Proceedings
of the
Society
for
Experimental Biology and Medicine

VOL. 97 JANUARY, 1958 NO. 1

SECTION MEETINGS

CLEVELAND, O.	
University Hospitals	October 21, 1957
	December 16, 1957
DISTRICT OF COLUMBIA	
George Washington University	December 5, 1957
ILLINOIS	
Billings Hospital, Chicago	November 12, 1957
IOWA	
State University of Iowa	October 29, 1957
OHIO VALLEY	
University of Louisville Medical School	November 15, 1957
PACIFIC COAST	
Stanford University	November 1, 1957
SOUTHEASTERN	
Medical College of Virginia	November 1, 1957
SOUTHERN CALIFORNIA	
University of California, Los Angeles	October 24, 1957
WESTERN NEW YORK	
Cornell University	November 16, 1957

Use of a Radioactive Gas (Kr^{85}) in Diagnosis of Cardiac Shunts.* (23629)

RICHARD J. SANDERS (Introduced by R. W. Berliner)
Clinic of Surgery, Nat. Heart Inst., Bethesda, Md.

Accurate localization of left-to-right intra- and extracardiac shunts is not always possible by the measurement of differences in oxygen content of the blood among the right heart chambers. The nitrous-oxide test(1), which depends upon the large arterio-venous difference which normally occurs during the inhalation of an inert gas, has been demonstrated to be more sensitive than the oxygen method. However, analysis of blood samples for nitrous-oxide content requires at least 20 minutes, and precludes the use of the results of the test in the course of the catheterization. The substitution of a radioactive inert gas offered the possibility of a sensitive test, the results of which would be available within a few minutes. The present communication describes the application of krypton^{85} in detection of experimental atrial septal defects.

Materials and method. Atrial septal defects were created in 10 dogs, weighing from 10 to 25 kg. The defects were produced under direct vision during a brief period of inflow occlusion. The interatrial septum was elevated with a traction suture and a portion of the septum, 0.5 to 2.0 cm in diameter, was excised. At intervals of 1 to 16 weeks after operation, cardiac catheterizations were per-

* The author wishes to thank Dr. Niels A. Lassen for his assistance in this study.

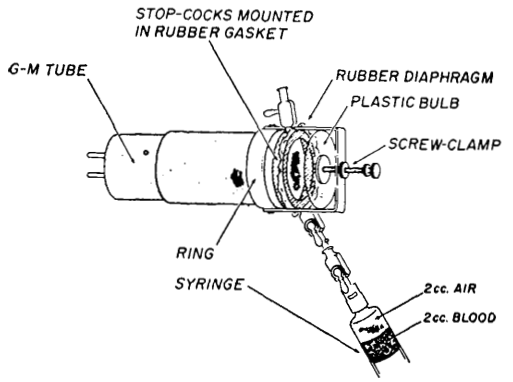

FIG. 1. An air-tight counting chamber over the end of a Geiger tube. A vacuum was first produced in the chamber with suction. The air containing the Kr^{85} was then inj. into the evacuated chamber through the bottom stop-cock. The chamber was easily cleaned by opening both stop-cocks and applying suction for a few seconds.

formed. Under sodium pentothal anesthesia, the trachea was intubated, a cannula placed in a femoral or carotid artery, and a No. 6 or 7 cardiac catheter passed from the femoral or jugular vein into the pulmonary artery. A blood sample for blank determination was drawn from the cardiac catheter immediately before each test. A mixture containing Kr^{85} was prepared by injecting 0.5 to 1.0 mc of the radioactive gas into a breathing bag of 5 liters capacity.† The gas was then diluted to a concentration of 0.1 to 0.25 mc per liter by the addition of oxygen. The mixture was administered to the dog through a closed system consisting of the breathing bag and a carbon dioxide absorption canister. The gas was inhaled for one minute. Blood samples, 2 cc each, were drawn simultaneously from the systemic and pulmonary arteries after 5, 10, 30 and 50 seconds of inhalation. Three more blood samples were drawn at 1, 3 and 5 minutes after the inhalation was discontinued. Repeat tests were done with the same breathing bag by replenishing it with oxygen but without adding more Kr^{85}. The concentration of the gas was thus reduced in each successive test. The test was sometimes performed with the catheter tip in the right ventricle or right atrium, and always repeated in the inferior or superior vena cava. In some instances, 2 cardiac catheters, or double lumen catheters were used to sample 2 areas simultaneously. Five of the dogs were catheterized on 2 separate occasions. The 2 cc blood samples were each drawn into 10 cc oiled, heparinized, Luer-lock syringes. Because Kr^{85} is a beta-ray emitter, much higher counts were obtained by first extracting the Kr^{85} from the blood: Two cc of air were drawn into the syringe which was then closed with a one-way stop-cock. An additional partial vacuum was produced by pulling the plunger of the syringe back another 2 cc. The syringe was then agitated by hand for one minute to accelerate the release of the gas into the air. The 2 cc of air were transferred to an air-tight chamber, previously evacuated by suction, and fixed over the window of a Geiger-Mueller tube (Fig. 1). The samples were counted for one minute and were then washed out of the chamber by opening both stop-cocks and applying suction to one of them. The chamber was usually clear within five seconds.

Results. The Kr^{85} content of systemic arterial blood rose rapidly between the fifth and twentieth second of inhalation and approached its saturation level within 60 seconds (Fig. 2). The appearance of Kr^{85} in vena caval blood was delayed by the circulation time and its concentration then rose much more slowly due to tissue absorption.

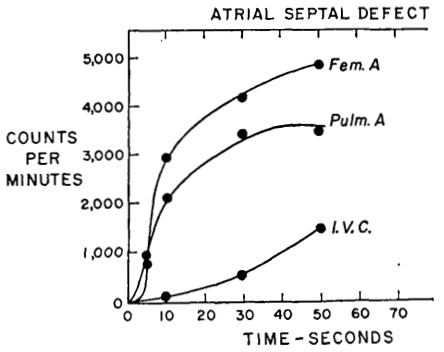

FIG. 2. The saturation curves of arterial, vena caval, and pulmonary arterial blood during one min. of Kr^{85} inhalation in a dog with an interatrial septal defect. The pulmonary arterial curve is the resultant of mixing left atrial and venous blood in the right atrium. Background counts were about 30/min.

† The Kr^{85} was supplied by the AEC and had previously been diluted with atmospheric air to concentration of 1 mc/cc.

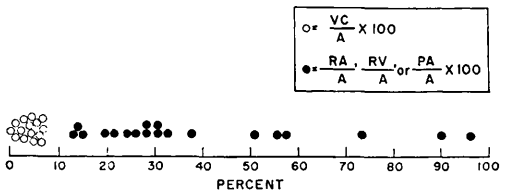

FIG. 3. The 10 sec. vena caval, right heart, and pulmonary artery krypton^{85} concentrations expressed in % of the corresponding arterial concentrations. The vena caval samples were all proximal to the shunts while the right atrial, right ventricular, and pulmonary arterial samples were all distal to the shunts. A ratio of 10% divides the positive from the negative tests.

The Kr^{85} content of pulmonary arterial blood was intermediate between systemic arterial and vena caval samples and reflected the presence of the left-to-right shunt. However, the 5 second pulmonary arterial samples often contained more radioactivity than the systemic arterial samples. This was probably attributable to the more rapid circulation between left atrium and pulmonary artery than between left atrium and a systemic artery. Desaturation was 90 to 95% complete in 5 minutes.

The arterial samples, after 10 seconds of inhalation, contained from 300 to 3800 counts per minute after the blank values of 30 to 100 counts per minute had been subtracted. The levels depended upon the gas concentration and depth of respiration. However, the arterial level was used only in relation to the right heart or vena caval level, and its absolute value was unimportant. The contents of the right heart and vena caval samples were thus expressed in relation to the simultaneous arterial content (Fig. 3). In all 15 studies, the vena caval samples, proximal to the shunts, were less than 8% of the arterial samples. The right atrial, right ventricular, and pulmonary arterial samples, distal to the shunts, all exceeded 12%. The 3 dogs with concentrations between 10 and 20% of the arterial levels each had repeat tests with concentrations of 20 to 30%. All of the experimental animals were sacrificed and in each the presence of a patent atrial septal defect was confirmed.

Discussion. The superiority of an inert gas in the detection of left-to-right shunts has been demonstrated in studies comparing the nitrous-oxide test and the method of oxygen differences(1). The inert gas concentrations are independent of the patient's metabolic state and samples proximal to the site of the shunt are unnecessary. A radioactive gas would appear to be superior to nitrous-oxide in several respects. The analysis is much simpler and the results are available within a few minutes. Levels 10 to 100 times the blank value are easily achieved and the analytic error is thereby minimized. Thus, it is likely that diagnostic ratios may be established at far lower levels than with nitrous-oxide.

Kr^{85} was selected in the present study because it was readily available and its applicability had been demonstrated in clinical studies of cerebral blood flow(2). The gas is stable and is rapidly excreted through the lungs. Since it is essentially a weak beta-ray emitter(3), it is relatively safe for laboratory personnel. Kr^{85} is certainly not the only radioactive gas that can be used for the detection of left-to-right shunts. I^{131}, as trifluoroiodomethane, is being investigated in this laboratory and appears to give results similar to those obtained with Kr^{85}. A disadvantage of I^{131} is its half-life of 8 days, and any gas containing it must be obtained at frequent intervals. On the other hand, a single supply of Kr^{85}, with a half-life of about 10 years, can be used virtually indefinitely.

With the low concentrations of Kr^{85} employed in these studies, high counts in one minute were best obtained by extracting the gas from the blood. An advantage of I^{131}, a gamma emitter with a more penetrating radiation, is that it can be counted in blood without extraction. However, for the same reason, it is somewhat more hazardous to personnel. Continuing investigations will determine which isotope and compound is most suitable.

Summary. A method is described for the use of tracer doses of krypton^{85} in the localization of left-to-right cardiac shunts. Fifteen studies were performed in 10 dogs with atrial septal defects. As the gas was inhaled, blood samples were drawn simultaneously from a vena cava, a right heart chamber, and a sys-

temic artery. The samples were analyzed for their radioactivity. The diagnosis of a shunt could be made when the ratio of radioactivity in right heart or pulmonary artery samples to that in systemic artery samples exceeded 10%. The apparent advantages of the method and the possible usefulness of other radioactive gases are discussed.

1. Morrow, A. G., Sanders, R. J., Braunwald, E., *Circulation,*

2. Lassen, N. A., Munck, O., *Acta Phys. Scand.,* 1955, v33, 30.

3. Radiological Health Handbook, U. S. Dept. Health, Education and Welfare, Sanitary Engineering Center, Cincinnati, O., 1954.

Received September 16, 1957. P.S.E.B.M., 1958, v97.

Detection of Circulatory Shunts by Use of a Radioactive Gas.* (23630)

R. B. CASE, H. W. HURLEY, R. P. KEATING, P. KEATING, H. L. SACHS, AND E. E. LOEFFLER (Introduced by R. W. Berliner)

Department of Medicine, St. Luke's Hospital, N. Y. City

The most widely used technic for detection of left-to-right circulatory shunts requires the demonstration of a sudden increase in oxygen content at or past the site of the shunt. The widely varying flow rates and oxygen contents of blood entering the right atrium from the superior vena cava, inferior vena cava, azygous vein, and coronary sinus sometimes make it difficult to estimate the mixed venous oxygen content before the site of the shunt is reached. The oxygen contents of the cavae, which constitute the major part of the venous return, may differ by as much as 4 vol. %, and usually have a difference of one to 1½ vol. % (1). The comparative flow rates in the cavae, usually taken as a 2:1 ratio, are merely an estimate in any patient. Attempts to circumvent these problems have been made by the introduction of a foreign substance into the circulation. Swan and Wood(2) injected dye into the right side of the circulation and recorded dye dilution curves with an earpiece oximeter. Use of a foreign gas, nitrous oxide, was suggested by Callaway† and has been utilized in a large series of patients by Morrow, Sanders and Braunwald (1). They were able to detect 41 out of 43 shunts by taking an integrated one minute sample simultaneously from an intracardiac catheter and a peripheral artery during the inhalation of 15-25% nitrous oxide. However, the shunt was missed in 11 of these 43 patients by use of the oxygen "step-up" method. The superiority of the nitrous oxide method is evident, but there are disadvantages. Analyses of nitrous oxide samples are difficult and time consuming. A high blank value is always present, and it may sometimes be difficult to achieve a significant arterial level. The use of an innocuous foreign gas which is easily absorbed and analyzed would simplify the situation. Dr. Louis Dotti of this hospital suggested a radioactive gas. This paper describes our experiences with ethyl iodide, containing radioactive I^{131}. This gas (without the I^{131}) was used extensively 32 years ago in human cardiac output determination(3) and was proved to be without ill effects. Analysis of blood containing radioactive ethyl iodide is achieved simply by placing a one half or one cc sample in a well counter for one or 2 minutes. The I^{131} half life of 8 days provides a safety factor and facilitates easy handling.

Method. Dogs weighing from 10 to 20 kg were anesthetized with pentobarbital, and a Cournand catheter was inserted (under fluoroscopic guidance) into the pulmonary artery via the jugular vein. This position was confirmed by pressure traces before and after each ethyl iodide administration and by withdrawal pressure tracings. Catheters were also

* This work was subsidized by N. Y. Heart Assn. and Natl. Heart Inst., N.I.H.

† Unpublished data.