THE KRYPTON⁸⁵ INHALATION TEST FOR THE DETECTION OF LEFT-TO-RIGHT SHUNTS

BY

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One of the primary reasons for performing cardiac catheterization in patients known to have, or suspected of having, congenital heart disease is to determine whether a left-to-right shunt is present and the site at which it enters the right side of the heart. Although a variety of techniques for the detection of such shunts has been developed (Wood *et al.*, 1957, 1958; Zimmerman, 1959; Braunwald and Morrow, 1960) relatively little specific information regarding their reliability has been published. The inhalation of an inert foreign gas and the determination of its concentration in blood sampled from the right side of the heart and the systemic arterial bed forms the basis of a sensitive test for the determination of left-to-right circulatory shunts (Morrow *et al.*, 1958; Sanders *et al.*, 1959; Braunwald *et al.*, 1960). Radioactive krypton (Kr⁸⁵) has been found to provide substantial advantages over other gases and it has therefore been employed routinely in this laboratory for the past several years (Sanders and Morrow, 1959; Braunwald *et al.*, 1960).

It is the purpose of this communication to analyse the results obtained from the application of the Kr⁸⁵ inhalation test in 323 patients, in all of whom the specific cardiac diagnosis was subsequently established. In this analysis particular emphasis was placed upon: (1) an evaluation of the reliability of the Kr⁸⁵ inhalation test in the detection of left-to-right shunts, (2) the establishment of specific criteria for the interpretation of the results of the test, (3) an evaluation of the ability of the test to localize the site of entry of a left-to-right shunt, and (4) the usefulness of the test in detecting multiple left-to-right shunts.

CLINICAL MATERIAL

All of the Kr⁸⁵ inhalation tests performed at the National Heart Institute between December 1958 and December 1960 form the basis of the present report. A total of 809 tests were performed in 410 patients during right heart catheterization. In 87 of these patients the diagnosis has not been firmly established and the results of studies in them have been excluded. This group includes tests performed in patients with congenital heart disease who have not been operated upon, as well as those studies which were carried out post-operatively; the latter were eliminated from the analysis because the presence of a residual or recurrent shunt could not be established with certainty by an independent method.

The diagnosis in the remaining 323 patients was established with certainty; 161 had left-to-right cardiac shunts and in each instance the anatomic defect responsible for the shunt was identified at the time of corrective operation (Table I). The other 162 patients did not have left-to-right shunts. The majority of them (116) had clinical evidence of rheumatic valvular heart disease; this diagnosis

was confirmed in every instance by left heart catheterization, and in 73 at operation also. The remaining patients without shunts were 12 with isolated congenital pulmonary valvular stenosis, in all of whom the diagnosis was confirmed at operation, and 35 who had no evidence of heart disease. The age range and average age of all patients are presented in Table I.

TABLE I
DIAGNOSIS AND AGE RANGE OF 323 PATIENTS INVESTIGATED BY THE Kr^{85} INHALATION TEST

Diagnosis	Number of patients	Age range years	Average age years
Atrial septal defect	83	4 -54	25
Ventricular septal defect	34	1·3-49	15
Ventricular septal defect with pulmonary stenosis	17	4·5-49	13
Atrio-ventricular canal	7	5 -44	26
Patent ductus arteriosus	17	2 -59	19
Aorto-pulmonary window	2	7 -11	9
Ruptured sinus of valsalva aneurysm into right atrium	1	28	28
Rheumatic mitral stenosis and/or regurgitation	65	7 -58	35
Congenital and acquired aortic stenosis	50	5 -57	30
Isolated congenital pulmonary stenosis	12	5 -37	18
No heart disease	35	2·5-48	2
Total	323	1·3-59	20

METHOD

All of the Kr^{85} inhalation tests were carried out in a similar manner. The tip of the cardiac catheter was generally positioned first in one of the main branches of the pulmonary artery. If the test at this position indicated a shunt it was repeated first with the catheter tip in the outflow tract of the right ventricle and then in the right atrium immediately proximal to the tricuspid valve.

The Kr^{85} was supplied, in a concentration of 0·4 microcuries/l. of air, in tanks containing 200 litres.* The tanks, when not in use, were stored in a chemical hood to minimize the hazard of a leak. The tank was connected, through a demand valve,† to a mouthpiece. After the cardiac catheter had been properly positioned, a sample of blood was withdrawn either from it or a systemic artery and its radioactivity determined to provide a background or blank count. The mouthpiece was then inserted and the tubing between the tank and the mouthpiece was thoroughly flushed with the gas mixture. The patient then inhaled the Kr^{85} and air mixture for 30 seconds, either ventilating normally or hyperventilating slightly; hyperventilation was sometimes necessary to trip the demand valve. The expired gas was either collected in a Douglas bag which was subsequently emptied out-of-doors or it was led into the ventilation exhaust. Between the fifth and tenth seconds of inhalation a small volume of blood (1 to 2 ml.) was withdrawn through the catheter and discarded. Between the tenth and thirtieth seconds of inhalation, 5-ml. blood samples were withdrawn simultaneously and at a constant rate from the cardiac catheter and from an indwelling needle in a systemic artery. The radioactivity in these samples was then immediately determined in a continuous flow Geiger-

* Supplied by the Matheson Co., East Rutherford, N. J.

† Manufactured by Southern Oxygen Co., Bladensburg, Md.

Muller tube* attached to a decade scaler.† After subtraction of the activity in the blank, the ratio of radioactivity in the samples from the right heart and systemic artery was expressed as a percentage.

FIG. 1.—Results of the Kr⁸⁵ test in 323 patients. The solid circles represent tests in patients proved to have left-to-right shunts and open circles represent tests in patients without shunts. The horizontal lines represent the mean values for each group.

FIG. 2.—Results of Kr⁸⁵ tests performed in the right atrium in patients with atrial septal defects (A.S.D., closed circles), ventricular septal defects and patent ductus arteriosus (V.S.D. and P.D.A., open circles).

RESULTS

The results of Kr⁸⁵ inhalation tests in all 323 patients are plotted in Fig. 1. In many of the patients tests were performed at various sites in the right side of the heart. The one obtained with the most distal sampling site was used in this analysis. Two hundred and forty of these tests were carried out with pulmonary artery sampling and the remaining 83 in the right ventricle. In the 161 patients subsequently proved to have left-to-right shunts the results ranged from 13 per cent to 113

* Model M-4, Nucleonic Corp., New York, N. Y.

† Model 181A, Nuclear Instrument Corp., Chicago, Ill.

per cent. In contrast, in the 162 patients without shunts the results of the tests ranged from 0 per cent to 12 per cent; the average value was 3.6 per cent and one standard deviation was 4.6 per cent. There was no overlap in the results in the two groups of patients.

FIG. 3.—Results of Kr^{85} tests performed in the right ventricle in patients with left-to-right shunts entering into or proximal to the right ventricle (closed circles) and into the pulmonary artery (P.D.A.—patent ductus arteriosus, A.P.—aortopulmonary, open circles). The open circles and crosses represent the results of studies in the patients with patent ductus arteriosus and pulmonary regurgitation.

108 per cent. A total of 17 Kr^{85} tests were performed in the right ventricles of patients with left-to-right shunts entering the pulmonary artery. In this group the results ranged from 4.4 per cent to 19.5 per cent and averaged 10 per cent (Fig. 3). The four highest Kr^{85} values in this group were recorded in patients with patent ductus arteriosus and pulmonary hypertension. All had early diastolic murmurs along the left sternal border, their pulmonary artery systolic pressures averaged 62 mm. Hg and they were therefore considered to have pulmonary regurgitation. In these four cases the Kr^{85} tests in the right ventricle ranged from 15.0 to 19.5 per cent and the average value was 16.9 per cent. Blood that had been shunted from the aorta to the pulmonary artery and

In an attempt to determine the accuracy of the Kr^{85} test in localizing the sites of entry of left-to-right shunts, the results of the tests performed in each location in the right side of the heart were analysed. A total of 368 tests was performed in the 161 patients proved to have left-to-right shunts. One hundred and thirty-five of the tests were carried out in the right atrium, 105 in the right ventricle, and 128 in the pulmonary artery. Among the 135 patients who had tests in the right atrium, there were 83 with atrial septal defects. In them the results ranged from 17 per cent to 100 per cent. In the other 52 patients, the left-to-right shunts entered distal to the tricuspid valve and the results of right atrial tests ranged from 2.3 per cent to 21.7 per cent averaging $9.9 \text{ per cent} \pm 4.4 \text{ per cent}$ (Fig. 2). The six patients in this latter group who had the highest results all had ventricular septal defects and, in each, tricuspid regurgitation was palpable at operation. In them the Kr^{85} tests in the right atrium ranged from 15 to 21 per cent and averaged 19.6 per cent. The high values for the Kr^{85} tests in the right atria of these patients can, of course, be accounted for by blood which had been shunted from the left to the right ventricle and then regurgitated into the right atrium. In the other 46 cases with left-to-right shunts blood from the left side of the heart was not shunted into the right atrium and the results of the Kr^{85} tests in the right atrium did not exceed 14 per cent.

Of the 105 patients with left-to-right shunts in whom Kr^{85} tests were performed in the right ventricle, 88 had shunts entering either into this chamber or into the right atrium. In these patients (33 with atrial septal defects, 43 with ventricular septal defects, and 12 with a combination of these two lesions) the Kr^{85} tests in the right ventricle ranged from 12 per cent to

FIG. 4.—Results of the Kr⁸⁵ tests in patients with atrial septal defects (A.S.D.) performed in the right atrium (R.A.) right ventricle (R.V.) and pulmonary artery (PA). The lines join observations on the same patient.

then regurgitated into the right ventricle accounted for the elevation of the Kr⁸⁵ test in the right ventricle in these patients. In the 13 patients in whom aortic blood was not shunted into the right ventricle, the Kr⁸⁵ tests in the right ventricle did not exceed 14 per cent.

In order to determine the value of the Kr⁸⁵ test in the diagnosis of two discrete left-to-right shunts, the variations in the results of the tests performed in more than one chamber in the same patient were analysed. Twenty-four patients with uncomplicated atrial septal defects had Kr⁸⁵ tests performed in the right atrium, right ventricle, and pulmonary artery. The differences in the results between the tests performed in the right atrium and right ventricle (RA Kr⁸⁵–RV Kr⁸⁵) ranged from +41 per cent to –34 per cent (Fig. 4). Regardless of sign, the differences averaged 11.9 per cent and one standard deviation of the differences equalled 11.4 per cent. The differences between the Kr⁸⁵ tests performed in the right ventricle and pulmonary artery of patients with atrial septal defects were considerably smaller; these differences (RV Kr⁸⁵–PA Kr⁸⁵) ranged from +25 to –9 per cent. The average difference, regardless of sign, was 6.4 per cent, while one standard deviation of the differences equalled 5.2 per cent. Thirty-four patients with ventricular septal defects had Kr⁸⁵ tests performed both in the right ventricle and in the pulmonary artery. The differences between the two tests in any patient ranged from +31 to –15 per cent. The average difference, regardless of sign, was 6.6 per cent; while one standard deviation of the differences equalled 5.4 per cent (Fig. 5).

FIG. 5.—Results of the Kr^{85} tests in patients with ventricular septal defects (V.S.D.) performed in the right ventricle (R.V.) and pulmonary artery (PA). The lines join observations on the same patient.

COMMENT

The detection, localization, and measurement of circulatory shunts are of fundamental importance in the evaluation of patients with congenital cardiac malformations. Before surgical treatment became feasible, detailed diagnosis was of lesser importance than it is now; perhaps in the future open corrective operations will be possible at a very low risk in the large majority of patients with congenital heart disease and when surgical methods reach this point precise pre-operative assessment may not be as imperative as it is today.

The principle of the use of Kr^{85} , an inert foreign gas, in the determination of left-to-right shunts, has previously been discussed in detail (Sanders and Morrow, 1959; Braunwald *et al.*, 1960). During the first 30 seconds of its inhalation, the concentration of Kr^{85} in the blood in the pulmonary veins, the left side of the heart and in the systemic arterial bed rises rapidly. Since Kr^{85} diffuses freely from the intravascular compartment and is soluble in the interstitial fluid and in the cellular compartment, its passage into the systemic veins is greatly delayed. In the absence of a left-to-right shunt the concentration of Kr^{85} in blood in the right side of the heart and in the pulmonary artery constitutes a small and relatively constant percentage of the arterial concentration. In the presence of a left-to-right shunt, blood from the left side of the heart, rich in Kr^{85} , is shunted into the right side of the heart, elevating the Kr^{85} content of its blood and the ratio of the concentration of Kr^{85}

in right heart to systemic arterial blood. The value and accuracy of the foreign gas tests in the measurement of left-to-right shunts has been described previously (Sanders *et al.*, 1959) as has the use of injections of Kr⁸⁵ in saline solution for determining right-to-left cardiac shunts (Long *et al.*, 1960a), localizing the site of left-to-right shunts (Braunwald *et al.*, 1960; Long *et al.*, 1960a) defining the presence of port-system venous collaterals (Long *et al.*, 1960b), and in the measurement of cardiac output (Cornell *et al.*, 1961).

The present data obtained in 323 patients clearly show that the Kr⁸⁵ test successfully separated those patients proved to have left-to-right shunts from those without shunts; the results of the test were less than 13 per cent in all 162 patients without shunts and exceeded 13 per cent in all 161 patients with shunts. Although the shunts in the majority of these patients were sizeable, and large enough to warrant surgical correction, it is notable that among them were several patients in whom they were extremely small, e.g. patients with a very narrow patent ductus arteriosus. The results of the Kr⁸⁵ test are determined primarily by the magnitude of the left-to-right shunt, but are also influenced by other factors, such as the systemic circulation time and the size of the patient. It would therefore seem likely that an overlap in the results obtained from patients with small shunts and those without shunts could occasionally occur. In instances in which the results of the test are in the neighbourhood of the empirical dividing line (13%), repetition of the test at a point in the circulation proximal to the site of entry of any shunt, i.e. the vena cava, will help to resolve the problem.

It is noteworthy that the Kr⁸⁵ test, in addition to providing information regarding the presence or absence of a shunt is also capable of accurately predicting its site of entry into the right side of the heart. However, when multiple left-to-right shunts coexist the test is of less value in defining the distal shunt, unless the two shunts are separated by the right ventricle, as in patients with an atrial septal defect and a patent ductus arteriosus.

The Kr⁸⁵ inhalation test provides a number of advantages over the standard methods for the detection of left-to-right shunts. The test may be carried out in less than one minute and the results, expressed in terms of the pulmonary/systemic flow ratio, are immediately available to the physician. Radiation exposure is minimal, only small blood samples are required, the test may be repeated as necessary, and the technicians' time required for analysis is brief. Most important of all, the accuracy of the Kr⁸⁵ test in the detection of left-to-right shunts, as demonstrated in the present study, is far superior to the use of the standard "oxygen technique" (Morrow *et al.*, 1958; Sanders and Morrow, 1959). The Kr⁸⁵ inhalation test may be likened to the double catheter dye-dilution technique for the determination of left-to-right shunts, introduced by Wood and his associates (Wood *et al.*, 1958). In contrast to the latter technique, however, the Kr⁸⁵ test permits a more convenient introduction of the indicator into the central circulation via the respiratory tract.

SUMMARY

The results of inhaled Kr⁸⁵ tests, carried out in 323 patients in whom the diagnosis was firmly established, were analysed. Blood samples were drawn while the patients inhaled a Kr⁸⁵ and air mixture and the results of the test were expressed as the ratio of the radioactivity in blood obtained from the right side of the heart to that obtained from a systemic artery. In the 161 patients subsequently proved to have left-to-right shunts the results of the test ranged from 13 to 113 per cent. In the 162 patients without cardiac shunts the results ranged from 0 to 12.2 per cent. The Kr⁸⁵ test may thus be employed with confidence for determining the presence or absence of a left-to-right shunt. In addition, when the test is successively performed in the pulmonary artery, right ventricle, and right atrium the site of entry of the shunt into the right side of the heart may be correctly localized. The advantages of the technique in the assessment of patients with heart disease are discussed.

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