Action of Nitroglycerin on the Coronary Circulation in Normal and in Mild Cardiac Subjects

By Norman Brachfeld, M.D., John Bozer, M.D., and Richard Gorlin, M.D.

With the technical assistance of Morris H. Smith and Elin Alexander

Nitroglycerin has been used extensively as a coronary vasodilator. Its remarkable clinical effect has been presumed to be related to a direct action on the smooth muscle of the coronary arteriole. No observations have been made of nitroglycerin action on the coronary circulation in man. This report presents studies of changes induced by the drug in 10 normal or nearly normal subjects. The authors present evidence that although coronary vasodilatation does indeed occur, it appears to be secondary to changes in myocardial oxygen requirements. Hemodynamic observations revealed a general decrease in pressures in both peripheral and pulmonary circuits; caution is urged concerning the occasional severe hypotensive effects of nitroglycerin.

In 1867 Sir Lauder Brunton first reported the use of nitrites in the relief of hypertensive crisis and status anginosus. At that time, he attributed the remarkable clinical effect of the drug to its actions of peripheral vasodilatation and in lowering blood pressure. It remained for other investigators to demonstrate in the experimental animal that this dilatation was not confined to the periphery, but in fact took place in the coronary vessels as well. In 1940 Essex and co-workers, and Boyer and Green independently reported that nitroglycerin increased coronary blood flow in experimental animals. In 1947, however, Eckenhoff and co-workers found only inconstant changes in coronary blood flow when more elaborate technics were used. They also stated that the coronary vasodilator effect in the dog persisted only so long as the blood pressure did not fall. Eckstein and his co-workers and Sarnoff, Case, and Macruz have measured myocardial oxygen consumption before and after nitroglycerin in the dog and found no changes. Despite its widespread clinical use and the many assumptions regarding its mode of action, there have been no published reports concerning the effect of nitroglycerin on the coronary circulation in man. It is the purpose of this communication to describe such changes and also to report on the general circulatory effects of sublingually administered nitroglycerin.

Materials and Methods

Ten patients were studied by cardiac catheterization. One patient had clubbing with normal pulmonary and cardiac diagnostic studies; 1 had a small atrial septal defect; 1 a grade-I diastolic murmur of aortic insufficiency without changes in blood pressure; 2 had basal systolic murmurs of grade-II intensity without other abnormality; 1 had a functional apical grade-II systolic murmur, and 4 had completely normal cardiac examinations. These patients had had hepatic vein catheterization with measurement of blood flow and pressure for evaluation of recovery from an earlier acute hepatitis; all studies of liver function were normal.

Cardiac catheterization was performed in the usual fashion; an indwelling no. 17 Riley needle was inserted into the brachial artery. Any diagnostic studies that were required were carried out before this investigation. Pressures were measured in the pulmonary wedge position, pulmonary artery, right ventricle, and right atrium before and after administration of nitroglycerin, by means of a Statham P-23D manometer, recorded directly on a Sanborn twin-channel recorder. Cardiac outputs were measured by the direct Fick method in all, and by indicator-dilution technics in 5. The catheter was then inserted into the
coronary sinus. Coronary blood flow calculated as ml./100 Gm. left ventricular muscle/min. was measured by the nitrous oxide technic\textsuperscript{11} as modified by Goodale and Hackel.\textsuperscript{12} Four minutes after 0.6 mg. of nitroglycerin had been given sublingually, the second flow was begun with samples collected continuously from 0 to 1 min., 1:15-1:45, 2:45-3:15, 4:45-5:15, 6:45-7:15, following cessation of nitrous oxide breathing. From this, a nitrous oxide curve could be constructed\textsuperscript{12} of the veno-arterial nitrous oxide difference during "desaturation" of nitrous oxide from the myocardium.\textsuperscript{*} During the 7-minute period required for determining coronary flow, arterial pressure, heart rate, and indicator-dilution output were measured. Following determination of the coronary flow after nitroglycerin, the catheter was returned to the pulmonary artery in 8 patients.

Blood samples drawn from the coronary sinus, pulmonary artery, and brachial artery were analyzed for oxygen and carbon dioxide content by the technic of van Slyke and Neil,\textsuperscript{14} and pH was measured in a Cambridge pH meter. Partial pressures of oxygen and carbon dioxide were calculated via conversion factors devised by Milch et al.\textsuperscript{15} Mean systolic and mean diastolic pressures and systolic and diastolic time periods were measured on the brachial arterial pressure pulse recorded during the coronary flow.

By means of formulas described elsewhere\textsuperscript{16} left and right ventricular work were calculated as Kg.m./min./M.\textsuperscript{2} and systemic and pulmonary resistances were calculated as dynes sec. cm.\textsuperscript{-5} Coronary vascular resistance was calculated by the standard formula\textsuperscript{11}:

\[
CVR_m = \frac{(BAdm - Ram) \times 1332}{CF}
\]

where

\[
CVR_m = \text{mean coronary vascular resistance (dyne sec. cm.}^{-5})
\]
\[
BAdm = \text{brachial arterial mean pressure, mm. Hg}
\]
\[
Ram = \text{right atrial mean pressure, mm. Hg}
\]
\[
CF = \text{coronary flow, ml./100 Gm./sec.}
\]
\[
1332 = \text{conversion of mm. Hg to dynes/cm}^{-2}
\]

\textsuperscript{*}Previous studies have shown that nitroglycerin begins to act between 1 and 5 minutes after sublingual administration,\textsuperscript{13} as evidenced by fall in blood pressure, change in pulse pressure contour, and increase in cardiac rate. Its peak effect is between 5 and 10 minutes and lasts from 15 to 30 minutes. Continuous direct monitoring of blood pressure and heart rate served to indicate onset and persistence of circulatory effects of nitroglycerin during the flow study which was carried out between the fourth and the eleventh minute. Unpublished studies measuring coronary blood flow within 1 minute of sublingual administration of the drug showed no deviation from the procedure reported herein.

Coronary vascular resistance was also computed according to the following formula\textsuperscript{9} in order to introduce the factor of shortened diastolic time:

\[
CVR_m = \frac{(BAdm - Ram) \times DFP \times 1332}{CF \times 0.75}
\]

where

\[
CVR_m = \text{diastolic coronary vascular resistance (dynes sec. cm.}^{-5})
\]
\[
BAdm = \text{brachial arterial diastolic mean pressure (mm. Hg)}
\]
\[
DFP = \text{diastolic filling period, sec./min.}
\]

0.75 = \text{fraction of coronary flow occurring in diastole\textsuperscript{17}}

Resistance calculated at widely divergent perfusion pressures may not necessarily be comparable.\textsuperscript{18} Perfusion pressure, however, decreased only 10 per cent in this group. Furthermore, changes in resistance in this group will be ultimately compared to changes in resistance in other groups of patients with similar declines in blood pressure following nitroglycerin.

Myocardial oxygen consumption was computed as the product of oxygen extraction and coronary flow. This was calculated per 100 Gm. muscle and for the total left ventricular weight by the formulas of Smith,\textsuperscript{19} with an error estimated at \pm 10 per cent. Myocardial oxygen consumption was also computed per second of systolic contraction;\textsuperscript{9} oxygen consumption per systolic second was then divided by Kg. M. of work per minute. These arithmetical indices served to relate oxygen consumption to the hemodynamic parameters at the moment.\textsuperscript{†}

Mechanical efficiency was calculated both per 100 Gm. muscle and for the total left ventricle according to previously described formulas.\textsuperscript{17}

\textbf{Observations}

\textbf{General Hemodynamic Changes (Table 1). Cardiac output averaged 3.3 L./min./M.\textsuperscript{2} and}

\textsuperscript{*}0.23 per cent of body weight in kilograms for males, 0.21 per cent for females.

\textsuperscript{†}The numbers so derived obviously have no biological significance, but do indicate the manner in which oxygen is expended. Time spent in contraction and the amount of work done per minute are independent variables each affecting total oxygen utilization.\textsuperscript{8} For example, patients with different cardiac rates having identical work outputs per minute will have different myocardial oxygen consumptions per minute.\textsuperscript{9} Therefore, when variations in oxygen consumption have been arithmetically related to variations in heart rate and work, any deviations from the normal values suggest a non-hemodynamic factor influencing myocardial oxygen metabolism. For this artificial derivation "basal contractile" cardiac oxygen consumption is assumed to be constant and has not been subtracted from the total figure.\textsuperscript{20}
TABLE 1.—Action of Nitroglycerin on Systemic and Pulmonary Hemodynamics

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Body surf.电阻 (mm.)</th>
<th>Heart rate per min.</th>
<th>Cardiac output (L/min./M.²)</th>
<th>Brachial artery</th>
<th>Pressures (mm. Hg)</th>
<th>Ventricular work (Kg.M./min./M.²)</th>
<th>Vascular resistance (dyne sec. cm.⁻²)</th>
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</thead>
<tbody>
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<tr>
<td>1</td>
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<td>Clubbing † cause</td>
<td>70*</td>
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<td>87</td>
<td>78</td>
<td>65</td>
<td>18</td>
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<td>90</td>
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<td>Normal</td>
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<td>102</td>
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<td>20</td>
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<td>60</td>
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<td>120</td>
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<td>87</td>
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<td>100</td>
<td>85</td>
<td>18</td>
<td>4</td>
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<tr>
<td>7</td>
<td>27</td>
<td>Grade I basal diastolic murmur</td>
<td>72</td>
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<td>Functional systolic murmur</td>
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<td>Change (%)</td>
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<td>—9</td>
<td>—9</td>
<td>—</td>
<td>—</td>
<td>—10</td>
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</table>

*Before nitroglycerin.
†After nitroglycerin.

showed no significant change following nitroglycerin. All parameters of brachial arterial pressure were reduced an average of 9 per cent over the control values. Left ventricular work averaged 4.4 Kg.M./min./M.² and changed insignificantly to 3.93 following nitroglycerin. Pulmonary arterial pressure averaged 16 mm. Hg in 3 patients and dropped to 11 mm. Hg following nitroglycerin. Pulmonary capillary wedge pressure averaged 9 mm. Hg at rest and fell to 6 mm. Hg in 8 observations. Right atrial mean pressure averaged 4 mm. Hg and decreased to 1 mm. Hg following nitroglycerin. Right ventricular work and pulmonary vascular resistance were satisfactorily measured in only 3 studies. Although they both decreased, no significance was attached to so small a group. Systemic vascular resistance showed no consistent or significant change. Cardiac rates increased from 73 to 83 beats per minute with a 1.8 second lengthening of systole per minute and a reciprocal shortening in diastole per minute.

Coronary Hemodynamic Changes (Table 2). Coronary blood flow as measured per 100 Gm. of left ventricular muscle per minute averaged 66 ml. at rest and increased 63 per cent
to a value of 108 ml./100 Gm./min. This increase in flow was accomplished by a 42-per cent reduction in coronary vascular resistance.

Changes in Myocardial Gaseous Metabolism (Table 3). Coronary venous blood had an average oxygen content of 5.3 volumes per cent at rest, a saturation of 29 per cent, and oxygen tension of 19 mm. Hg. There were no significant changes in these values following the administration of nitroglycerin. Coronary venous carbon dioxide content averaged 53.7 volumes per cent and partial pressure 54 mm. Hg and did not change after nitroglycerin.

Extraction of oxygen and production of carbon dioxide remained unaltered.

Myocardial oxygen utilization at rest was 8.3 ml./100 Gm./min. and increased to 13.6 ml./100 Gm./min. (table 2). This increase in myocardial oxygen consumption paralleled the increased coronary flow, while oxygen ex-
ttraction remained fixed. Although oxygen consumption increased, there was no change in left ventricular work per minute. Consequently, left ventricular efficiency per 100 Gm., which was 26 per cent at rest, decreased to 13 per cent with nitroglycerin. Column 11, table 2, reveals that the oxygen consumption per second of systole was 0.34 ml. at rest, but increased to 0.53 following nitroglycerin. When this oxygen consumption was then expressed as ml. per systolic second per Kg.M. of work (column 12) the value nearly doubled from a normal figure of 0.079 ml. at rest to 0.143 with nitroglycerin. This indicated that changes in oxygen consumption were not related solely to changes in hemodynamics.

**DISCUSSION**

**Basic Action of Nitroglycerin.** An agent which acts as a pure vasodilator does not alter the metabolism of the organ under study. If flow to the organ is increased through lowering of regional vascular resistance, then oxygen extraction and carbon dioxide removal per ml. of blood are correspondingly decreased. Hydralazine for example, has such an action on the coronary circulation: when flow increased, oxygen extraction decreased as evidenced by an increased coronary venous oxygen content, and cardiac oxygen consumption remained unaltered.21

Previous animal experiments have revealed varying reactions to nitroglycerin. Essex et al.4 and Boyer and Green5 showed an increase in coronary flow, but did not measure cardiac work or oxygen consumption. Foltz et al.22 demonstrated a 12-per cent decrease in cardiac oxygen extraction during the first minute following a single 0.6-mg. dose of nitroglycerin intravenously in the dog, but did not measure cardiac work or oxygen consumption. Smaller doses had no such effect but did accelerate the heart and cause a small decrease in blood pressure. Eckstein and co-workers7 injected nitroglycerin directly into a coronary artery in 3 dogs. They found a 25-per cent increase in flow in 2 of 3 and an unchanged oxygen consumption, but cardiac work was not measured. Sarnoff and associates in the isolated dog heart with fixed work and heart rate, showed that nitroglycerin acted as a "pure dilator" with decreased arteriovenous oxygen extraction as coronary flow increased.4

In our own studies of the intact dog under varying anesthetic agents, when nitroglycerin was given as a constant intravenous infusion to the point of constant hypotension (at least 20 per cent below control value) we could not consistently demonstrate either coronary dilatation or decreased oxygen extraction; nevertheless a decrease in cardiac efficiency was always seen.23 The difference between our findings and those of others remains unexplained.

**TABLE 3.—Action of Nitroglycerin on Myocardial Gaseous Metabolism**

<table>
<thead>
<tr>
<th>Patient</th>
<th>D0 content (vol. %)</th>
<th>CO2 content (vol. %)</th>
<th>Oxygen (mm. Hg)</th>
<th>Carbon dioxide (mm. Hg)</th>
<th>O2 extraction (%)</th>
<th>Oxygen</th>
<th>Carbon dioxide</th>
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<td>1</td>
<td>4.0*</td>
<td>51.9</td>
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<td>20</td>
<td>53</td>
<td>29</td>
<td>12.4</td>
<td>8.1</td>
</tr>
</tbody>
</table>

*Before nitroglycerin.
†After nitroglycerin.
The presently reported studies in man would indicate that myocardial oxygen consumption is increased during the administration of nitroglycerin. This is based on the fact that coronary flow increased by 63 percent while the oxygen extraction remained unchanged. Coronary venous oxygen samples drawn at various times from 1 to 10 minutes after sublingual administration of nitroglycerin did not increase in content over the control value.

An alternative explanation of the experimental findings is a redistribution of blood flow within the myocardium, such that there was shunting of blood via other venous channels than the coronary sinus, and that this blood had very little oxygen extracted from it (as with arteriovenous fistula). This would not explain the fact that while the coronary artery-coronary sinus difference for oxygen was unchanged, the same samples revealed a narrowed arteriovenous difference for nitrous oxide. This would confirm the presence of increased outflow of blood from that portion of left ventricle drained via the coronary sinus and that oxygen consumption of that portion of myocardium seemed increased.

This increase in oxygen utilization is not altogether surprising in the light of in vitro studies of the biochemical action of the nitrites. Hunter has shown that the various nitrites increase oxygen utilization in a manner similar to dinitrophenol, namely, uncoupling of oxidative phosphorylation. The very same action which relaxes smooth muscles may affect cardiac muscle contraction. Other stimuli are known to evoke greater increases in coronary blood flow than nitroglycerin. The increase of coronary flow may be solely that demanded by the increased myocardial needs for oxygen under the influence of nitroglycerin.

While cardiac oxygen consumption was elevated, cardiac work remained unaltered: cardiac efficiency decreased. This change in efficiency was not attributable to increased heart rate [oxygen consumption was still increased when computed per second of contraction (table 2)], or large increase in cardiac diastolic volume.

Other Hemodynamic Changes Induced by Nitroglycerin. There was remarkably little change in cardiac work. Blood pressure fell slightly while output remained the same or increased slightly. These findings agree with Starr's early studies but not with Wegria's ballistocardiographic findings of marked increase in output. Eldridge reported similar observations on cardiac output and work, and also demonstrated that nitroglycerin modified the blood pressure response to exercise as well.

Johnson et al. recently reported that nitroglycerin lowered pulmonary arterial pressure. This pressure decrease may be attributed to a decrease in central blood volume and in the diastolic filling pressure of the two ventricles, presumably related to a loss of venomotor tone. We have occasionally seen profound hypotension in the recumbent position when acute arterial bleeding of 100 ml. is superimposed on nitroglycerin administration. This severe hypotension is attended by a concomitant fall in cardiac output and an unchanged systemic resistance. It is quickly reversed by non-cardiotropic vasopressor agents.

Summary

In 10 normal or mild cardiac subjects, observations of coronary and systemic circulatory dynamics and myocardial gaseous metabolism were made before and after the administration of nitroglycerin. Following nitroglycerin, myocardial oxygen consumption increased. Presumably related to this increased oxygen demand, coronary flow increased, mediated by a lowered coronary vascular resistance. The increase in myocardial metabolism was associated with unchanged cardiac work and a fall in myocardial efficiency. These changes were considered consistent with in vitro observations of increased oxygen consumption induced by nitrites during oxidative phosphorylation.

In these patients, cardiac output was essentially unchanged, while blood pressures decreased minimally. There were, however, significant decreases in pulmonary artery, pulmonary wedge, and right atrial pressures suggesting a relaxation of venomotor tone.


Medical Eponyms

By Robert W. Buck, M.D.

_S Curve of Ellis._ At a meeting of the Boston Society for Medical Improvement, October 13, 1873, Professor Calvin Ellis (1826-1883) of the Harvard Medical School discussed “The Line of Dullness in Pleuritic Effusion.” His remarks were reported in the _Boston Medical and Surgical Journal_ 90: 1314 (January 1) 1874.

“In a certain number of cases where the effusion is quite large, if an accurate line be drawn, the flatness will be found to describe a curve, gradually approaching the spine toward the base of the chest, having a space from one to three or more inches broad between the spine and the line of flatness. In this space, resonance will still be detected, and respiration heard. As the effusion increases, this line approaches nearer and nearer the spine, until the whole back becomes flat.”

The attention of Dr. Ellis was called to the fact that Damoiseau had described a similar curve, and he said that until his attention had been called to this, he had not been aware that the point had been observed but that Damoiseau’s description of this curve agreed with his observation.

His (first) article on “The Curved Line of Pleuritic Effusion” appeared in the _Boston Medical and Surgical Journal_ 95: 689-697 (December 14) 1876. It consists of a series of case histories and several diagrams showing a curve on the posterior aspect of the thorax in the form of an S, whose tail begins at the vertical column and whose tip descends into the axilla towards the sternum. The text contains no description of the term. The term _S Curve of Ellis_ was applied by Garland (cf. Garland’s Triangle).
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Circulation. 1959;19:697-704
doi: 10.1161/01.CIR.19.5.697

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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