Intracardiac Injection of Radioactive Krypton

Clinical Applications of New Methods for Characterization of Circulatory Shunts

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In recent years the efforts of many groups have been directed to the development of more refined methods for the precise characterization of cardiac shunts. The application of inhaled foreign gases and the various extensions and improvements in the dye dilution method have already proved of considerable value in the study of patients with congenital heart disease. In the course of clinical studies in which the radioactive gas krypton (Kr\textsuperscript{85}) was inhaled\textsuperscript{2} it was found that the isotope was slowly soluble in saline solution. When such solutions were injected into a systemic vein, the right side of the heart, or pulmonary artery, the isotope could be immediately detected in expired air and little passed through the lung into arterial blood.\textsuperscript{2,3} When injections were made proximal to an experimental right-to-left shunt, a significant fraction bypassed the lung and high levels were found in systemic arterial blood.\textsuperscript{4} In other experiments injections of the dissolved gas were made into the chambers of the left heart and aorta. Under such circumstances, the appearance of the isotope in the pulmonary circulation and expired air was delayed by its passage through the systemic bed. When an injection was made into the left heart proximal to the origin of a left-to-right shunt, however, the Kr\textsuperscript{85} was detected almost immediately and in high concentration in expired air.\textsuperscript{5}

Following these experimental studies, these methods were applied in the study of patients undergoing diagnostic evaluation at the National Heart Institute.\textsuperscript{6,7} The present report presents the experiences with these technics in 48 patients.

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Methods

Gaseous Kr\textsuperscript{85} was prepared for injection by equilibrating it in a sealed plastic container with sterile normal saline solution. A solution containing approximately 10 μc per ml was obtained when 1.5 μc of the gas (about 2.5 ml) were mixed with 100 ml of saline. Solutions were prepared weekly, and were assayed by counting a diluted aliquot in the same gas flow Geiger-Müller tube\textsuperscript{8} utilized for the counting of whole blood.\textsuperscript{2} In general, 5 ml of the solution were employed for each injection in patients above the age of 12 years and 3 ml were given in children. The studies were carried out in a well-ventilated laboratory. During the first 3 minutes after each injection, the patient's expired air was collected in a Douglas bag, the contents of which were discarded into a fume hood, or he was allowed to exhale into a specially constructed exhaust vent over the catheterization table.

For the detection of a right-to-left shunt, arterial blood samples were drawn at a constant rate into oiled heparinized syringes during the 15 seconds following the beginning of the injection. These samples were counted for 1 minute in the gas flow tube, and the radioactivity was compared to that of a blank sample obtained immediately before the injection. The result of each study was expressed as a fraction relating the corrected arterial count to the total number of counts per minute contained in the solution that was injected (the arterial Kr\textsuperscript{85} index): 
\[
\frac{C_{AS} - C_{blank}}{C_{inj} \times ml. injected}
\]

the count per minute obtained from the arterial sample and \( C_{inj} \), the count per minute per milliliter of the injected solution.

For the detection of a left-to-right shunt the patient's expired air was directed across the face of a thin-window G-M tube\textsuperscript{9} inserted into the expiratory line of the closed breathing circuit. The patient was usually instructed to hyperventilate for several seconds after the injection to decrease the time interval required for the gas to traverse the tracheobronchial tree. The output of the tube was integrated by a count-rate meter and recorded continuously on a direct-writing oscillograph.

*Model M-4, Nuclear Corporation of America, New York, N. Y.
†Model TCG-2, Tracerlab-Kelket, Waltham, Mass.
In every patient the presence or absence of a shunt was verified by the findings at operation or autopsy or other diagnostic technics, including selective angiography, the results of nitrous oxide or Kr\textsuperscript{85} inhalation tests, and dye-dilution curves.

**Results**

In 19 patients Kr\textsuperscript{85} was injected into the right side of the heart or into the pulmonary artery, either in the absence of or distal to the origin of a right-to-left shunt. The ratio of the arterial blood radioactivity to the total radioactivity injected ranged from 0.0 to 9.0 \( \times 10^{-5} \), and the mean value was 2.5 \( \pm 2.6 \times 10^{-5} \) (fig. 1). Kr\textsuperscript{85} was injected into the right side of the heart proximal to the origin of a right-to-left shunt in 9 patients. Under these circumstances the ratio of the arterial blood activity to the total activity injected ranged from 8.2 \( \times 10^{-5} \) to 81 \( \times 10^{-5} \) with a mean of 30.1 \( \pm 22.7 \times 10^{-3} \) (fig. 1).

Injections were made into the left side of the heart proximal to the origin of a left-to-right shunt in 22 patients. The appearance time in the expired air ranged from 1.0 to 7.8 seconds, and the mean appearance time was 4.0 \( \pm 1.6 \) seconds (fig. 2). The appearance times in expired air ranged from 1.0 to 6.0 seconds with a mean of 3.3 \( \pm 1.5 \) seconds in the 17 patients in whom the Kr\textsuperscript{85} was injected into the right side of the heart or pulmonary artery. Kr\textsuperscript{85} was injected into the left side of the heart or aorta distal to the origin of a left-to-right shunt or in the absence of a shunt in 18 patients. The appearance time in expired air ranged from 6.5 to 33.0 seconds, with a mean of 15 \( \pm 5.0 \) seconds (fig. 2). In 5 patients Kr\textsuperscript{85} was injected into the right heart or pulmonary artery as well as into the left side of the heart in the absence of, or distal to, the origin of the left-to-right shunt. The appearance time from the right-heart injection preceded that from the left-heart injection by 7 to 15 seconds, and the average difference was 10.8 \( \pm 2.9 \) seconds. In 10 patients injections were made into the left side of the heart both proximal and distal to the origin of the left-to-right shunt. The appearance in expired air following the injections proximal to the origin of the shunt preceded the appearance following injections distal to the origin of the shunt by 3.0 to 16.5 seconds, with an average of 10.5 \( \pm 4.9 \) seconds. The ascending limbs of the expired air curves were

**Figure 1**

Arterial Kr\textsuperscript{85} indices determined following injections proximal to right-to-left shunts (open squares) and either distal to them or in patients without shunts (solid circles). The highest index obtained (81) is not plotted.
Appearance times of Kr85 in expired air following injections at various sites. Lines connect multiple observations in the same patient. The arrow designates the highest value, which was 33 seconds.

Illustrative Applications of the Methods

Case 1

W. M., a 46-year-old man with congenital heart disease and cyanosis was found at right heart catheterization to have a large left-to-right shunt at the atrial level. The right ventricular pressure was elevated but the pulmonary artery could not be entered. Injection of Kr85 solution into the inflow tract of the right ventricle yielded an arterial index of 5.8 × 10^-3, indicative of no venoarterial shunt originating at, or distal to, the right ventricle. Injection into the right atrium, however, yielded an index of 81 × 10^-3, clearly proving a large right-to-left shunt across the interatrial septum. Total anomalous pulmonary venous drainage into the right atrium and the associated atrial septal defect were corrected at open operation. Thus, in this cyanotic patient the normally low arterial level recorded following right ventricular injection localized the origin of the shunt to a level proximal to the competent tricuspid valve.

Case 2

E. H., a 5-year-old boy had been mildly cyanotic and had had a heart murmur since birth. At right heart catheterization the catheter crossed the interatrial septum and the right atrial nitrous oxide test was 25 per cent, indicative of a small left-to-right shunt at this level. The catheter entered a posterior ventricular chamber where the systolic pressure was markedly elevated and near systemic arterial systolic pressure; it could not be advanced into the pulmonary artery or aorta. After injection of 30 μe. of Kr85 into this ventricle the arterial index was found to be only 1.0 × 10^-5, indicating that the entire outflow from this ventricle perfused the lungs and identifying it as the right ventricle. A selective angiocardiogram with the catheter in this position confirmed that it was the right ventricle and demonstrated dextroversion of the heart with valvular pulmonary stenosis. The ventricular septum was intact.

In many patients with right ventricular hypertension, proper identification of the ventricle or great vessel entered by the catheter may be difficult. While the appearance times of injected dye may be helpful, these studies may be inconclusive, particularly in children with an extremely brief pulmonary transit time. The drainage path or paths of a cardiac chamber may be readily determined if the appearance of the isotope in expired air is monitored and its level in arterial blood is also determined. In this patient the very low level of the gas in arterial blood proved that the entire output of the ventricle perfused the lungs and by exclusion localized the right-to-left shunt responsible for the cyanosis to the atrial level.

Case 3

L. B., a 22-year-old laborer had the clinical findings of persistent atrioventricular canal. At catheterization a large left-to-right shunt entered the right atrium and the catheter easily crossed the interatrial septum and entered the left atrium and left ventricle. In order to determine whether left ventricular blood contributed to the shunt, both cardio-green dye and Kr85 injections were made into the left ventricle. The dye was detected in brachial arterial blood by technics previously described, and the appearance and concentration of Kr85 were recorded in expired air (fig. 3). It was difficult to determine from the contour of the descending limb of the dye curve whether or not a small shunt from the ventricle was present. The prompt appearance (2.5 seconds) of Kr85 in the expired air, however, clearly proved that left ven-
triculair blood passed to the pulmonary artery. At operation a complete form of persistent atrioventricular canal was found with both interatrial and interventricular communications.

Case 4

R. T., a 24-year-old man, was thought to have an atrial septal defect of the usual type. Right heart catheterization was performed through the saphenous vein, and a large left-to-right shunt was found at the atrial level, the nitrous oxide index in the right atrium being 69 per cent. The catheter was passed through the atrial defect into the left atrium and left ventricle. Kr$^{85}$ injected into the left ventricle appeared in expired air in 18 seconds. The catheter tip was then withdrawn into the left atrium and a Kr$^{85}$ injection then resulted in an appearance time of 3 seconds. These findings localized the origin of the left-to-right shunt to the left atrium and proved that left ventricular blood did not contribute to it. These findings lent support to the diagnosis of an ostium secundum atrial septal defect. This lesion was demonstrated and repaired at operation.

Case 5

A. R., a 17-year-old student, was intensely cyanotic and only a single sound was audible at the base of the heart and only a soft precordial systolic murmur was present. When operation was planned, the differentiation of tetralogy of Fallot from pulmonary atresia or trunca arteriosus became necessary. The right ventricular systolic pressure was equal to the systemic and although the catheter easily entered the aorta it could not be passed into the pulmonary artery. Kr$^{85}$ appeared in expired air 6 seconds after right ventricular injection, and the concentration rose abruptly. An injection in the aortic arch gave an identical appearance time, but Kr$^{85}$ injected into the abdominal aorta appeared in expired air only after 18 seconds and in low concentration (fig. 4). Indicator-dilution curves from all these sites were similar and resembled normal curves after left ventricular injection, demonstrating no evidence of pulmonary blood flow. The early appearance of Kr$^{85}$ after injection into both the thoracic aorta and right ventricle indicated that blood from the aorta perfused the lungs. Selective angiography and subsequent operation proved the lesion to be pulmonary atresia and that the pulmonary flow originated from dilated bronchial arteries.

Case 6

A. R., a 42-year-old housewife, presented the classic findings of patent ductus arteriosus. The pulmonary artery nitrous oxide test was 39 per cent. At operation, a ductus 8 mm. in diameter was isolated and occluded with a Blalock clamp. Injections of a mixture of Kr$^{85}$ and cardio-green dye were then made into the left atrium, as the gas was monitored in expired air, and dye curves were recorded from the brachial artery. Following in-
jections with the ductus closed, the clamp was opened until a faint systolic thrill was palpable in the main pulmonary artery and the injections were repeated. The contours of the dye curves (fig. 5) were similar but the appearance time of Kr\(^{85}\) was 11 seconds earlier when the tiny shunt was functioning.

Discussion

The injection of Kr\(^{85}\) solution into the cardiac chambers and large vessels and its subsequent detection in arterial blood and expired air provides another sensitive and convenient method for the detection and localization of circulatory shunts. The small amounts of Kr\(^{85}\) employed and its extremely brief biological half-life make its use safe for both the patient and laboratory personnel.

When Kr\(^{85}\) in solution is injected into the circulation, it does not act as a simple intravascular indicator such as Evans blue or tri-carbocyanine. The gas is soluble and diffuses freely into the extracellular and intracellular spaces and thus is delayed in its passage through the systemic circulation. Similarly, Kr\(^{85}\) easily crosses the alveolar capillary membrane and 95 per cent of it is eliminated from blood by 1 passage through the pulmonary circulation.\(^3\) These properties of the isotope make it particularly suitable in studies such as those described, as well as in the detection of valvular regurgitation\(^11\) and portal-systemic venous communications.\(^12\)

In the detection of left-to-right shunts the appearance time of Kr\(^{85}\) in expired air after its injection into the left side of the heart is apparently a more sensitive method than indicator-dilution curves recorded from a systemic artery after either right or left heart injection (figs. 3, 4, and 5). This advantage relates

Figure 4

Expiration Kr\(^{85}\) curves and indicator-dilution curves recorded after aortic injections in a patient with pulmonary atresia. The difference in Kr\(^{85}\) curves proves that the origin of the pulmonary blood flow is from the thoracic aorta. Vertical arrows indicate midpoint of injection and oblique arrows appearance time.
to the fact that a finite point, the appearance time of the gas, is utilized rather than an analysis of the contour of a time-concentration curve. In some instances, however, it may be necessary to compare appearance times from various injection sites to determine whether a shunt is present, since the normal systemic and pulmonary circulation times vary widely from patient to patient (fig. 2); the size of the patient and the degree of compensation are, of course, important determinants. If the appearance time is between 6 and 8 seconds, the area of overlap, a more proximal left heart injection or a right heart injection will indicate the diagnostic significance of the original value. No comparison has as yet been made of the relative accuracy of the Kr$^{85}$ injection method with indicator-dilution curves recorded from the right heart after left heart,$^{13}$ pulmonary arterial,$^{14}$ or intravenous injection.$^{15}$ These latter technics have definite advantages over arterial dilution curves but may require the insertion of 2 catheters.

For the detection of right-to-left shunts integrated samples of arterial blood were counted. Although shunts could be detected and localized with this technic, time concentration curves of the isotope in arterial blood will undoubtedly prove to be superior. In the present study no effort was made to calculate the magnitudes of right-to-left shunts, but this may conveniently be done by appropriate application of the Stewart-Hamilton formula.$^{16}$

$$F = \frac{i}{ct}; \text{ rearranging }$$

$$c = \frac{i}{Ft}; \text{ c may be calculated (}C_{\text{calc}}\text{) if it is assumed that none of the Kr}^{85} \text{ injected in the right heart is cleared by the lungs and the sampling time embraces the entire dilution curve. The magnitude of the shunt may be estimated by relating the counts observed (}C_{\text{obs}}\text{) to the calculated value (}C_{\text{calc}}\text{). Cor-}$$

**Correction** must be made in $C_{\text{obs}}$, for the small portion of the isotope that normally appears in arterial blood ($C_{\text{nor}}$).

3. $C_{\text{nor}}$ is dependent upon the total amount of Kr$^{85}$ injected and if $C_{\text{nor}}/i$ is assumed to be constant, $C_{\text{nor}}$ may be determined by an injection distal to the origin of the shunt, or an average for this value may be calculated from the data in control injections shown in figure 1. This average value was found to be $2.5 \times 10^{-5} \times i$.

Thus, the right-to-left shunt (fraction of systemic venous return bypassing the lungs) = $C_{\text{obs}} - C_{\text{nor}}$ $C_{\text{calc}}$

The data obtained in patient W. M. above may be analyzed in this manner. The systemic flow (Fick) was 4.2 L./min. (70 ml./sec.) and $1.3 \times 10^6$ counts per minute were injected each time ($i$). The arterial count after right ventricular injection ($C_{\text{nor}}$) was 75 cts./min./ml. and after right atrial injection ($C_{\text{obs}}$) was 1045 cts./min./ml. $C_{\text{calc}} = 1.3 \times 10^6$

$$\frac{7 \times 10^4 \times 1.5 \times 10^1}{1240} = 1240 \text{ cts./min./ml.}$$

Right-to-left shunt = $\frac{1045 - 75}{1240} = 78\%$
Summary

Following injection of krypton$^{85}$ in solution into the right side of the heart, approximately 95 per cent is cleared during 1 passage through the pulmonary circulation. Arterial blood activity is low when radioactive Kr$^{85}$ is injected in the absence of, or distal to, the origin of a right-to-left shunt. However, when injected proximal to the origin of such a shunt, a fraction of the Kr$^{85}$ bypasses the pulmonary capillary bed and appears in arterial blood. Thirty to 50 $\mu$C Kr$^{85}$ were injected into the right heart, and arterial blood was sampled during the next 15 seconds. In 19 patients without right-to-left shunts, the activity per milliliter of arterial blood was always less than $9.0 \times 10^{-5}$ and averaged $2.5 \pm 2.6 \times 10^{-5}$ of the total radioactivity injected. In 9 patients with proved right-to-left shunts, the radioactivity per milliliter of arterial blood always exceeded $8.2 \times 10^{-5}$ and averaged $30.1 \pm 12.2 \times 10^{-5}$ of the total activity injected. By appropriate rearrangement of the Stewart-Hamilton formula the data permit calculation of the magnitude of the right-to-left shunt.

Following injection into the left heart, proximal to the origin of a left-to-right shunt, Kr$^{85}$ promptly arrives in the pulmonary vascular bed and immediately appears in the expired gas, where it may be readily detected. In 22 such patients Kr$^{85}$ appeared in the expired gas in an average of 4.0 $\pm$ 1.6 seconds. However, after injection distal to the origin of a left-to-right shunt in 18 patients, the appearance of Kr$^{85}$ in the expired gas was delayed to a mean of 15.0 $\pm$ 5.0 seconds.

The techniques described are convenient, simple to apply during cardiac catheterization, and sufficiently sensitive to detect and localize even small cardiac shunts.

Summario in Interlingua

Post le injection de krypton radioactif in forma de solution a in le latere dextere del corde, approximativamente 95 pro cento es eliminate in le curso de un sol passaage per le circulation pulmonar. Le radio-activitate in sanguine arterial es basse quando le Kr$^{85}$ es injete in le absentia de un derivation dextero-sinistre o quando in le presentia de un tal le injection es effectuate a un puncto distal con respecto a su origine. Tamen, quando le injection es effectuate a un puncto proximal con respecto al origine de un derivation dextero-sinistre, un fraction del Kr$^{85}$ evita le vasculatura pulmono-capillar e apare in le sanguine arterial. Inter 30 e 50 $\mu$C de Kr$^{85}$ esseva injicite in le corde dextere, e specimen de sanguine arterial eseva obtenite durante le sequente 15 secundas. In 19 patientes sin derivations dextero-sinistre, le activitate per millilitro de sanguine arterial eseva semper minus que $9.0 \times 10^{-5}$ con un valor medie de $2.5 \pm 2.6 \times 10^{-5}$ del quantitate total de radioactivitate injicite. In 9 patientes con demonstrate derivations dextero-sinistre, le radioactivitate per millilitro de sanguine arterial excedeva semper $8.2 \times 10^{-5}$, con un valor medie de $30.1 \pm 12.2 \times 10^{-5}$ del quantitate total de activitate injicite. Per medio de un appropriate re-arrangimento del formula de Stewart-Hamilton, le datos permitte le calculation del magnitute del derivation dextero-sinistre.

Post injectiones in le corde sinistre, proximal al origine de un derivation sinistro-dextere, Kr$^{85}$ arriva promptemente in le vasculatura pulmonar e appare immediatemente in le expiration ubi illo es facile a detegere. In 22 tal patientes, Kr$^{85}$ appareva in le gas del expiration intra 4.0 $\pm$ 1.6 secundas. Tamen, post-injectiones distal con respecto al origine del derivation sinistro-dextere, le apparitio de Kr$^{85}$ in le del expiration, studiate in 18 tal patientes, occurreva solmente post 15,0 $\pm$ 5,0 secundas.

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References

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RADIOACTIVE KRYPTON

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Metabolic studies are reported on patients with advanced cardiac disease and congestive failure during the development of hyponatremia and during the restoration of a normal serum sodium concentration. While hospitalized in a metabolic ward, measurements of water, sodium, potassium, chloride, and nitrogen balance were made. The results indicated that abnormalities both in external excretion and internal distribution of water and electrolytes exist in these patients, either of which may be the predominant factor in the pathogenesis of this syndrome. For example, a loss of water in excess of fixed cation accounted for the correction of hyponatremia in certain subjects. In others, primary water retention, leading to dilution of body fluids, was responsible for hyponatremia. In still others, this was due to internal redistribution of electrolyte.

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