The Diagnosis of Circulatory Shunts
by the Nitrous Oxide Test

Improvements in Technic and Methods for Quantification of the Shunt

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The nitrous oxide test for the detection and localization of left-to-right shunts has previously been studied clinically. Further experience with the method has shown that a higher N₂O concentration and an earlier sampling period result in a larger arteriovenous N₂O difference that increases the sensitivity of the test and further minimizes the importance of possible analytic errors. In addition, a method is described of determining the magnitude of the shunt from the results of a N₂O test. The results of 150 N₂O tests performed with the improved technic are presented, and compared to the results obtained with the O₂ method in a group of patients on whom both tests were carried out.

The usefulness of the nitrous oxide test in the detection and localization of left-to-right circulatory shunts has been established. The test takes advantage of the large arteriovenous difference following inhalation of an inert gas. In the technic originally described, 15 per cent N₂O was inhaled for 60 seconds as integrated blood samples were drawn simultaneously from the pulmonary artery or a right heart chamber and a systemic artery. The presence or absence of a left-to-right shunt was indicated by the ratio of the N₂O content of right heart or pulmonary arterial blood to that of systemic arterial blood. The superiority of this test over the method of determining O₂ differences was shown in 148 patients in whom both technics were employed.

The experience with 15 per cent N₂O and the 60-second sampling period indicated that in some patients an adequate arterial level was not achieved while in others, particularly in children, a rapidly rising venous level had decreased the arteriovenous difference by the end of this period of time (figs. 1 and 2). Accordingly, studies were undertaken to evaluate different N₂O concentrations and various sampling periods; these have led to an improved method of performing the N₂O test. In addition to the detection and localization of left-to-right shunts, the results of the N₂O test can be used to estimate their magnitudes. This method for quantification as well as the modifications of the original N₂O test are described in the present report.

Materials and Methods

In 98 patients, 150 satisfactory N₂O tests were performed. With 4 exceptions, all patients had pulmonary artery N₂O tests; in addition, 30 patients had right ventricular tests and 26 had right atrial tests. Sixty-nine of the tests were performed on children under 15 years of age and the remaining 81 on adults.

Seventy-eight tests were performed on 63 patients without left-to-right shunts. Forty-five of these control patients had rheumatic heart disease; the others had various forms of congenital heart disease without a shunt or were children with normal hearts and functional murmurs. Seventy-two tests were carried out in 35 patients with left-to-right shunts. Of these, 16 had atrial septal defects, 15 ventricular septal defects and 2 had patent ductus arteriosus. Of the 2 remaining patients one had an aortico-pulmonary window and the other a fistula between the right coronary artery and the right atrium. All patients had confirmatory evidence of the presence or absence of a shunt: in the majority of patients the diagnosis was confirmed at operation, and in the others by other studies including aortic catheterization, right and left heart catheterization, indicator-dilution curves, thoracic aortography, and selective angiocardiography.

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The $\text{N}_2\text{O}$ tests were carried out in the following manner. The tip of a cardiac catheter was placed in a right heart chamber or the main pulmonary artery, and a needle was inserted into a systemic artery. The patient was then instructed to breathe deeply a mixture of 50 per cent $\text{N}_2\text{O}$, 20 per cent $\text{O}_2$, and 30 per cent $\text{N}_2$ for 30 seconds. Integrated blood samples were drawn simultaneously from the catheter and needle during the last 20 seconds of inhalation at the rate of 1 ml. every 4 seconds. The gas was administered through a 3-way valve and either a face mask or mouthpiece. The blood samples were capped and analyzed manometrically for $\text{N}_2\text{O}$ content.5

At least 5 and preferably 10 minutes were allowed for $\text{N}_2\text{O}$ desaturation before a test was repeated in another heart chamber. A blood specimen for a blank determination was always obtained from the catheter immediately prior to each test. This blank was then subtracted from the $\text{N}_2\text{O}$ content of each sample and the result of the test was expressed as the ratio of the pulmonary arterial or right heart sample to the arterial sample:

$$\frac{P_A, \, R_V \, or \, R_A \, N_2O \, content}{Arterial \, N_2O \, content} \times 100$$

From 43 patients (31 with shunts) blood samples were obtained for the determination of $\text{O}_2$ content. Two samples from the pulmonary artery and each vena cava, and 3 samples from each right heart chamber were analyzed. The average $\text{O}_2$ content of blood from each chamber was used to determine the $\text{O}_2$ differences between chambers and to calculate the pulmonary and systemic flows by the Fick method. The samples were analyzed manometrically,10 with 6 exceptions, in which a spectrophotometric method was employed.31

**RESULTS**

The results of the 150 $\text{N}_2\text{O}$ tests performed in all 98 patients are presented graphically in figure 3. Between the tenth and thirteenth seconds of inhalation of 50 per cent $\text{N}_2\text{O}$, the integrated arterial samples contained 2.0 to 14.0 vol. per cent $\text{N}_2\text{O}$. During the period of the study only 5 patients had arterial concentrations of less than 1.5 vol. per cent and these have been excluded, since analytic errors become of increased significance with such low gas concentration. The average arterial $\text{N}_2\text{O}$ content among the patients with rheumatic heart disease was $6.0 \pm 2.8$ vol. per cent (median = 5.8 vol. per cent). Adults with congenital heart disease had an average arterial level of $7.5 \pm 2.6$ vol. per cent (median = 7.4 vol. per cent), and the children had an average level of $7.9 \pm 2.5$ vol. per cent (me-
Fig. 3 Left. Results of 150 N₂O tests. Open figures represent control patients; solid figures, patients with left-to-right shunts. Percentage lines refer to the ratio of RA, RV, and PA samples × 100. The 15 per cent line appears to separate the shunt and control groups. Among the control patients, those with rheumatic heart disease have lower arterial levels and lower ratios than the nonrheumatic patients.

Fig. 4 Right. Conversion of N₂O test into terms relating the pulmonary flow to the systemic flow by comparing the systemic arteriovenous difference in N₂O concentration to the pulmonary arteriovenous difference, or \[ \frac{100\% - \text{PA} \%}{6\%} \] The solid line represents the related values when the mixed vena caval content is 6 per cent of the arterial content. The shaded area indicates the variations introduced by vena caval levels of 0 to 10 per cent. The box encloses the zone of N₂O tests between 40 and 60 per cent, which relate to pulmonary flows of 1.5 to 2.5 times systemic flows.

dian = 7.6 vol. per cent). In comparison, when 15 per cent N₂O was inhaled and a 1-minute integrated sample was drawn the range of arterial samples was 1.5 to 4.5 vol. per cent and the average was 3.0 vol. per cent. In the present study, with 50 per cent N₂O the arterial level was below 4.5 vol. per cent in only 32 of 137 tests in acyanotic patients; the majority of these patients were among the group with rheumatic heart disease. Patients with right-to-left shunts had lower arterial levels than the noncyanotic group; the average arterial level in 13 cyanotic patients was 3.6 vol. per cent and it exceeded 2.0 vol. per cent in all but 1 instance.

In the absence of a left-to-right shunt the venous N₂O level, measured in either the right atrium, right ventricle or pulmonary artery, was less than 15 per cent of the arterial level, and in all but 5 of the 96 control tests was less than 10 per cent. Again, a difference was found between rheumatic and nonrheumatic control patients. In those with rheumatic heart disease the average venous sample was 2.2 ± 2.4 per cent of the arterial sample. Among the control patients with nonrheumatic types of heart disease the venous samples of adults averaged 4.6 (± 3.4 per cent) while that of children averaged 6.1 (± 4.0 per cent) of the arterial sample. Among all children control tests in the right atrium averaged 6.0 per cent, in comparison to an average value of 6.3 per cent for tests in the right ventricle and pulmonary artery. The 5 control patients whose tests revealed values between 10 and 15 per cent all had congenital heart disease.

Seventy-two N₂O tests were performed in 35 patients with left-to-right shunts. With 1 exception, tests at or beyond the entrance of the shunt revealed venous levels exceeding 15 per cent of the corresponding arterial levels. The single false negative result (4 per cent) was a right ventricular test in a child.
with a high ventricular septal defect and a small shunt. It is probable that the catheter tip was not high enough in the right ventricular outflow tract for sampling shunted blood, since the pulmonary artery test was higher (17 per cent). The shunt was not revealed by oximetry, and the diagnosis of ventricular septal defect was established by a positive indicator-dilution curve from the left ventricle and a normal curve from the ascending aorta. A thoracic aortogram was also normal. In 1 patient with an atrial septal defect, the right atrial sample was 109 per cent of the arterial sample. Presumably, the catheter tip was lying in or facing the left atrium during the test. A subsequent test in the right ventricle was 51 per cent.

Quantification of the Shunt

The presence of a left-to-right shunt permits the mixing of venous and arterialized blood containing different concentrations of N\textsubscript{2}O. The N\textsubscript{2}O content of mixed venous blood proximal to the shunt may be assumed to equal that observed in nonrheumatic control patients. This value was found to be 6 ± 6 per cent of the arterial level. The N\textsubscript{2}O content of shunted blood may be considered to be essentially the same as that of arterial blood.

The N\textsubscript{2}O concentration in blood distal to the shunt (usually sampled from the pulmonary artery) reflects the mixing of systemic and shunted flows. Since the pulmonary arterial concentration is measured and the other 2 levels may be closely estimated, the relative amounts of systemic and shunted blood required to produce the observed concentration of N\textsubscript{2}O in pulmonary arterial blood can be determined.

Since, in the presence of a left-to-right shunt, the pulmonary flow is equal to the systemic flow plus shunt flow, then the amount of N\textsubscript{2}O passing through the pulmonary circuit must be equal to the sum of the amounts returned to the heart from the systemic veins and that added by the shunt:

\[ Q_{pa} = Q_{sys} + Q_{sh} \]

Since the quantity of N\textsubscript{2}O traversing any chamber in a given time is equal to the product of the blood flow and its N\textsubscript{2}O concentration, then:

Pulmonary flow \( (Q_{pa}) \times \text{PA N}_2O \) test \( (C_{paN2O}) \) =

systemic flow \( (Q_{sys}) \times \text{mixed venous N}_2O \) test \( (C_{cvN2O}) \) + shunt flow \( (Q_{sh}) \times \text{arterial N}_2O \) level \( (C_{aN2O}) \)

or

\[ Q_{pa} C_{paN2O} = Q_{sys} C_{cvN2O} + Q_{sh} C_{aN2O} \] (2)

since

\[ Q_{sh} = Q_{pa} - Q_{sys} \] (from equation 1)

Substituting equation 1 into equation 2:

\[ Q_{pa} C_{paN2O} = Q_{sys} C_{cvN2O} + (Q_{pa} - Q_{sys}) C_{aN2O} \] (3)

and rearranging:

\[ Q_{sys} (C_{aN2O} - C_{cvN2O}) = Q_{pa} (C_{aN2O} - C_{paN2O}) \]

or

\[ \frac{Q_{pa}}{Q_{sys}} = \frac{C_{aN2O} - C_{cvN2O}}{C_{aN2O} - C_{paN2O}} \] (4)

The above analysis has been carried out under the assumption that the rate of change of concentrations of N\textsubscript{2}O in the blood of the heart chambers is zero. This represents the so-called “steady state” solution of the differential equations governing the system. Some preliminary mathematical analysis has shown that formula 4 is also valid, under conditions thus far investigated, for the more general case where the concentrations of N\textsubscript{2}O vary with time.\textsuperscript{12}

The formula derived above is similar to that described by others\textsuperscript{13, 14} for the application of
the Fick principle in calculating pulmonary and systemic flows with \( O_2 \) samples:

\[
Pulmonary \text{ flow} = \frac{C_{aO_2} - C_{vCO_2}}{C_{aO_2} - C_{pO_2}}
\]

\[
Systemic \text{ flow} = \frac{C_{aO_2} - C_{pO_2}}{C_{aO_2} - C_{vCO_2}}
\]

Both methods of determination are based upon the arteriovenous differences proximal and distal to the shunt. They differ only in that one method utilizes relative blood \( N_2O \) concentration and the other blood \( O_2 \) content.

When the \( N_2O \) arteriovenous difference is used, only the concentration distal to the shunt need be measured, since the concentration proximal to the shunt will be close to 6 per cent of the arterial concentration (fig. 3). Thus, by assuming a normal venous level 6 per cent of the arterial one, it is possible to convert all of the \( N_2O \) percentages into ratios relating pulmonary flow to systemic flow (fig. 4). This figure also demonstrates that if the \( N_2O \) ratio in blood proximal to the shunt varies from 0 to 10 per cent, the resulting calculation of the magnitude of the shunt is altered only slightly. The enclosed area illustrates that \( N_2O \) ratios of 40 and 60 per cent correspond to pulmonary flow: systemic flow ratios of 1.5:1 and 2.5:1 respectively.

When the results of the \( N_2O \) tests are expressed as ratios of pulmonary to systemic flow, a basis is provided for comparison with the method of \( O_2 \) differences. In figure 5 these ratios calculated by both methods, are plotted for 31 patients with shunts and 12 patients without shunts. With the \( O_2 \) method the 7 patients with small left-to-right shunts (plotted on the abscissa in fig. 5) had pulmonary/systemic flow ratios in the range observed among control patients (0.8:1 and 1.3:1). Six of these 7 patients had \( O_2 \) step-ups of less than 1 vol. per cent and were thus considered false negative tests by \( O_2 \) differences. In comparison, the \( N_2O \) calculations in the control patients never indicated pulmonary flows exceeding 1.1 times systemic flow. The 7 patients with shunts who could not be separated from the control patients by \( O_2 \) determinations were easily distinguished from the controls by \( N_2O \) measurements (see ordinate, fig. 5) although with but one excep-

tion the ratio of pulmonary flow to systemic flow was less than 1.5:1.

With larger shunts, the ratios of pulmonary to systemic flow determined by the \( N_2O \) method were not so great as those calculated by the \( O_2 \) method. In 6 patients the calculated pulmonary flows exceeded 3 times the systemic flows by \( O_2 \) determinations; in only 1 of these patients did the ratio exceed this value when calculated by the \( N_2O \) method.

The reliability of a single \( N_2O \) test for estimating the size of a shunt is demonstrated in figure 6. Twenty-one patients with either atrial or ventricular septal defects and 4 control patients had tests performed in both the pulmonary artery and right ventricle in the course of the same catheterization. The 2 ratios were within 10 per cent of each other in 21 of the 25 patients, and within 6 per cent of each other in 17 patients. It was of interest that relatively well-mixed blood was obtained in the right ventricular outflow tract in patients with ventricular septal defect; 9 of 12 such patients had right ventricle ratios within 5 per cent of their pulmonary artery ratios.

**DISCUSSION**

The inhalation of 50 per cent \( N_2O \) for short periods of time is relatively innocuous. Occasionally a patient experiences slight dizziness after the test, but this is transient. The advantages of this high concentration is that a larger arteriovenous difference is achieved, rendering technical and analytic errors of less importance. Among cyanotic patients, for example, adequate arterial levels were virtually always achieved with 50 per cent \( N_2O \), while more than half of the tests previously done with 15 per cent \( N_2O \) were considered unsatisfactory because of low arterial levels.

The need of an earlier sampling period became apparent as increasing numbers of infants and children were studied. In these patients the circulation time is much shorter than in adults with rheumatic heart disease. In children arterial saturation with \( N_2O \) was frequently complete within 30 seconds, and the venous level often rose to 25 or 35 per cent of the arterial level by the end of the first
minute of inhalation (fig. 2). It therefore became necessary to determine an earlier sampling period during which the venous level in patients with rapid circulation times would still approximate zero, and yet the arterial level in patients with slow circulation times would be adequate. A study of different sampling periods resulted in the selection of an integrated sample drawn between the tenth and thirtieth seconds of inhalation. This technic yielded satisfactory tests in more than 95 per cent of patients studied. In an occasional patient with an exceptionally long circulation time, it is necessary to use a later sampling interval, such as 30 to 50 seconds. It should be noted that chronic lung disease with impairment of pulmonary diffusion may also be responsible for a low arterial level.

With the earlier sampling period the venous content never exceeded 15 per cent and was usually less than 10 per cent of the arterial content in control patients. With the original 1-minute sampling period, levels as high as 20 per cent in the pulmonary artery and 30 per cent in the right atrium were observed in control patients. This difference between chambers has not been observed in the present study and the same diagnostic criteria may now be applied to tests performed in all 3 areas. On the basis of the 150 tests summarized in figure 3, it is now considered that the diagnosis of a shunt can be made when the right heart or pulmonary artery level is 20 per cent or more of the arterial level. The absence of a shunt is assured by a venous level less than 15 per cent of the arterial level. Tests between 15 and 20 per cent are equivocal and should be repeated.

It is not difficult to detect large left-to-right shunts by the demonstration of a difference in O₂ content of blood sampled from the venae cavae, right heart, and pulmonary artery. However, with small shunts this method is limited by the magnitude of the systemic arteriovenous O₂ difference. To produce an increase in O₂ content of 1.0 vol. per cent distal to a shunt, the flow through the shunt must be at least 33 per cent of systemic flow when the systemic arteriovenous difference is

4.0 vol. per cent. If the systemic arteriovenous difference is 8.0 vol. per cent, the flow through the shunt need only be 17 per cent of systemic flow to produce the same increase in O₂ content. Thus, the sensitivity of the O₂ method is directly proportional to the magnitude of the systemic arteriovenous difference. The sensitivity of the N₂O test, on the other hand, is not altered by the large range of arteriovenous differences in N₂O content. Although the highest arterial N₂O level in this series was 7 times larger than the lowest arterial level, and the resulting arteriovenous differences were similarly distributed, this variation was equalized by expressing the venous levels as percentages of the corresponding arterial levels. Shunts less than 15 per cent of systemic flow could uniformly be detected with the N₂O test (fig. 5).

Calculations of the magnitude of left-to-right shunts from the systemic and pulmonary arteriovenous O₂ differences have long been recognized to be little better than estimates and subject to considerable error. The inaccuracies of the method are due in part to the difficulty in obtaining a representative mixed venous sample proximal to the shunt, particularly when caval sampling is necessary in

![Fig. 6. The reproducibility of repeat N₂O tests in the right ventricle and pulmonary artery of 25 patients. The solid diagonal line indicates the points where the 2 tests were the same. The boxed-in area includes the ratios between 40 and 60 per cent.](image-url)
shunts at the atrial level. A larger source of error is introduced as the pulmonary arteriovenous difference approaches 1.0 vol. per cent. In this range, the small analytic errors in determining the O₂ content of the 2 blood samples can assume very large proportions. This may well be the explanation for the errors introduced as the pulmonary flow ratio in excess of 3:1 would support this hypothesis.

However, the calculation of the size of a shunt from N₂O data is also subject to criticism. The arteriovenous difference in N₂O content is rapidly changing throughout the test, and the rise in N₂O content of peripheral arterial blood lags behind that of shunted blood by the circulation time between the left heart and the peripheral artery used for sampling. The use of integrated blood samples averages the changing levels and the dead space in the catheter tends to compensate for the circulation time delay. It is anticipated that comparison of the N₂O and O₂ methods in experimental animals with metered flows will indicate the accuracy of each technic. Such studies are now in progress. In terms of clinical evaluation and preoperative selection of patients, shunts need only to be considered as small, medium, or large. The N₂O ratios provide a convenient means for such a classification. A pulmonary artery test between 40 and 60 per cent indicates a moderate-sized shunt, estimated to produce a pulmonary to systemic flow ratio of 1.5 to 2.5:1 (fig. 4). Pulmonary arterial N₂O tests of 20 to 40 per cent indicate relatively small shunts, and ratios over 60 per cent are associated with large shunts. The 21 patients with atrial and ventricular septal defects represented in figure 6 are so divided according to the size of their shunts. The reproducibility of the test is shown by the fact that in 17 of 21 repeat tests a given patient’s classification was not changed.

SUMMARY

The localization of left-to-right circulatory shunts by the nitrous oxide test has been facilitated by modifications of the original technic. In the course of right heart catheterization, patients inhaled 50 per cent N₂O for 30 seconds as integrated blood samples were drawn simultaneously from the pulmonary artery or right heart and a systemic artery. In 78 tests performed in patients without shunts, the N₂O content of blood from the right atrium, right ventricle, or pulmonary artery was always less than 15 per cent of the arterial content. Among 72 tests carried out in patients with left-to-right shunts, the venous sample exceeded 20 per cent of the corresponding arterial sample in all but 2 instances.

The magnitude of a left-to-right shunt could be calculated from the results of the N₂O test by the application of a formula relating systemic and pulmonary N₂O arteriovenous differences. A simpler estimate of the shunt could be made directly from the N₂O ratio: small shunts gave ratios of 20 to 40 per cent; intermediate shunts with pulmonary to systemic flow ratios of 1.5 to 2.5:1 gave ratios of 40 to 60 per cent; large shunts were associated with N₂O ratios exceeding 60 per cent. In 43 patients the N₂O test was compared with the method of O₂ differences. It was found that with the N₂O test, shunts comprising less than 15 per cent of the pulmonary flow could uniformly be detected, while with the O₂ method, shunts 25 per cent of the pulmonary flow often escaped recognition.

SUMMARIO IN INTERLINGUA

Le localisation de sinistro-dextere derivationes circulatori per medio del test a oxydo nitrose poter esser simplificate per modifications del technica original. In le curso de catheterismo dextero-cardiac, le patientes inhala 50 pro cento de oxydo nitrose durante 30 secundas, e simultaneemente specimenes de sanguine integrate es prendite ab le arteria pulmonar o ab le corde dextere e ab un arteria systemic. In 78 tests in patientes sin derivation, le contento de oxydo nitrose in specimenes de sanguine ab le atrio dextere, le ventriculo dextere, o le arteria pulmonar esseva semper minus que 15 pro cento del contento de oxydo nitrose in specimenes de sanguine arterial.
Inter 72 tests effectuate in patientes con derivationes sinistro-dextere, le specimen venose monstrava un contento de oxydo nitrose de plus que 20 pro cento del contento arterial de oxydo nitrose in omne casos con 2 exceptiones.

Le magnitude del derivation sinistro-dextere poteva esser calculate ab le resultatos del test a oxydo nitrose per le application de un formula que interrelationa le systemic con le pulmonar differentias arterio-venose de oxydo nitrose. Un plus simple estimation del derivation pote esser facite directemente super le base del proportion de oxydo nitrose. Miere derivationes monstrava proporciones de 20 a 40 pro cento. Derivationes de magnitudes intermediari (con proporciones inter fluxo pulmonar e fluxo systemic de inter 1,5 e 2,5 a 1) monstrava proporciones de 40 a 60 pro cento. Grande derivationes esseva associate con proporciones de plus que 60 pro cento. In 43 patientes le test a oxydo nitrose esseva comparate con le methodo a differentias de O₂. Esseva constatate que le test a oxydo nitrose esseva uniformemente capace a deteger derivationes amontante a minus que 15 pro cento del fluxo pulmonar. Del altere latere, le methodo a O₂ resultava frequentemente in le non-detection de derivationes amontante a 25 pro cento del fluxo pulmonar.

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