An Evaluation of the Nitrous Oxide Method for the Quantification of Left-to-Right Shunts

An Experimental Comparison of the Gasometric Technic with Directly Metered Blood Flows

By RICHARD J. SANDERS, M.D., THEODORE COOPER, M.D., PH.D., AND ANDREW G. MORROW, M.D., F.A.C.S.

Extensive clinical use has now been made of the nitrous oxide test for the detection and localization of left-to-right circulatory shunts. On theoretical grounds the magnitude of such a shunt should be related to the systemic and pulmonary arteriovenous differences in nitrous oxide content measured early in the period of inhalation. In order to determine the validity of the nitrous oxide method for the quantification of a left-to-right shunt, total pulmonary and shunt flows were directly measured in experimental animals as nitrous oxide tests were performed simultaneously.

UNTIL METHODS are available for the direct measurement of total pulmonary and systemic blood flows in the intact patient, the clinical physiologist must rely upon estimates of their magnitude obtained by various indirect means. Many forms of congenital heart disease are associated with an abnormal intracardiac or extracardiac communication resulting in a left-to-right circulatory shunt and a pulmonary blood flow in excess of the systemic. Since the majority of such conditions may now be corrected, intelligent preoperative evaluation should include precise localization of the defect and a reliable estimate of the blood flow through it. The ratio of pulmonary to systemic blood flow is most commonly determined by relating the arteriovenous differences in oxygen content in the 2 circulations.1, 2 The application of indicator-dilution technics for this purpose has been recently summarized by Wood and his co-workers.3, 4 Clinical studies with nitrous oxide and the radioactive gas krypton55 have shown that the large arteriovenous difference that exists shortly after the onset of inhalation of such inert gases may also be used to estimate the ratio of pulmonary to systemic flow and the relative magnitude of a left-to-right shunt.5-7

The present study was designed to assess the reliability of the nitrous oxide method for the quantification of left-to-right shunts, by comparing the results of this technic with those obtained with directly metered blood flows in the experimental animal.

METHODS

Mongrel dogs, weighing 11 to 25 Kg. were anesthetized with intravenous thiopental and ventilated with 100 per cent oxygen except during nitrous oxide tests. Polyethylene catheters were inserted into each femoral artery and into the right atrium for pressure recordings and blood sampling. Following endotracheal intubation, a left thoracotomy was performed, and the left fourth and fifth ribs were removed. The left and right pulmonary arteries were freed extrapericardially and the left pulmonary artery was divided 1 cm. distal to its origin. Heparin (3 to 5 mg./Kg.) and digoxin (0.1 mg./Kg.) were given intravenously after completion of the dissection. The proximal and distal ends of the left pulmonary artery were then cannulated with Tygon tubing of 1-cm. internal diameter and circulation was reestablished through a flow meter, as shown diagrammatically in figure 1. Intermittent diversion of the total pulmonary flow through the flow meter could then be accomplished by occlusion of the right pulmonary artery with a ligature. A left-to-right shunt was created by connecting the left subclavian and brachiocephalic arteries to the pulmonary circuit through a second flow meter (fig. 1). The magnitude of the shunt was regulated by adjustment of a screw clamp on the
NITROUS OXIDE METHOD

Fig. 1. Schematic representation of the method employed for the direct measurement of total pulmonary flow and left-to-right shunt flow in the dog.

tubing. It was frequently found desirable to support or alter the systemic pressure by intravenous infusion of a solution of norepinephrine (8 mg./L.).

Total pulmonary flow and shunt flow were measured with 2 electromagnetic blood flow meters, which were adjusted to record identical deflections for equal rates of flow. The stability of each meter was often checked and zero flows were recorded frequently during each experiment without interruption of the total pulmonary flow by appropriate manipulation of the accessory "bypass" line around the flow meter (fig. 1). In each dog the 2 meters were simultaneously calibrated by opening the shunt line and occluding the left pulmonary artery while the right pulmonary artery remained open. A given quantity of blood could thus be directed from the shunt through both meters into a graduated cylinder during a measured time interval. Figure 2 illustrates a typical standardization of the 2 meters both before and after the shunt and total pulmonary flows were measured. The calibrations of the flow meters did not vary in their reproducibility by more than 5 per cent on any occasion.

Pulmonary and systemic arterial pressures were measured by means of Statham P-23A and P-23D pressure transducers. Both pressures and flows were recorded on a direct-writing multichannel oscillograph. The mean pressures and flows during the periods of sampling were obtained by planimetric or electronic integration of the records.

Nitrous oxide tests were performed by ventilating the dogs with a gas mixture containing 50 per cent nitrous oxide and 50 per cent oxygen or 100 per cent nitrous oxide for 30 seconds. Between the tenth and thirtieth seconds of inhalation, integrated blood samples were drawn simultaneously from the femoral artery, the right atrium, and from the pulmonary artery distal to the entrance of the shunt (fig. 1). A sample for nitrogen blank determination was always obtained immediately prior to each test. The nitrous oxide contents of the right atrial and pulmonary arterial samples were expressed as percentages of the corresponding femoral arterial samples, $\frac{RA or P_A}{Art.} \times 100 \%$. Only those samples obtained during a steady state, as indicated on the flow meter records, were included in the series.

The blood samples were drawn into oiled, heparinized syringes which were closed with mercury-filled caps, and their nitrous oxide content was determined manometrically. Duplicate determinations were frequently carried out to determine the analytic error, which never exceeded 0.2 vol. per cent.

Results

The results of 18 nitrous oxide tests and the metered blood flows during the respective sampling periods of each test are summarized
TABLE 1.—Pulmonary to Systemic Flow Ratios Determined from Simultaneous Nitrous Oxide Tests and Metered Blood Flows

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Weights Kg.</th>
<th>Total pulmonary flow (ml/min.)</th>
<th>L.A. vent. (ml/min.)</th>
<th>Systemic flow (ml/min.)</th>
<th>Pulmonary arteriovenous difference,*</th>
<th>Samples</th>
<th>Ratios</th>
<th>Mean pressures (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>19.1</td>
<td>1320</td>
<td>850</td>
<td>470</td>
<td>2.8</td>
<td>9.0</td>
<td>6.0</td>
<td>2.9</td>
</tr>
<tr>
<td>4</td>
<td>18.3</td>
<td>1330</td>
<td>710</td>
<td>620</td>
<td>2.1</td>
<td>10.6</td>
<td>4.2</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>12.0</td>
<td>890</td>
<td>370</td>
<td>520</td>
<td>1.7</td>
<td>13.6</td>
<td>6.9</td>
<td>0.5</td>
</tr>
<tr>
<td>6</td>
<td>19.5</td>
<td>1530</td>
<td>790</td>
<td>740</td>
<td>2.1</td>
<td>16.5</td>
<td>9.2</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>18.4</td>
<td>1440</td>
<td>410</td>
<td>1040</td>
<td>1.4</td>
<td>18.7</td>
<td>8.1</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>25.3</td>
<td>1110</td>
<td>810</td>
<td>290</td>
<td>4.0</td>
<td>16.0</td>
<td>12.3</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>11.5</td>
<td>910</td>
<td>690</td>
<td>220</td>
<td>4.2</td>
<td>8.8</td>
<td>7.0</td>
<td>0.8</td>
</tr>
<tr>
<td>11</td>
<td>20.2</td>
<td>1380</td>
<td>630</td>
<td>750</td>
<td>1.8</td>
<td>9.5</td>
<td>4.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>1060</td>
<td>340</td>
<td>720</td>
<td>1.5</td>
<td>11.1</td>
<td>3.9</td>
<td>0.3</td>
<td>35 3</td>
</tr>
<tr>
<td></td>
<td>1250</td>
<td>430</td>
<td>820</td>
<td>1.5</td>
<td>11.0</td>
<td>4.4</td>
<td>0.3</td>
<td>40 0</td>
</tr>
<tr>
<td></td>
<td>1580</td>
<td>790</td>
<td>790</td>
<td>2.0</td>
<td>14.3</td>
<td>7.7</td>
<td>0.3</td>
<td>54 2</td>
</tr>
</tbody>
</table>

*FA, PA, and RA refer to femoral arterial, pulmonary arterial, and right atrial samples respectively.
†When a right atrial nitrous oxide sample was not obtained, an assumed value of 3 per cent was employed in calculating the flow ratio. This value represents the average of the control tests that were obtained under similar conditions.

The magnitude of each shunt was expressed as the ratio of pulmonary to systemic flow. This ratio was obtained by relating the systemic arteriovenous difference in nitrous oxide concentration to the pulmonary arteriovenous difference,* or \( \frac{C_{n2o} - C_{ran2o}}{C_{n2o} - C_{pas2o}} \) Since all nitrous oxide concentrations are expressed as a per cent of the arterial concentration, \( (C_{n2o} = 100 \text{ per cent}) \), the formula becomes

\[
\frac{\text{Pulm. flow}}{\text{Syst. flow}} = \frac{100\% - RA\%}{100\% - PA\%}.
\]

The metered ratios ranged from 1.4 to 4.6 and averaged 2.4.

The pulmonary:systemic flow ratios determined from metered flows are compared to the corresponding ratios derived from the nitrous oxide tests in figure 3. There is no systematic difference between the flow ratios determined by the 2 methods. The coefficient of correlation for these data is 0.96.

When the shunt was closed, mean pulmonary arterial pressures were elevated 5 to 20 mm. Hg above normal. Upon opening of the shunt, mean pulmonary arterial pressure uniformly rose and mean systemic pressure fell. The pressures recorded during each period
of sampling and flow measurement are included in table 1.

Discussion

The introduction of a plastic loop having a capacity of approximately 100 ml. into the pulmonary circulation resulted in a mild increase in pulmonary arterial pressure. This pressure was further elevated by occlusion of the right pulmonary artery and diversion of the entire pulmonary flow through the loop and the left lung. Under these conditions, a left-to-right shunt was not always well tolerated. Systemic pressure fell and pulmonary arterial pressure rose even further, thus reducing the systemic-pulmonary arterial gradient and limiting the magnitude of the shunt. The right ventricle usually became dilated and the output of both ventricles fell. However, although the output was low, it was possible to maintain a steady flow during which nitrous oxide tests could be performed. In order to relieve the load on the heart, the shunt was closed and the right pulmonary artery opened between sampling periods. Care had to be taken in inserting the cannula into the proximal left pulmonary artery, so that it did not extend too far into the main pulmonary artery and occlude the right.

Frequently, shunts that produced pulmonary to systemic flow ratios in excess of 3:1 were poorly tolerated. Several tests were discarded from the series because they were performed while the flows were falling during the sampling period and their results served only to emphasize the importance of a stable preparation during the sampling. Under these unstable conditions, the magnitude of the shunt was grossly overestimated by the nitrous oxide.

The excellent correlation between metered flows and calculations based upon the nitrous oxide test (fig. 3) establishes the reliability of the inert gas technic for the estimation of the magnitude of a left-to-right shunt. It should be pointed out, however, that only occasionally was it possible to obtain reliable data with shunts producing pulmonary flows in excess of 3 times systemic flow. With these larger shunts, the effects of analytic errors became more important with both the direct and indirect technics, and the correlation between them became correspondingly poorer.

The limitations of the oxygen method for determining the magnitude of a shunt are well recognized. These are the difficulties in obtaining representative samples of mixed venous blood from the venae cavae; a small pulmonary arteriovenous difference; and the normal variations in oxygen content that occur with changes in the metabolic state. With the nitrous oxide test, these shortcomings are minimized. Vena caval samples, proximal to a shunt, are not necessary because the normal nitrous oxide concentration of systemic venous blood is always close to zero during the first 30 seconds of inhalation. In a group of 150 tests carried out in patients, the normal venous content ranged from 0 to 15 per cent of the arterial content and averaged 6 per cent. In the present study, the average systemic venous content was 3 per cent. In the practical applications of the test, it has been found that the average value may be used in calculating the magnitude of shunt without significantly altering the results. In the nitrous oxide test, samples are not drawn while the pulmonary and systemic arterial levels of the gas are constant but during a
time when both are rising. The use of integrated samples drawn simultaneously during most of the period of inhalation minimizes this source of error.

The present study supports the conclusion drawn from extensive clinical application that the nitrous oxide test provides a reliable method for the quantification of a left-to-right shunt as well as for its identification and localization.

SUMMARY

Total pulmonary blood flow and blood flow through an artificial left-to-right shunt were measured directly in the dog by means of electromagnetic flowmeters in an extracorporeal extension of the pulmonary circulation. Nitrous oxide tests were then performed while shunts of various magnitudes were functioning. The ratios of pulmonary to systemic flow determined by the nitrous oxide tests correlated well with the ratio obtained from the metered flow measurements, and confirmed the validity of the nitrous oxide technic for the estimation of the magnitude of a left-to-right shunt.

SUMMARIO IN INTERLINGUA

Le total fluxo pulmonar de sanguine e le fluxo de sanguine in un derivation artificial sinistro-dextere in un can eseva mesurate directemente per medio de fluxometros electromagnetic in un extension extracorporee del circulation pulmonar. Tests a oxydo nitrose eseva afore affectede durante que derivaciones de varie magnitudes eseva in function. Le proportion inter fluxo pulmonar e fluxo systemic eseva determinate per medio del test a oxydo nitrose e se provava ben correlationate con le proportion obtenite per mesura-

tion directe del fluxo. Le resultato del studio es un confirmation del validitate del technica a oxydo nitrose in le estimation del magni-
tude de derivationes sinistro-dextere.

REFERENCES

1. COURNAND, A., BALDWIN, J. S., AND HIMMEL-
vest. 20: 127, 1941.

nary blood flow using the indicator-dilution technic in patients with a central arterio-

5. MORROW, A. G., SANDERS, R. J., AND BRAU-

wald, E.: The nitrous oxide test: An improved method for the detection of left-to-

7. ---, AND ---: The identification and quantifica-
8. RICHARDSON, A. W., DENISON, A. B., JR., AND GREEN, H. D.: A newly modified electro-
An Evaluation of the Nitrous Oxide Method for the Quantification of
Left-to-Right Shunts: An Experimental Comparison of the Gasometric Technic
with Directly Metered Blood Flows
RICHARD J. SANDERS, THEODORE COOPER and ANDREW G. MORROW

Circulation. 1959;19:898-902
doi: 10.1161/01.CIR.19.6.898
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1959 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/19/6/898