Use of Krypton\textsuperscript{85} for the Measurement of Cardiac Output by the Single-Injection Indicator-Dilution Technique

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When radioactive krypton (Kr\textsuperscript{85}), a beta-emitting radioisotope, is introduced into the circulation, it does not act as a simple intravascular indicator. As this substance, in solution in the bloodstream, traverses the systemic capillary bed, it diffuses freely into the interstitial and intracellular spaces. When blood containing Kr\textsuperscript{85} passes through the pulmonary capillary bed, approximately 95 per cent of this isotope crosses the alveolar-capillary membrane, and this fraction is eliminated from the circulation.\textsuperscript{1} These properties of Kr\textsuperscript{85}, as well as the ease with which its concentration can be determined in blood and in air, have made it useful for the measurement of cerebral blood flow,\textsuperscript{2} for the characterization of circulatory shunts,\textsuperscript{3,4} and in the study of intrapulmonary ventilation-perfusion relationships.\textsuperscript{5}

It has been demonstrated in previous investigations in this laboratory that the fraction of systemic venous blood which bypasses the lungs in patients with right-to-left cardiac shunts can be measured by means of the Stewart-Hamilton formula by determining the radioactive in systemic arterial blood following the injection of Kr\textsuperscript{85} into a peripheral vein or the right side of the heart.\textsuperscript{4} These observations suggested the use of a similar approach for the measurement of the cardiac output. The present communication details the experimental validation and the initial clinical applications of this technique.

Theory

When Kr\textsuperscript{85} is injected into the left side of the heart and blood is sampled from a systemic artery, or when it is injected into a peripheral vein and blood is sampled from the pulmonary artery, only the primary time-concentration curve is obtained. Recirculation, for all practical purposes, is eliminated by the diffusion of the Kr\textsuperscript{85} into the extravascular space and its loss from the pulmonary capillary bed. Determination of the radioactivity in a single blood sample, withdrawn at a constant rate, permits calculation of the average concentration of Kr\textsuperscript{85} during the dilution curve. Since neither the appearance nor the disappearance times are known exactly, a sampling period which is certain to bracket the entire curve must be selected. If the amount of indicator injected, its mean concentration during the sampling period, and the exact duration of this period are all known, the Stewart-Hamilton formula may be applied for the measurement of ventricular output.

Example:

(1) Radioactivity injected: $1 \times 10^6$ counts per minute (c.p.m.)/ml., 3 ml.
(2) Mean concentration during sampling period: $2 \times 10^2$ c.p.m./ml.
(3) Sampling period: 24 seconds.

Substituting into the Stewart-Hamilton formula:

$$F = \frac{i}{c t}$$

where $F =$ flow in liters/minute,

$i =$ Kr\textsuperscript{85} injected in c.p.m.,

c = mean concentration of Kr\textsuperscript{85} in arterial blood in c.p.m./ml.,

t = time of sampling period in seconds.

Thus: $F = \frac{60 \times 3 \times 10^5}{2 \times 10^2 \times 24} = 3.75$ L/min.

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 \mu c. per ml. was obtained when 1.5 mc. of the gas (about 2.5 ml.) was mixed with 100 ml. of saline. Aliquots of this solution were stored in 100-ml. syringes, and great care was taken to prevent the entry of air bubbles. The radioactivity of these solutions was determined by counting a 1:100 dilution for one minute with a continuous gas flow GM tube\textsuperscript{*} and a decade scaler. All samples obtained in the course of the

\textsuperscript{*}Model M-4, Nucleonic Corporation, New York, New York.
A comparison of the flow rates of water through a circulatory model determined by the Kr\textsuperscript{85} technique with the actual flow rates determined simultaneously by timed collections into a graduated cylinder.

flow-rate determinations were counted in a similar manner. In all instances, the radioactivity was expressed as counts per minute per milliliter minus background. Three systems were employed to test the accuracy of this technique.

1. The first was a circulatory model consisting of a pump which delivered water at a steady rate through a cylinder filled with glass beads to insure complete mixing. The flow rate was determined by timed collections of the water in a graduated cylinder. The Kr\textsuperscript{85} was rapidly injected into the tubing leading to the cylinder, and sampling was performed from the tubing which led from the cylinder. The flow rate calculated by the Kr\textsuperscript{85} technique was compared with the actual flow rate in 27 experiments.

2. In a series of anesthetized, open-chest dogs the cardiac output, determined by the single-injection Kr\textsuperscript{85} technique, was compared with that determined simultaneously by means of a recording rotameter\textsuperscript{6} which was inserted into the thoracic aorta in the manner described by Sarnoff and Bergland,\textsuperscript{7} and which thus metered total systemic blood flow, i.e., left-ventricular output minus coronary blood flow. The latter was assumed, on the basis of the experiments of Eckenhoff et al.,\textsuperscript{1} to equal 5 per cent of the systemic flow.\textsuperscript{8} In a validation of the dye-dilution technique for the measurement of cardiac output, Shadle, Ferguson, Gregg, and Gilford\textsuperscript{9} had also used this figure to estimate total left-ventricular output from the metered systemic blood flow. A total of 26 separate cardiac-output measurements were made in three dogs; in each dog, the output was varied by bleeding and transfusions. In 17 comparisons, the Kr\textsuperscript{85} was injected into the left atrium and sampled from the aorta. In 9 comparisons, Kr\textsuperscript{85} was injected into the femoral vein and sampled from the pulmonary artery.

3. A total of 22 comparisons of the Kr\textsuperscript{85} technique with the cardiogreen indicator-dilution technique was carried out in a group of eight adult patients during the course of diagnostic transseptal left-heart catheterization.\textsuperscript{10} None of these patients had circulatory shunts; all had valvular heart disease of widely varying severity. The dye-dilution curves were obtained by means of a cuvette densitometer.\textsuperscript{11} The details and reproducibility of the technique have been presented previously.\textsuperscript{12} Both indicators were injected into the left atrium in rapid succession and the dye curve, as well as the Kr\textsuperscript{85} concentration, was obtained from blood which was withdrawn from an indwelling needle placed in the brachial artery.
A comparison of the cardiac outputs determined by the Kr\textsuperscript{85} technique with outputs determined by the dye-dilution technique in patients with valvular heart disease.

**Results**

**Circulatory Model**

The results of the 27 experiments in which flow rates of water through the mixing chamber, determined by the Kr\textsuperscript{85} technique, were compared with the actual flow rates are plotted in figure 1. The flow rates determined by the Kr\textsuperscript{85} technique averaged 30 ml./min., or 0.7 per cent, less than the actual flow rates; one standard deviation of the differences equaled 164 ml., or 5.1 per cent of the actual flow rate; the maximum difference equaled 390 ml./min., or 11.3 per cent of the actual flow rate.

**Dog Experiments**

The results of the 26 comparisons of the cardiac output of the dog determined simultaneously by means of the rotameter and the Kr\textsuperscript{85} technique are plotted in figure 2. The cardiac output determined by the Kr\textsuperscript{85} technique averaged 48 ml./min., or 5.2 per cent, greater than the output determined by the rotameter; one standard deviation of the differences equaled 92 ml./min., or 8.4 per cent of the cardiac output determined by the rotameter; the maximum difference equaled 292 ml./min., or 26.1 per cent of the cardiac output determined by the rotameter. The site of Kr\textsuperscript{85} injection did not appear to influence the results (fig. 2).

**Patients**

The results of the 19 comparisons of the cardiac output determined by the cardio-green dye-dilution method and the Kr\textsuperscript{85} technique are illustrated in figure 3. The outputs determined by the Kr\textsuperscript{85} technique averaged 96 ml./min., or 1.5 per cent, greater than the cardiac outputs determined by the dye-dilution method; one standard deviation of the differences equaled 570 ml./min., or 11.0 per cent of the cardiac outputs determined by the dye technique. The maximum difference equaled 1,450 ml./min., or 21.5 per cent of the cardiac output determined by the dye-dilution technique.

**Discussion**

Following the injection of Kr\textsuperscript{85} into the circulation, recirculation is, for all practical purposes, eliminated, and this isotope is therefore admirably suitable for use as an indicator in the measurement of cardiac output. As demonstrated in this study, with the use of Kr\textsuperscript{85}, cardiac output can be calculated by means of the Stewart-Hamilton formula without analyzing an actual time-concentration curve. Chidsey and associates also made use of Kr\textsuperscript{85} in the measurement of cardiac output by the constant-infusion indicator-dilution technique.\textsuperscript{1}

The technique described in the present report offers a number of distinct advantages over methods that employ indicators which are confined to the vascular system. First of all, the procedure is greatly simplified, since the blood does not need to flow through a densitometer or oximeter, but is merely pulled by hand into a syringe. The volume of blood required for each cardiac-output determination is reduced to 5 ml., since calibration of a densitometer is unnecessary. A substantial amount of calculation is also avoided, since there are no dilution curves to be analyzed and replotted on semilogarithmic paper. The actual value of the cardiac output can be made available to the investigator within two
minutes following injection of Kr\textsuperscript{85}. Furthermore, since it is not necessary to wait for equilibration of the indicator in the circulation, it is possible to repeat cardiac-output determinations at intervals of less than 30 seconds. In the presence of congestive heart failure or of valvular regurgitation, the presence of recirculation may obscure the primary dye-dilution curve, even when the latter is replotted on semilogarithmic paper; under these circumstances, the cardiac output cannot be determined with accuracy by the dye techniques. This problem, too, is completely eliminated by the use of Kr\textsuperscript{85}.

In clinical practice, the Kr\textsuperscript{85} technique appears to be particularly useful in the determination of the cardiac output in the course of left-heart catheterization of patients with valvular heart disease. Furthermore, right- and left-ventricular outputs can be determined separately in patients with circulatory shunts, and in this manner, the magnitude of the shunt can be assessed. For example, in a patient with a left-to-right shunt through an atrial septal defect, the right-ventricular output may be determined when the isotope is injected into the left atrium and blood is sampled from a systemic artery, or when it is injected into a peripheral vein and sampled from the pulmonary artery; left-ventricular output may be determined by injecting the isotope into the left ventricle or aorta. The difference between these two outputs represents the magnitude of the left-to-right shunt.

Among the disadvantages of the Kr\textsuperscript{85} technique, in comparison with the dye-dilution technique, are that the contour of the dilution curve is not provided, nor is it possible to determine the appearance or mean circulation times. In view of the relative insolubility of Kr\textsuperscript{85} in blood and saline, considerable care must be taken to avoid the entrance of even the smallest air bubbles into the injectate and the arterial sample. Finally, it is necessary to withdraw arterial blood at a constant rate; this may be accomplished manually with the aid of a metronome or by means of a constant-withdrawal syringe.

Summary

When krypton\textsuperscript{85} in saline solution is injected into the left side of the heart and sampled from a systemic artery, or is injected into a peripheral vein and sampled from the pulmonary artery, only the primary time-concentration curve is obtained. Recirculation is eliminated by the diffusion of this indicator into the extravascular space and its loss from the pulmonary capillary bed. Determination of the radioactivity in a single blood sample, withdrawn at a constant rate throughout the period during which the Kr\textsuperscript{85} passes across the sampling site, permits calculation of the average concentration of Kr\textsuperscript{85} during the inscription of the primary curve. The validity of this technique was tested in a circulatory model against actual flow determined by timed collection. One standard deviation of the differences in 27 trials equaled 5.1 per cent. In 26 comparisons of cardiac output determined simultaneously in dogs by a rotameter and the Kr\textsuperscript{85} technique, one standard deviation of the differences equaled 8.4 per cent. In 19 comparisons of cardiac output in patients, determined by dye-dilution and Kr\textsuperscript{85} techniques, one standard deviation of the differences equaled 11 per cent. The Kr\textsuperscript{85} technique is simpler technically and requires less blood, instrumentation, and calculation than the standard dye techniques.

References


BOOK REVIEW


Graduate conferences on various subjects are held twice weekly at the Faculty of Medicine in Paris. The conferences here reported are on arterial disease of the lower limbs, treatment of genitourinary prolapse, and muco-hemorrhagic rectocolitis. The emphasis is on surgical treatment. In the conference on arterial disease, the following aspects are considered: unilateral adrenalectomy for thromboangiitis obliterans, with and without sympathectomy, thromboendarterectomy, grafting and bypassing with natural and synthetic materials, and the fashioning of a therapeutic arteriovenous fistula and considerations of amputation.
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