Detection and Quantitation of Intracardiac Left-to-Right Shunts by an Oximetric Inert Gas Technic

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It is well known that small left-to-right shunts of less than 20 per cent of the pulmonary blood flow in patients with congenital heart disease usually cannot be detected by conventional blood oxygen saturation methods during right heart catheterization. Numerous supplementary methods have been devised to locate and to quantitate small shunts in the cardiovascular system. These methods include venous dye-dilution curves, inhalation of foreign gases, thermal dilution, and external scanning technics.

Venous dye-dilution curves allow precise quantitation of a shunt. However, this method is technically difficult because insertion of two catheters usually is required, one for the injection of dye and one for sampling the resultant dye-blood mixture from various sites in the right heart and great vessels.

Nitrous oxide was the first foreign gas used as an indicator. This was followed rapidly by the use of the radioactive gases Krypton-85, Iodine-131, Ethyl and methyl iodides, and more recently hydrogen and hydrogen plus ascorbic acid. All technics using foreign gases require the use of special detecting equipment and, in addition, many of these methods do not allow for quantitation of the left-to-right shunt.

In the presence of a left-to-right shunt, a continuous recording of the oxygen saturation of pulmonary arterial blood during a sudden transient change from breathing air to breathing a gas mixture containing no oxygen will reveal a decrease in the oxygen saturation of pulmonary artery blood, which occurs simultaneously with that in systemic arterial blood.

This results from an intracardiac left-to-right shunt of the reduced hemoglobin caused by transient reduction in the oxygen content of blood returning to the left heart from the lungs during the period the inert gas is breathed. This simple inert gas technic for detecting left-to-right shunts has the advantage that only one right heart catheter is used and no special detecting equipment other than that required for routine diagnostic right heart catheterization procedures is required. The reliability and sensitivity of the method were studied in dogs with experimentally created atrial septal defects. It was found that maximal sensitivity was attained if the animals were hyperventilated at a rapid rate before, during, and after the transient change to ventilation with helium or nitrogen.

Methods

Six mongrel dogs (weight, 15 to 25 Kg.) with atrial septal defects created 2 to 3 years prior to these observations were studied under morphine-pentobarbital anesthesia. Number 6F French cardiovascular catheters with birdseye tips were inserted percutaneously into the jugular veins, and the tips of the catheters were positioned in (1) the main pulmonary artery, (2) the right ventricular outflow tract, (3) the inferior vena cava, and (4) the superior vena cava. The catheters were connected to P23D Statham strain gages for recording pressures. A cuvette oximeter was connected by means of a three-way stopcock to one of the venous catheter-strain gage assemblies. The connection of the cuvette oximeter to the venous catheters could be interchanged rapidly, so that withdrawal of blood for determination of oxygen saturation or for recording dye or inert gas curves could be carried out immediately and interchangeably from each of these four sites in the right heart.

A 60-cm. Nylon catheter (outside diameter, 0.9 mm.; inside diameter, 0.5 mm.) was advanced to the thoracic aorta after percutaneous puncture of the left femoral artery and was connected to a P23G Statham strain gage for recording aortic pressure. A second Nylon catheter 15 cm. in

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length (O.D. 1.2 mm.; I.D. 1.0 mm.) was introduced into the right femoral artery and connected to a Statham P23G strain gage-cuvette oximeter assembly for recording indicator-dilution curves or blood oxygen saturation. Blood was withdrawn through the cuvettes at a constant rate of 10 ml. per minute by means of Harvard withdrawal-infusion syringes. Recording was carried out as described previously.15

A cuffed endotracheal tube was inserted and attached to an intermittent positive pressure respirator a and the respiratory rate was set at 35 to 40 breaths per minute. A Y-tube assembly was connected to the input of the respirator so that the gas mixture being delivered to the dog could be interchanged immediately. The pressure in the endotracheal airway was recorded continuously by means of a strain-gage manometer. The maximal inspiratory positive pressure was adjusted to 20 cm. of water. Five per cent carbon dioxide was added to all gas mixtures to compensate for the loss of carbon dioxide that would occur with hyperventilation.

The oximeter cuvettes were calibrated for each dog by recording their deflections when withdrawing blood samples through them. The samples were analyzed subsequently for oxygen content by the method of Van Slyke and Neil16 and for oxygen capacity by the method of Sendroy17 as modified by Roughton and associates.18 These blood samples were obtained from the femoral artery and from the two sites in the right heart with the highest and lowest blood oxygen saturations. This procedure allowed three-point calibrations of both cuvettes based on manometric determinations of the oxygen saturation of the blood of each animal undergoing study.

Samples of blood were then withdrawn in rapid succession through the venous cuvette from the pulmonary artery, inferior vena cava, superior vena cava, and the femoral artery for determination of a left-to-right shunt by the conventional blood oxygen saturation step-up method. Dye curves were carried out by injecting 1.25 mg. of indocyanine green dye19 into the main pulmonary artery, while withdrawing blood continuously through cuvette oximeters from the right ventricular outflow tract and the femoral artery. The circuitry used in conjunction with the cuvette oximeters was arranged so that the devices could be used immediately and interchangeably as oximeters or as densitometers for indocyanine green.19,20 The simultaneous single and double scale method of operation was used.20 These dilution curves were repeated at intervals throughout the procedure.

Inert gas curves were made while the animals breathed each one of three different control gases: (1) 95 per cent air and 5 per cent carbon dioxide, (2) 12 per cent oxygen, 5 per cent carbon dioxide and 83 per cent helium, and (3) 8 per cent oxygen, 5 per cent carbon dioxide, and 87 per cent helium. Continuous recordings of the oxygen saturation of blood being withdrawn simultaneously from the femoral artery and from a selected site in the right heart were obtained. Sampling was begun while the animals were breathing the control gas. Approximately 30 seconds after sampling was started the control gas was suddenly switched to the inert gas (helium or nitrogen); sampling was continued during three to six breaths of inert gas and for 30 or more seconds after switching back to the control gas mixture.

Left-to-right shunts were calculated from the venous dilution curves by the forward triangle method as described by Wood and co-workers.21 The same method was applied to calculate the left-to-right shunts from inert gas curves; in such cases the change in oxygen saturation from the base line to the peak change in the venous and arterial curves was used instead of the concentration of indocyanine green dye.

Results

The magnitude of the left-to-right shunt as determined by venous dye-dilution methods varied from 8 to 65 per cent in the six dogs with surgically created atrial septal defects. In two of these animals, no left-to-right shunt could be detected by the usual oxygen saturation step-up methods in spite of the fact that samples of blood for determination of oxygen saturation were obtained in rapid succession from the various right heart chambers. In all dogs, however, it was possible to detect a left-to-right shunt by the inert gas method as well as by the dye-dilution technic.

Figure 1 shows a comparison of the venous indicator-dilution and oximetric inert gas curves in three dogs. The early appearance of indicator recorded in the right ventricular outflow tract after injection of dye into the main pulmonary artery and the early drop in oxygen saturation at the site of pulmonary artery sampling after breathing the inert gas indicate the presence of a left-to-right shunt.
Figure 1
Comparative demonstration of left-to-right shunts by right heart and arterial dye and inert gas curves in three dogs (designated as A, B, and C) with surgically created atrial septal defects. The duration of the period of helium breathing is shown by the two arrows connected by a bar for each pair of inert gas curves. Note that the estimated magnitudes of the left-to-right shunts based on the pulmonary and femoral arteries' inert gas curves (middle panels) were closely similar to those obtained by the dye-curve technic (left panels). These left-to-right shunts were not demonstrable when sampling from the superior vena cava (right panels) indicating that they were occurring downstream to this site, that is, into the right atrium. The dye and inert gas curves shown in this and other figures are photographs of photostats of the original curves which were cut from the original photokymographic recordings, realigned to correct for the dead space of the catheter-oximeter sampling systems, and then rephotographed.

This early drop in oxygen saturation is not present when sampling from the superior vena cava (right panels), as would be expected in the presence of an atrial septal defect. There is a close similarity between the venous dye-dilution and inert gas curves. The arterial inert gas curves, however, do not have some of the characteristics of the arterial dilution curves. The buildup and disappearance slopes of the inert gas curves are not so sharply defined as in the dilution curves because of the more gradual change in oxygen saturation resulting from breathing the inert gas as compared to the rapid injection of a "bolus" of indicator dye. In addition there is no recirculation peak in the inert gas curves since, on return of the desaturated blood to the lungs, oxygen is again available to bring the saturation of blood to near control values.

The results of a comparison of the left-to-right shunt by dye-dilution and oxygen saturation step-up methods and by dye-dilution and inert gas methods in all dogs are shown in figure 2. In two dogs no left-to-right shunt could be detected by the oxygen saturation step-up method; however, in all dogs a left-to-right shunt could be detected by the inert gas as well as the dye-curve techniques. The correlation of values for the left-to-right shunt by inert gas and dye-curve methods is similar.
to that for oxygen saturation step-up and the dye-curve technique.

Improved sensitivity of the inert gas method was obtained by breathing gas mixtures of decreased oxygen content prior to breathing the inert gas; mixtures of 8 to 12 per cent oxygen in nitrogen were used (fig. 3). When the dog breathed room air, prior to breathing four breaths of helium, the decrease in pulmonary artery oxygen saturation resulting from the shunt was small; after three breaths of helium this drop in pulmonary artery oxygen saturation was difficult to distinguish from artifact. However, the decrease in pulmonary artery oxygen saturation was greater and less likely to be confused with artifact when 12 or 8 per cent oxygen was breathed even with only three breaths of helium. There was also a clearer separation of the drop in saturation resulting from shunted and normally recirculating systemic venous blood when three breaths of inert gas were given as compared to four breaths. When hyperventilating with 12 per cent oxygen, there was relatively little change in the femoral arterial oxygen saturation in relation to values obtained when breathing air normally. When hyperventilating with 8 per cent oxygen the femoral arterial oxygen saturation was reduced to less than 90 per cent (fig. 3).

Helium and nitrogen were compared as inert gases to determine if differences in density and the associated changes in resistance to gas flow and diffusion in the gas phase of the lung were of importance in the attempt to produce a more rapid decrease in alveolar oxygen tension. The example of paired comparisons between breathing helium and breathing nitrogen in two dogs shown in figure 4 indicates that there were no apparent differences in the contour of the curves recorded after breathing helium and nitrogen. Eight

Figure 2
Comparison of values for left-to-right shunts by oxygen saturation step-up and dye-curve methods (left panel) and by oximetric inert gas and dye curve methods (right panel) in six dogs with surgically created atrial septal defects. The solid line is the line of identity and dashed lines represent values 10 per cent above and below the line of identity. Note that no left-to-right shunt was detected by the oxygen saturation step-up method in two of the six dogs (left panel) but that left-to-right shunts were detected in all dogs by the inert gas method (right panel). The correlation between the estimated values for left-to-right shunt by the inert gas and the dye-curve methods was similar to that between the values estimated by the oxygen saturation step-up and the dye-curve methods.
A comparative demonstration of a left-to-right shunt by oximetric inert gas method when breathing base gases containing 20, 12, and 8 per cent oxygen in conjunction with use of either three or four breaths of helium. The curves were recorded from a dog with an atrial septal defect created surgically 12 months prior to this study. See figure 1 for description of inert gas curves. Note that when a base gas with 20 per cent oxygen (top panels) was breathed prior to either three or four breaths of helium, the decreases in oxygen saturation of pulmonary artery blood (indicated by arrows) were smaller than when either 12 or 8 per cent oxygen was used as the base gas. Also, there was a more distinct separation of the decreases in oxygen saturation of pulmonary artery blood produced by the left-to-right shunt and by normally recirculating systemic venous blood when three breaths as compared to four breaths of helium were used.

Paired comparisons were made between breathing helium and nitrogen in the six dogs studied. In order to see if there was any significant difference in the important parameters in the curves while breathing nitrogen and while breathing helium, comparisons were made of the buildup times and the change in oxygen saturation of the femoral arterial curves. When breathing helium as the inert gas, the average time for the oxygen saturation curve recorded at the femoral artery to decrease to its minimal value was 6.1 seconds as compared to 6.3 seconds while breathing nitrogen. The individual differences ranged from -0.9 to +1.6 seconds. The average decrease in femoral artery oxygen saturation was 17 per cent when breathing helium and 15.5 per cent when breathing nitrogen with differences in saturation ranging from -3.2 to +4.5 per cent. These average differences were not statistically significant.

This technic is now used routinely to exclude or to detect and localize the site of small left-to-right shunts in patients referred for cardiac catheterization. In all instances left-to-right shunts comparable to those obtained by venous dye-dilution curves have been obtained. The optimal procedure has been to have the patients hyperventilate with 10 or 12 per cent oxygen with 5 per cent carbon dioxide.
oxide for 30 seconds prior to the two or three breaths of inert gas. An example of the results obtained is shown in figure 5. There was no definitive evidence for a left-to-right shunt by the oxygen saturation step-up method in this 39-year-old woman. The venous dye-dilution curve, however, did show the presence of a small left-to-right shunt. Its estimated magnitude was 14 per cent of the pulmonary flow. Inert gas curves also clearly showed the presence of a left-to-right shunt estimated to be 17 per cent when sampling from the pulmonary artery. The shunt was not demonstrable when sampling from the right atrium, thus indicating that it was occurring downstream to the tricuspid valve.

**Discussion**

An early difficulty encountered in detecting and quantitating left-to-right shunts by the inert gas method stemmed from the respiratory variations of blood oxygen saturation normally present in the right heart. In control recordings of the variations in oxygen saturation in the right heart made when breathing quietly at a normal rate and when deep breaths were taken, the changes in the oxygen saturation at the venous sites caused by the change in respiration were difficult to distinguish from the change in oxygen saturation caused by breathing the inert gas. It was found possible to eliminate this problem by hyperventilation. When the respiratory rate is constant at 35 to 40 breaths per minute, the changes in blood oxygen saturation due to respiration were decreased, and because of the slow dynamic response of the cuvette oximeter-catheter system, these smaller variations in oxygen saturation are "smoothed out." This technic provides a
stable base line of venous blood oxygen saturation so that the changes due to left-to-right shunting of reduced hemoglobin can be detected with maximal sensitivity.

The sensitivity of this method was further improved by breathing gas mixtures of decreased oxygen content prior to breathing the inert gas. Due to the flatness of the oxygen dissociation curve of hemoglobin at oxygen tensions above 100 mm. of mercury, if room air with 20 per cent oxygen is breathed, a relatively large decrease in the oxygen tension in the alveoli is required to produce a large decrease in the oxygen saturation of pulmonary venous blood. However, because of the steepness of this curve at lower oxygen tensions, if the gas mixture being breathed contains a smaller percentage of oxygen, the same change in oxygen tension produces a greater change in the oxygen saturation of blood, and fewer breaths of the inert gas are required to produce the temporary marked increase in reduced hemoglobin content of pulmonary venous blood required for maximal sensitivity in detection of the left-to-right shunt as is shown in figure 3.

It was found that as few breaths of the inert gas as possible should be taken in order to obtain a more distinct separation between the decrease in venous oxygen saturation caused by the left-to-right shunt and the decrease due to the normally recirculating systemic venous blood. For example, at a respiratory rate of 30 breaths per minute, six breaths of the inert gas would occupy a period of 12 seconds. During the latter portion of this 12-second period, reduced hemoglobin would be entering the right side of the heart via the septal defect simultaneously with the step-up in reduced hemoglobin in the blood returning from the systemic veins. If three breaths of inert gas were given, they would occupy a period of only 6 seconds, so that the reduced hemoglobin from pulmonary venous blood entering the right heart via the shunt would be more nearly completed before the step-up in reduced hemoglobin from the systemic veins returned to the right heart. Even fewer breaths of the inert gas would be

Figure 5

Comparative demonstration of a left-to-right shunt by dye and inert gas curves in a 39-year-old woman with a ventricular septal defect. When indocyanine green was injected into the distal pulmonary artery with sampling from the main pulmonary artery and radial artery (top panel), early appearing dyed blood was detected at the pulmonary artery sampling site. This represents a left-to-right shunt estimated on the basis of these curves to be 14 per cent of the pulmonary flow. Inert gas curves carried out sampling from the pulmonary and radial arteries (middle panel) showed an early decrease in the oxygen saturation of pulmonary artery blood caused by the left-to-right shunt. The magnitude of the shunt was estimated from these curves to be 17 per cent of pulmonary flow. This shunt was not demonstrable when sampling from the right atrium, indicating that it was occurring downstream to this site, that is, into the right ventricle. Demonstration of the shunt by the oxygen saturation step-up method was equivocal. Hyperventilation of a gas mixture of 10 per cent oxygen and 5 per cent carbon dioxide in nitrogen was carried out 30 seconds prior to, and for 25 seconds after, the two breaths of the inert gas which consisted of helium containing 5 per cent carbon dioxide.

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desirable if the resulting decrease in oxygen saturation of right heart blood were great enough to be detected with certainty. It has been found that patients who breathe both deeply and rapidly in response to instructions obtain a satisfactory decrease in blood oxygen saturation from only two breaths of the inert gas as shown in figure 5.

The example shown in figure 1 (top panel), in which the left-to-right shunt was less than 10 per cent, indicates that this technic is of value in detecting left-to-right shunts that are too small to be detected with certainty by the ordinary blood oxygen saturation step-up method. This relatively simple method has the advantage over most other inert gas techniques in that quantitative as well as qualitative information concerning the shunt can be readily obtained.

**Summary**

A method is described for detecting and quantitating small left-to-right shunts by recording continuously and simultaneously the changes in blood oxygen saturation at a systemic artery and at selected sites in the right heart chambers or great vessels produced by a few breaths of an inert gas such as helium or nitrogen.

The advantages of this technic for detecting and quantitating left-to-right shunts are (1) the same instrument, namely, the cuvette oximeter, used to determine blood oxygen saturation and indicator-dilution curves in conjunction with routine diagnostic catheterization procedures, also is used to record the inert gas curves, (2) only one right heart catheter is needed, (3) the method is relatively simple, (4) the shunt can be quantitated, and (5) shunts of less than 10 per cent of pulmonary flow can be detected.

It is concluded that the technic is of considerable practical value as a means of excluding the presence of or demonstrating and determining the magnitude of small left-to-right shunts.

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