right heart pressures during simultaneous inscribing of dye-dilution curves, we repeated the amyl nitrite test after 15 min in five cases, when the effect of the first inhalation had worn off, thus completing the study by measurements of either pressure or flow.

Blood flow in the forearm, hand, calf, and foot was measured by means of venous occlusion plethysmography. Air-filled rubber cuff plethysmographs* were used. The forearm and calf plethysmographs* enclosed a 5-cm long segment of the proximal muscular part of the extremities. The hand plethysmographs enclosed the whole hand and the foot plethysmographs, the distal part of the foot. The blood flow in the forearm and calf were recorded simultaneously while applying a venous occlusion pressure of 50 mm Hg on the upper arm and thigh and an occlusion pressure of 80 mm Hg on the cuff distal to the segment plethysmographs. During inhalation of amyl nitrite the diastolic blood pressure was in some cases lower than the venous occlusion pressure. This can probably reduce the arterial inflow. As the effective occlusion pressure decreases in centripetal direction, especially on the thigh, the remaining difference between the occlusion pressure and the arterial inflow pressure ought to be of relatively little importance. Hand and foot blood flows were also measured.

*Elema-Schönander, Ltd, Stockholm.

†Gilford Instrument Laboratories Inc, Oberlin, Ohio.
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The venous tone was measured as pressure change in superficial veins of the distal forearm or foot in six subjects by means of the occluded limb technic. A pneumatic cuff 12 cm wide was applied on the upper arm or above the ankle and during each experiment inflated to 250 to 280 mm Hg. A 1.0 gauge needle was inserted in a superficial vein and connected to a pressure transducer (Sanborn 268 B). The reference level for the venous pressure measurements was taken at the tip of the needle. In each experiment the amyl nitrite inhalation was not started before the venous tone was at a stable level. The maximal duration of one arterial occlusion did not exceed 6 min.

Respiration was recorded with a pneumatic cuff around the chest wall connected to an electrical pressure transducer.

Results

Central Circulation

The observations on the central circulatory effects of amyl nitrite inhalation in the main group, consisting of 11 patients with isolated aortic insufficiency, are summarized in tables 1 to 3. There was a marked decrease in systemic blood pressure with the maximal fall occurring at a time varying from 30 to 50 sec after the inhalation had started. The systolic pressure fell more (27%) than the diastolic did (18%). In four cases the pressure was measured in the aorta and in another four cases in the brachial artery. The pressure reactions were of about the same magnitude in both the arterial sites. In all cases the heart rate increased and effective cardiac output rose markedly. In most cases we also found an increase of effective stroke volume, which was statistically significant considering the average value. As a result of the fall in systemic arterial pressure and the rise in cardiac output, the calculated total peripheral resistance was markedly decreased. This decrease, determined in five cases, averaged 56%. Simultaneously with these systemic reactions a

Table 1

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Before amyl nitrite</th>
<th>HR</th>
<th>SpO2</th>
<th>Diastolic</th>
<th>Systolic</th>
<th>Percent change</th>
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<td>19</td>
<td>75</td>
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<td>86</td>
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<td>40</td>
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<td>108</td>
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<tr>
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<td>108</td>
<td>73</td>
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<td>65</td>
<td>105</td>
<td>30</td>
<td>15</td>
<td>+38</td>
</tr>
</tbody>
</table>

†HR = heart rate.

Values in italics are brachial arterial pressures; the other values are central aortic pressures.
Table 2
The Effect of Amyl Nitrite on the Systemic Flow in the Main Group of Patients with Isolated Aortic Insufficiency

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Before amyl nitrite</th>
<th>Peak effect of amyl nitrite</th>
<th>Increase during the inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR (L/min)</td>
<td>SV (ml)</td>
<td>CO (L/min)</td>
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<td>1</td>
<td>19</td>
<td>70</td>
<td>4.9</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>75</td>
<td>7.4</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>70</td>
<td>4.6</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>78</td>
<td>4.4</td>
<td>56</td>
</tr>
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<td>5</td>
<td>18</td>
<td>67</td>
<td>6.2</td>
<td>92</td>
</tr>
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<td>6</td>
<td>35</td>
<td>56</td>
<td>5.6</td>
<td>56</td>
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<td>7</td>
<td>49</td>
<td>65</td>
<td>8.1</td>
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</tr>
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<td>8</td>
<td>38</td>
<td>78</td>
<td>7.0</td>
<td>90</td>
</tr>
</tbody>
</table>

Abbreviations: HR = heart rate; CO = cardiac output (effective forward flow); SV = stroke volume (effective).

Table 3
Summary of the Central Effects of Amyl Nitrite in the Main Group of Patients with Isolated Aortic Insufficiency: Mean Value (Range within Parentheses)

<table>
<thead>
<tr>
<th>Heart rate (/min)</th>
<th>Cardiac output eff. forward flow (L/min)</th>
<th>Stroke volume effective (ml)</th>
<th>Systemic arterial pressure (mm Hg)</th>
<th>LV end-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest before amyl nitrite</td>
<td>70 (56-78)</td>
<td>6.0 (4.4-8.1)</td>
<td>87 (56-124)</td>
<td>129 (116-143)</td>
</tr>
<tr>
<td>Peak effect of amyl nitrite</td>
<td>101 (72-130)</td>
<td>10.4 (7.3-14.5)</td>
<td>104 (71-128)</td>
<td>94 (75-121)</td>
</tr>
<tr>
<td>% change</td>
<td>+44</td>
<td>+77</td>
<td>+23</td>
<td>-27</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 4
Summary of the Central Effects of Amyl Nitrite in the Additional Heterogeneous Group of Patients: Mean Value (Range within Parentheses)

<table>
<thead>
<tr>
<th>Heart rate (/min)</th>
<th>Cardiac output eff. forward flow (L/min)</th>
<th>Stroke volume effective (ml)</th>
<th>Systemic arterial pressure (mm Hg)</th>
<th>LV end-diastolic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest before amyl nitrite</td>
<td>71 (53-84)</td>
<td>4.7 (3.8-5.6)</td>
<td>69 (45-106)</td>
<td>140 (120-163)</td>
</tr>
<tr>
<td>Peak effect of amyl nitrite</td>
<td>98 (82-110)</td>
<td>7.6 (5.5-10.1)</td>
<td>80 (53-123)</td>
<td>99 (69-130)</td>
</tr>
<tr>
<td>% change</td>
<td>+39</td>
<td>+62</td>
<td>+17</td>
<td>-29</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

significant fall of left ventricular end-diastolic pressure was recorded. Observations of the right ventricular pressure were also made in three of these investigations. We found, as we did on the left side of the heart, a decline in the filling pressure. The right ventricular end-diastolic pressure fell by only 1 to 4 mm Hg from a low normal level to below zero during the inhalation. Likewise the right ventricular systolic pressure was little affected with a decrease or increase of 1 to 4 mm Hg, as were the pulmonary artery pressures also in our two recordings.

In the additional heterogeneous group of patients with aortic valve disease (table 4), the rise in heart rate and the fall in systemic
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Figure 1

The change of peripheral blood flow, induced by amyl nitrite inhalation.

arterial pressure during amyl nitrite inhalation were of about the same magnitude as in the main group. However, the average values of basal cardiac output and stroke volume were lower and the reaction to amyl nitrite was not quite so pronounced as in the main group, but the difference between the two groups was not statistically significant.

Peripheral Circulation

Blood Flow

As illustrated in figure 1, the pattern of blood flow in the forearm during inhalation of amyl nitrite varied and differed clearly from the blood flow in the calf. In the forearm the maximal blood flow with 32 ml/100 ml/min occurred and was followed by a slight decrease of blood flow. The average control value (4.9 ± 0.7 ml/100 ml/min mean value ± standard error of the mean) and the value after 50 sec of inhalation (9.8 ± 4.0) were not significantly different. However, in the calf a very uniform change of blood flow was observed and the decrease from the initial value of 3.4 ± 0.6 ml/100 ml/min to a minimal value of 1.3 ± 0.2 (after 50 sec of inhalation) was highly significant (P < 0.005). The blood flow in the hand decreased during amyl nitrite inhalation in almost all cases from the control value of 7.9 ± 1.4 ml/100 ml/min to 3.3 ± 0.8 (P < 0.001) at 40 to 50 sec. The foot blood flow was not significantly changed (control, 2.8 ± 0.8 ml/100 ml/min, after 50 sec of inhalation, 1.4 ± 0.6 ml).

In the additional heterogeneous group the peripheral blood flow reaction to amyl nitrite inhalation was practically the same as that of the main group, and there was no statistically significant difference between these two groups; arm:control value, 5.1 ± 0.9 ml/100 ml/min, 50 sec value, 5.2 ± 1.8; calf: control value 4.0 ± 0.5 ml/100 ml/min, 50 sec value, 1.7 ± 0.3 (P < 0.005).

Local Peripheral Resistance

In three patients arterial blood pressure in the brachial and femoral arteries as well as blood flow in the forearm and calf were determined simultaneously during amyl nitrite inhalation. The blood flow reaction in the forearm was opposite to that in the calf though only a slight difference existed between the brachial and femoral arterial blood pressures. Thus, a pronounced increase of vascular resistance in the calf was induced.

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by amyl nitrite, while it was decreased in the forearm, as illustrated in figure 2 (record from one patient).

**Shape of the Arterial Pulse**

The regional difference in circulatory reaction was also characterized by the different shape of the arterial pulse wave recorded during amyl nitrite inhalation (fig. 2). The dicrotic notch fell to the level of the diastolic pressure in the brachial artery, while it was not significantly changed in the femoral artery.

**Venous Tone**

In all cases amyl nitrite inhalation was accompanied by an increase of venous tone in the superficial veins of the distal forearm and hand. Also, in foot veins a similar increase of tone could be observed. The highest values were noted first 60 to 80 sec after the inhalation had started (fig. 3). The maximal change of venous tone was recorded with a mean value of $14 \pm 1.7$ mm Hg.

**Discussion**

Studies of the cardiovascular effects of such a drug as amyl nitrite with its prompt and short duration have several advantages. The inhalation test is safe, reproducible, and handy to perform. The hemodynamic response to this agent is more pronounced than to the other nitrites of longer duration and its effect disappears quickly, in our cases within 2 min after the start of the inhalation. A clear disadvantage of the use of such a short-acting drug is the difficulty in making accurate systemic flow determination, since a real steady state is probably never achieved. However, we have tried to record the dye-dilution curves during the maximal stable decrease in systemic arterial pressure and increase in heart rate. Even if the calculated flow values are only approximate, the directional changes are uniform and reliable. For technical reasons the central and
Peripheral circulatory studies could not be performed simultaneously in every patient. However, reproducibility was so good according to the increase in heart rate that we have not attached too much importance to this fact.

General Aspects on the Effect of Amyl Nitrite on the Central Circulation

It is well known that the inhalation of amyl nitrite causes peripheral vasodilatation, visible as flushing of the head, neck, and the upper part of the trunk above the umbilicus, a decrease in total peripheral resistance with a subsequent fall in systemic arterial pressure and, secondarily, an increase in heart rate provoked by the baroreceptor mechanism activated by the hypotension. Richter and co-workers state that a rise in heart rate of more than 10 beats/min should be needed to demonstrate a definite hemodynamic effect of amyl nitrite. Like Gilmore and Freis they found a more pronounced heart rate reaction in younger than in elderly people. Among our patients with aortic valve disease, ranging in age from 19 to 58 years, we have not noticed such an age-related difference in the effect of amyl nitrite.

The increase in cardiac output that was recorded immediately after the maximal fall in systemic arterial pressure is in agreement with the findings reported by many other investigators in both normal subjects and patients with cardiac disease. However, these authors did not find any significant rise in stroke volume, but we did, when considering the average value (wide ranges).

General Aspects of the Venous and Arterial Vascular Beds

Guyton, among others, has pointed out the great importance of changes in venous resistance for the regulation of cardiac output in contrast to the slight influence on systemic flow by altering the arterial resistance. Increased venous return is believed to play an important role in the rise in cardiac output. This suggestion is also in accordance with the decrease in mean recirculation time. Among the mechanisms responsible for the regulation of the venous bed, much interest and discussion have been centered upon the baroreceptor-mediated reflexes. Several investigators have demonstrated in open-chest dogs how reduction in carotid sinus pressure produces venoconstriction and elevation produces venodilatation. On the other hand, Browse and co-workers did not find any significant alterations of the venous tone in dogs, if the variations in carotid sinus pressures were within physiologic limits, nor did Bevegard and Shepherd nor Epstein and associates find them in studies in man. They concluded that only extreme stimulation of the carotid sinus leads to changes in the venous tone. Thus Epstein's group studying the reaction of the resistance and capacitance vessels during vasovagal syncope, found a dilatation of the former and a constriction of the latter vessels. They also concluded that there is a reflex dissociation of the behavior of arteries and veins.

The Effect of Amyl Nitrite on the Venous Bed

The investigations of the effect of amyl nitrite on the venous bed are hitherto few and to some extent contrary. Thus in open-chest dogs, Kot and associates found dilatation of both resistance and capacitance vessels. In agreement with them, Sharpex-Schaefer and Ginsburg reported the same result in man during administration both of nitroglycerin and of amyl nitrite. However, Mason and Braunwald have described an augmentation of venous tone in the forearm induced by amyl nitrite inhalation in contrast to the venodilatation occurring after nitroglycerin. In our investigation we could confirm this observation regarding the effect of amyl nitrite. We assume that this reflex venoconstriction is mainly mediated by a baroreceptor reflex. In some patients we observed that the venous tone remained essentially unchanged at the beginning of the inhalation test, while the arterial pressure fell rapidly and the heart rate rose. About 30 sec after the start of the inhalation, an immediate increase in venous tone occurred (fig. 4), which is fairly late to be a response to an emotional stimulus. The good correlation between the rise in heart rate...
and the maximal increase in venous tone (fig. 5) is a further finding suggesting that venoconstriction could be mediated through a baroreceptor reflex. On the other hand, the unpleasant feeling induced by inhalation of amyl nitrite could change heart rate and venous tone in the same way as the postulated baroreceptor reflex. This cannot be excluded, especially not in those cases in which the venoconstrictor response occurred early in the inhalation test. Probably both mechanisms, the baroreceptor reflex as well as the circulatory reactions to the emotional strain, are involved—certainly in varying degree in different individuals. Hyperventilation induces also an increase in venous tone, heart rate, and cardiac output and a decrease in peripheral resistance. Indeed, the ventilatory effort during the amyl nitrite inhalation is mild and of short duration, so its additional contribution to the action of amyl nitrite must be small, as Perloff and associates have also demonstrated.

**Regional Differences**

The opposite reactions of blood flow in the forearm and calf during inhalation of amyl nitrite seem to be a new observation; for as far as we know, they have not been reported previously. In agreement with Mason and Braunwald, we found in most cases, but within wide ranges, elevated forearm blood flow and marked fall in forearm vascular resistance. However, we could further demonstrate a uniform decrease of blood flow and a marked increase of vascular resistance in the calf at about the same level of the brachial and femoral arterial pressures. Regional differences in blood flow were also found in reactive hyperemia postoperatively in patients operated upon for heart disease and in normal subjects while doing mental arithmetic. This regional difference in vaso-motor reaction during inhalation of amyl nitrite is also manifested in the pronounced change in

**Figure 4**

Original record from a 50-year-old patient illustrating the typical late venous tone reaction 30 sec after the amyl nitrite inhalation had started.

**Figure 5**

Correlation between maximal change of heart rate (HR) and venous tone (VT) induced by amyl nitrite inhalation ($r = 0.85$).
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the contour of the brachial arterial pulse, while the femoral arterial pulse is practically unchanged, a behavior previously observed by Ferrer's group after administration of nitroglycerin. The reduced blood flow and the elevated vascular resistance in the calf cannot be explained in any other way than as an indirect counteraction to the direct vasodilating effect of amyl nitrite. When the blood flow during the inhalation is markedly diminished in the hemodynamically important large vascular bed of the lower extremities, arterial dilatation probably occurs in other vascular areas than in the skin and muscles of the upper half of the body. Animal experiments in cats have indicated dilatation of the splanchnic vascular bed during inhalation of amyl nitrite, but divergent opinions are presented.

The exceedingly large increase in blood flow in the forearm of one patient (fig. 1, patient 5), a rather vasolabile 18-year-old patient with isolated aortic insufficiency, is difficult to explain. He showed generally marked circulatory reactions to amyl nitrite, for example, signs of marked vasoconstriction in the calf (1.3 ml/100 ml/min) at the same time that maximal forearm dilatation occurred, an increase in heart rate of 48 beats/min, which was the highest percentage increase in heart rate in our series, and a marked venoconstriction in superficial hand and foot veins (18 mm Hg).

In contrast to assumptions in several previous reports, our investigations demonstrate that the total effect of amyl nitrite does not include general arteriolar dilatation. A clear difference was found in reaction between the muscular blood vessels of the upper and the lower extremities. Pronounced vasoconstriction was demonstrated in both the forearm and the calf. This effect should result in an increase in venous return which probably plays an important role in the observed elevation of cardiac output. The fall in left ventricular end-diastolic pressure during inhalation of amyl nitrite is interpreted as a sign of improved left ventricular function and of reduced regurgitation due to lowered peripheral resistance; the shortened diastole during the tachycardia also tends to reduce the regurgitation volume. In our main group of patients with isolated aortic insufficiency, the resting pressures in the right side of the heart were normal. In the few cases in which we observed the effect of amyl nitrite on the pulmonary or right ventricular pressures, these pressures were little affected.

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