A Comparison of Coronary Flow Determined by the Nitrous Oxide Method and by a Direct Method Using the Rotameter

By Donald E. Gregg, Ph.D., M.D., Frank H. Longino, M.D.; Paul A. Green, M.D., and Lawrence J. Czerwonka, B.S.

Coronary flow per minute per 100 Gm. of heart with venous drainage into the coronary sinus as measured by the nitrous oxide procedure was compared in the dog with left coronary artery inflow per 100 Gm. of heart perfused by this artery as measured by the rotameter. The error arising from epicardial leak of nitrous oxide was prevented or quantitated by appropriate coverage of the heart. Extremes of the comparisons were +21 and −22 per cent, with an average variation of ±12.4 per cent. The nitrous oxide method is regarded as giving semiquantitative coronary flow values per 100 Gm. of left heart in the dog.

The nitrous oxide procedure for determination of cerebral blood flow in man has been employed for measuring coronary blood flow in the anesthetized and unanesthetized dog and man. In this method, catheters are placed in an artery and in the coronary sinus (the major venous drainage channel of the left heart), and flow per minute per 100 Gm. of heart with venous drainage into the coronary sinus is determined by a variation of the Fick principle. The denominator of the Fick equation is found by computing the integrated difference between the concentrations of nitrous oxide in arterial and in coronary sinus blood during a period of equilibration with a 15 per cent concentration of nitrous oxide. The numerator is assumed to be equal to the product of the venous concentration of the gas (after equilibrium is established) and the partition coefficient of the gas between myocardium and blood. The accuracy of this method for quantitating coronary flow has been tested in the anesthetized dog with the bubble flow meter as the reference method. Although satisfactory agreement is reported in such comparisons, coronary inflow was intermittently measured through only a branch of the left coronary artery (which constituted only a portion of the blood draining into the coronary sinus); a time lag of approximately one minute existed between the arterial

blood passing through the bubble flow meter and that flowing through the uncanulated branch of the left coronary artery; and the venous samples for the nitrous oxide method were withdrawn from a cannula tied into the great cardiac vein, which prevented possible contamination of coronary sinus blood by blood from the right atrium. Because of the importance of this procedure as the only available method permitting measurement of coronary flow in the unanesthetized state, the necessity for confirmation of its accuracy is apparent.

The present investigation is an evaluation of the nitrous oxide method for measuring coronary blood flow by comparison with measurement of total left coronary artery inflow by a rotameter when the venous blood samples for the nitrous oxide procedure were withdrawn from a catheter lying free in the coronary sinus. The rotameter was used as the standard of reference, since it measures blood flow directly, continuously, and with a high degree of accuracy.

Methods

Flow measurements were made simultaneously by the nitrous oxide and the rotameter methods in 15 to 25 Kg. dogs, anesthetized with sodium pentobarbital, 20 to 30 mg./Kg., intravenously. Using artificial positive pressure respiration, the chest was opened by removal of portions of the third to seventh left ribs. The pericardium was incised over the origin of the left coronary artery, the artery carefully cleaned, at its origin, and a suture passed around it. In earlier experiments coagulation was prevented by an...
CORONARY FLOW DETERMINATIONS

Injection of pontamine fast pink (150 mg./Kg.) and heparin (10 mg./Kg.); in later experiments by heparin alone (10 mg./Kg.). In each experiment half the initial injection was repeated every 30 minutes.

Simultaneously to measurement of coronary flow by the nitrous oxide procedure, total left coronary inflow was determined directly by metering flow through the left coronary ostium with an optically recording rotameter (fig. 1). Blood was led from a trocar in a carotid artery through the rotameter, and then into the left coronary artery by a cannula inserted into it via the brachiocephalic artery and aorta, and tied in place. Except during the period of the actual test, blood was shunted around the rotameter. Time for blood to pass through the rotameter circuit approximated six seconds. Immediately after the test run, and in some experiments also before, the rotameter was calibrated with the dog's own blood at essentially body temperature and at the viscosity prevailing during the run. Mean flow per minute was calculated by planimetric integration of the area under the recorded flow curve, a correction being applied for the volume of blood drawn from the efferent tube of the rotameter for arterial samples and clearing of the catheter. Heart tissue fed by the left coronary artery was determined by weighing the amount of tissue (moist weight) taking up blue stain following injection of 0.5 per cent Evans blue dye through the left coronary artery cannula. This injection was made (1) by introducing the dye at a low pressure into the blood flowing into the coronary artery ante mortem, and then immediately inducing ventricular fibrillation; (2) by similar dye injection post mortem; (3) by removing the heart with the left coronary artery cannula still in place, cannulating the right coronary artery, and injecting contrasting dyes (0.5 per cent Evans blue and 1.4 per cent picric acid) simultaneously and at equal pressures of 100 to 150 mm. Hg into the right and left coronary arteries. Thus, left coronary flow per 100 Gm. of dyed heart was determined and could be compared with the flow value obtained with the nitrous oxide procedure.

For the venous samples in the nitrous oxide procedure, a catheter with tip varying from No. 4 F to 64 F was inserted 3 to 5 cm. into the coronary sinus via the external jugular vein, either with fluoroscopy before opening the chest, or visually and by palpation after exposure of the heart. For the arterial samples a catheter of identical capacity was attached to the efferent tube of the rotameter near the coronary cannula. The incised pericardium was not closed and the heart was thus partially exposed to the atmosphere. Just before the comparative test, the

![Fig. 1. Schematic drawing of arrangement of apparatus for measuring coronary flow by the nitrous oxide and rotameter methods.](http://circ.ahajournals.org/)

Dog was connected to a tank of nitrous oxide mixture which activated a second artificial respirator previously adjusted to approximately the same rate and depth as the compressed air respirator. During administration of the nitrous oxide mixture (15 per cent nitrous oxide, 64 per cent nitrogen, 21 per cent oxygen), blood samples were drawn manually into oiled syringes containing enough heparin solution to fill the terminal dead space. Periods of measurement of coronary flow ranged from 10 to 15 minutes. Samples were withdrawn throughout the first minute, and then for half-minute periods at 1.5, 3, 5, and 10 minutes, respectively, and in some experiments also at 7, 12, and 15 minutes. Immediately after withdrawal the syringes were capped, placed in ice water, and within two to four hours the nitrous oxide content of each sample was determined in duplicate, using the method of Orcutt and Waters, as modified by Kety. Flow comparisons were ex-
pressed as per cent deviation of the nitrous oxide flow values from the rotameter flow values.

After a group of experiments had been performed using the above technic, it was found that nitrous oxide could escape from the exposed surface of the heart. Therefore the following method was used to quantitate this escape. Dogs (12-20 Kg.) were anesthetized and the chest opened as before. The heart was covered by an appropriate material impervious to nitrous oxide, consisting of a latex rubber sac or a glass cardiometer, or the pericardium was avascularized and left intact.* The pericardial space was then filled with saline or air, the nitrous oxide mixture was administered for 10 to 15 minutes, and the concentration of nitrous oxide in the pericardial space at the end of this period was compared with that before administration of the gas. It was arbitrarily assumed that the volume of gas escaping from the left heart was equal to the product of total nitrous oxide collected and the ratio of left heart weight to total heart weight. Coronary flow was determined simultaneously by the nitrous oxide method during saturation as described above except that arterial samples were withdrawn from a catheter passed into the aorta.

A final group of experiments was then performed in which this leak of nitrous oxide was prevented or quantitated (and a correction applied to nitrous oxide flow values). These nitrous oxide flow values were compared with left coronary inflow as measured by the rotameter. Technic was identical with that of the first group of experiments except that after the animal had been prepared for an experiment, but before the nitrous oxide mixture was administered, the incised pericardium was carefully sutured and either the incision was made impervious to gas with colloid or a latex sac was fitted about the entire pericardium and evacuated. In 3 dogs 10 to 20 cc. of fluid was found in the pericardial space at the end of the nitrous oxide run. This was measured, analyzed for nitrous oxide, and a correction applied to the nitrous oxide flow value. After the run had been completed, in 4 dogs the pericardium was widely reopened to expose the heart, and after a 30 minute period for complete elimination of nitrous oxide, the experiment was repeated.

**Results**

In the initial 15 comparisons of flow in 10 dogs, the pericardium was left open and the heart was partially exposed. In the individual experiments the mean flow measured by the rotameter was either constant or showed a mild decrease during the test period. Under different dynamic states the rotameter flow per 100 Gm. dyed heart varied from 36 to 130 cc. per minute. The comparisons varied at random from extremes of +50 per cent to -18 per cent, with an average variation between the two methods of ±17 per cent (data not shown). These comparisons may not be valid, since after their completion it was found that nitrous oxide could diffuse through the epicardium in significant amounts.

In the second series of experiments the amount of nitrous oxide leaking from the left heart surface was calculated and compared with the amount of nitrous oxide absorbed by the left heart at equilibrium. Typical results are shown in table 1. Approximately 0.1 to 3.0 cc. of nitrous oxide leaked through the myocardial wall of the whole heart, irrespective of whether the atrial appendages were within or without the sac (20 experiments). When the left ventricular surface alone was covered, about 0.7 cc. of nitrous oxide was recovered from the surface of the left ventricle (3 experiments). Simultaneous measurements showed that this estimated leak of nitrous oxide from the left heart varied from 2 to 100 per cent of the nitrous oxide calculated to have entered the left heart during the determination of coronary flow with the nitrous oxide method. The concentration of nitrous oxide around the heart was indirectly related to the volume of the surrounding fluid or gas, and its concentration progressively rose during the 10 minute saturation period to reach a maximum of 1.0 to 4.0 volumes per cent. This maximum concentration was always considerably less than that in the coronary artery or in the coronary sinus.

In the final group of experiments comparative tests were made of the rotameter and nitrous oxide methods, first when this potential error was eliminated or controlled by an epicardial barrier, and then with the left ventricle partially exposed. Coronary flow values as measured with the rotameter were essentially constant or decreased slightly during the experiments. The data in four comparative tests (table 2) show that partial exposure of the

* The natural or rubber pericardium was shown to be essentially nonpermeable to nitrous oxide by failure to recover the gas from a glass cardiometer filled with saline, whose opening was closed with one of the membranes and which was immersed for 10 to 15 minutes in saline with a nitrous oxide concentration of 5 to 10 volumes per cent.
left heart causes the coronary flow as measured by the nitrous oxide method to be relatively lowered. This is in the direction of change which would be expected if the nitrous oxide leak comes from the left coronary vascular bed. Presumably, this epicardial leak arises from the cardiac exposure which was used in testing the nitrous oxide method. The probability that it occurs in the normal animal or human is somewhat remote.

With this potential error under control, nine comparisons (table 2) between the two flow methods vary between extremes of +21 per cent and -22 per cent, with an average variation of ±12.4 per cent.

### Table 1.—Measurement of Nitrous Oxide Escaping from the Surface of the Heart.

<table>
<thead>
<tr>
<th>Date</th>
<th>Pericardium</th>
<th>Volume Saline (S) or Air (A) cc.</th>
<th>N\O Escaped cc./10 min.</th>
<th>N\O Calc. Abs. by Left Heart cc./10 min.</th>
<th>N\O Coro. Flow cc./100 Gm/min.</th>
<th>Est. Error Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/17/50</td>
<td>Natural</td>
<td>10 S</td>
<td>0.29</td>
<td>5.9</td>
<td>140.0</td>
<td>4.0</td>
</tr>
<tr>
<td>1/30/50</td>
<td>Natural</td>
<td>10 S</td>
<td>0.22</td>
<td>4.4</td>
<td>59.4</td>
<td>4.0</td>
</tr>
<tr>
<td>2/2/50</td>
<td>Rubber</td>
<td>10 S</td>
<td>0.13</td>
<td>7.4</td>
<td>69.9</td>
<td>1.4</td>
</tr>
<tr>
<td>2/5/50</td>
<td>Rubber</td>
<td>10 S</td>
<td>0.35</td>
<td>7.4</td>
<td>69.8</td>
<td>3.8</td>
</tr>
<tr>
<td>2/27/50</td>
<td>Rubber (L.V.)*</td>
<td>35 S</td>
<td>0.66</td>
<td>7.5</td>
<td>80.4</td>
<td>9.0</td>
</tr>
<tr>
<td>2/28/50</td>
<td>Rubber (L.V.)*</td>
<td>75 S</td>
<td>0.76</td>
<td>3.7</td>
<td>42.5</td>
<td>24.0</td>
</tr>
<tr>
<td>1/26/50</td>
<td>Glass</td>
<td>100 S</td>
<td>2.12</td>
<td>3.9</td>
<td>67.6</td>
<td>43.0</td>
</tr>
<tr>
<td>1/27/50</td>
<td>Glass</td>
<td>80 S</td>
<td>1.10</td>
<td>5.8</td>
<td>62.9</td>
<td>15.0</td>
</tr>
<tr>
<td>1/30/50</td>
<td>Glass</td>
<td>55 S</td>
<td>1.25</td>
<td>3.8</td>
<td>59.4</td>
<td>26.0</td>
</tr>
<tr>
<td>2/16/50</td>
<td>Glass</td>
<td>110 A</td>
<td>1.94</td>
<td>6.5</td>
<td>47.9</td>
<td>24.0</td>
</tr>
<tr>
<td>2/17/50</td>
<td>Glass</td>
<td>63 A</td>
<td>2.88</td>
<td>6.0</td>
<td>65.4</td>
<td>47.0</td>
</tr>
</tbody>
</table>

* Left Ventricle.

### Table 2.—Comparison of Nitrous Oxide and Rotameter Flow Values.

<table>
<thead>
<tr>
<th>Date</th>
<th>Mean B.P. mm. Hg</th>
<th>Heart Weight (Gm.)</th>
<th>Left Coronary Blood Flow cc./min./100 Gm.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total %</td>
<td>N\O</td>
<td>Rotameter</td>
</tr>
<tr>
<td>3/2/50</td>
<td>110</td>
<td>159.0</td>
<td>79</td>
<td>72.0</td>
</tr>
<tr>
<td>3/3/50</td>
<td>100</td>
<td>105.3</td>
<td>85</td>
<td>83.6</td>
</tr>
<tr>
<td>3/2/50</td>
<td>102</td>
<td>105.9</td>
<td>79</td>
<td>59.3</td>
</tr>
<tr>
<td>3/8/50</td>
<td>82</td>
<td>104.5</td>
<td>84</td>
<td>80.3</td>
</tr>
<tr>
<td>3/9/50</td>
<td>124</td>
<td>138.7</td>
<td>84</td>
<td>89.2</td>
</tr>
<tr>
<td>3/21/50</td>
<td>92</td>
<td>182.1</td>
<td>81</td>
<td>68.0</td>
</tr>
<tr>
<td>4/10/50</td>
<td>83</td>
<td>149.2</td>
<td>82</td>
<td>44.0</td>
</tr>
<tr>
<td>5/2/50</td>
<td>52</td>
<td>152.9</td>
<td>79</td>
<td>41.6</td>
</tr>
<tr>
<td>5/5/50</td>
<td>111</td>
<td>121.5</td>
<td>83</td>
<td>62.6</td>
</tr>
</tbody>
</table>

* Left heart injected by dye which always included entire left atrium, left ventricle, interventricular septum and the peripheral fringe of the right ventricle.

### Discussion

Under the conditions of these experiments, a considerable difference exists between the coronary flow per minute per 100 Gm. of heart with blood supply draining into the coronary sinus (nitrous oxide method) and coronary flow per minute per 100 Gm. of heart fed by the left coronary artery (rotameter method). The scatter of results must be explained on the basis of errors in the two procedures and/or in their comparison.

In the nitrous oxide procedure, the technical error in determining the nitrous oxide arteriovenous difference can be judged from the fact that the average difference of duplicate nitrous
oxide analyses for the 120 pairs was 0.030 volumes per cent, the maximum difference being 0.065 volumes per cent. Such differences can possibly introduce an error approximating ±5 per cent, since the mean nitrous oxide arteriovenous difference during a test run varied in different experiments from 0.55 to 1.3 volumes per cent, with an average difference of 0.8 volumes per cent. Errors could also arise from entrance into the coronary sinus of blood from the nonmuscular tissue of the heart, from the right atrium, or from the left ventricular cavity via thebesian and arterio-luminal vessels; from diffusion of nitrous oxide through the endocardial wall into the left ventricular cavity; or from participation of nitrous oxide in the metabolic processes of the heart. Whether any of these errors actually exist would be difficult to determine and quantitate.

With the use of the rotameter the technical error is small. The rotameter used in these experiments has been shown to measure flow within ±3 per cent in the presence of considerable variation in flow pattern, blood viscosity, and blood temperature. The rotameter value per 100 Gm. of dyed heart can also be in error from over- or under-injection of the myocardium. The magnitude of this error is difficult to determine. However, it is believed that the dyed heart weight is an accurate index of weight of cardiac muscle supplied with flowing blood by the rotameter, since in 23 injected hearts the percentage of total heart weight dyed by the injection varied between the narrow limits of 78 to 85 per cent, irrespective of whether injection was made through the left coronary artery during life or post mortem, or simultaneously into both right and left coronary arteries (see table 2).

The calculated rotameter flow value can differ from the nitrous oxide flow value because the two methods do not measure flow through the same myocardial area. The rotameter flow value is based on the weight of the injected heart tissue (i.e., that supplied by the left coronary artery) which approximates 78 to 85 per cent of the total heart weight and is essentially all left heart (90 to 95 per cent), including all the left atrium, left ventricle, septum, and the peripheral fringe of the right ventricle. The nitrous oxide flow value is based on the nitrous oxide content of the coronary sinus blood and is a measure of the flow per minute through 100 Gm. of heart whose blood flow drains into the coronary sinus. This blood in the coronary sinus constitutes only 70 to 80 per cent of left coronary inflow and does not include the 20 to 30 per cent of left coronary inflow draining by the anterior cardiac veins of the right ventricle into the right atrium. In addition, in the dog occasionally up to 12 per cent of coronary sinus blood can come from the right coronary artery. However, this drainage is presumably not significant in our experiments, since comparison between the two methods was favorable when right coronary artery drainage into the coronary sinus was encouraged by reducing left coronary inflow 30 to 40 per cent with a screw clamp on the rotameter tubing during approximately half the period of the run (table 2, experiments 5/5/50 and 5/8/50).

Despite the multiplicity of possible errors in the nitrous oxide procedure, the method is believed to indicate semiquantitatively coronary flow per minute per 100 Gm. of left heart.

Although this work was performed on operated animals, there is no reason to believe that the degree of accuracy which has been demonstrated for the nitrous oxide method will be altered in the unanesthetized dog.

**Summary**

Coronary flow per minute per 100 Gm. of heart with venous drainage into the coronary sinus as measured by the nitrous oxide procedure was compared in the dog with left coronary artery inflow per minute per 100 Gm. of heart perfused by the artery as obtained with the rotameter. The error arising from epicardial leak of nitrous oxide was prevented or quantitated by appropriate coverage of the heart. A considerable difference was still found to exist between comparative values under different hemodynamic states, the extremes of comparisons being +21 and -22 per cent, with an average variation of ±12.4 per cent. The nitrous oxide method is regarded as giving semiquantitative coronary flow values per 100 Gm. of left heart in the dog.
ACKNOWLEDGMENTS

Acknowledgment is made of the technical assistance of Mr. Ray T. Fortenbach.

REFERENCES


5 Shipley, R. E.: To be published.


A Comparison of Coronary Flow Determined by the Nitrous Oxide Method and by a Direct Method Using the Rotameter
DONALD E. GREGG, FRANK H. LONGINÓ, PAUL A. GREEN and LAWRENCE J. CZERWONKA

Circulation, 1951;3:89-94
doi: 10.1161/01.CIR.3.1.89

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1951 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/3/1/89

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/