USEFULNESS AND RELIABILITY OF SHORT-LIVED RADIONUCLIDES FOR CARDIAC OUTPUT DETERMINATION

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Among the many methods devised to determine cardiac output, only two, the "Fick method" and the indicator-dilution technique, use no empiric constants. During recent years, the latter method has gained popularity because it is a shorter procedure, requires much less equipment, produces less anxiety and apprehension in the subject, and in most cases, affords a better indication of cardiac output (*1*).

A most popular adaptation of the dilution technique involves the use of dyes and cuvette densitometers. However, generator-produced radionuclides such as ^{113m}In and ^{99m}Tc also offer attractive physical properties making them potentially useful indicators for estimating cardiac output. The repeated introduction of carrier-free ^{113m}In or $Na^{99m}TcO_4$, for example, does not significantly change the body physiology or alter subsequent measurements of cardiac output. Moreover, this method permits continuous recording of radioisotope dilution curves and frequent cardiac output determinations with little radiation hazard to the subject.

METHODS

Detection apparatus. For cardiac output determination, a gamma scintillation detector and a recording ratemeter (Fig. 1) were used. The scintillation detector contained a 1-in.-diam by 1-in.-thick NaI(Tl) crystal shielded by 3 in. of lead. A length of polyethylene tubing, internal diameter 3.5 mm, transported the blood from the femoral artery past the detector at a constant flow rate of 38.2 ml/min using a motor-driven syringe. This arrangement exposed the detector to approximately 0.6 ml of a continuous sample at any given time. The withdrawal syringe was started just before injection of 1.0 ml of ^{113m}In or ^{99m}Tc. At the moment of injection the recorders were started, making a continuous recording of the concentration of the radioisotope in the arterial blood. The recording ratemeter operated with a chart speed of 30.5 cm/min; recordings were routinely made for approximately 30 sec, allowing sufficient time for recirculation to occur. After the output curve had been recorded, the blood was reinfused into the animal. The tubing was then rinsed with heparinized saline in preparation for the standard solutions. The counting rates for each standard were obtained by drawing it past the detector at the constant rate of 38.2 ml/min (Fig. 2).

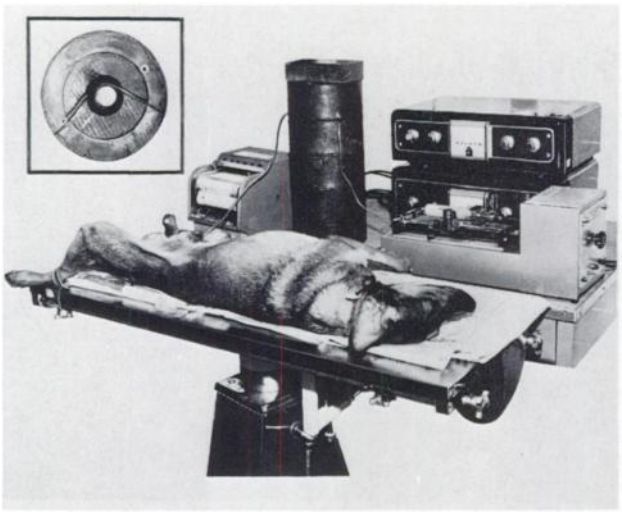

FIG. 1. Detection system with dog in place. Inset shows polyethylene tubing wrapped around scintillation crystal.

Dye-recording apparatus. A cuvette densitometer and indocyanine green dye (Cardio-Green*) were used to obtain the dye-dilution curve. Arterial blood was withdrawn from the femoral cannula into a 12-cm polyethylene tube and through the cuvette by the motor-driven syringe at a flow rate of 38.2 ml/min.

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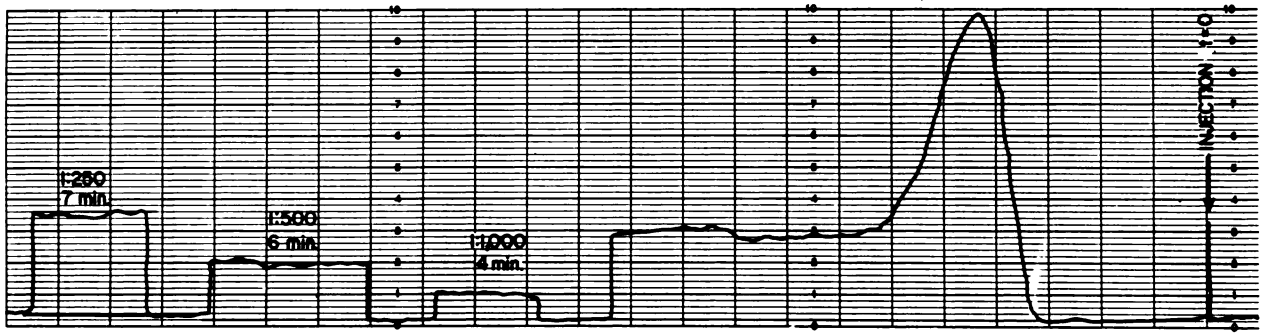

FIG. 2. Recording of ^{113m}In cardiac output (right) and three standard dilutions (left). Time after injection is indicated under dilution factor for each standard measurement. Syringe flow rate is 38.2 ml/min.

Isotope preparation. Indium-113m was obtained by eluting a ^{113}Sn-^{113m}In generator with 10 ml of 0.05 *N* HCl. The radiopharmaceutical was prepared in the manner described by Stern et al (*2*) for blood-pool scanning. Our laboratory procedure was as follows: 10 ml of the eluant from the ^{113}Sn-^{113m}In generator was placed in a vial in a 50°C water bath; 1 ml of 20% gelatin (USP) was added to the vial, and the solution was titrated to pH 4.0 with 0.5 *N* NaOH. One tenth millimeter of this stock solution was placed in 10 ml of distilled water. One millimeter of the resulting 1:100 dilution was then placed in a counting vial, and the activity per ml was evaluated. The ^{113m}In was assayed by comparing an aliquot of the diluted ^{113m}In with 10 μCi ^{133}Ba standard using a well gamma scintillation counter. On the basis of this assay, an aliquot of the stock solution of ^{113m}In was prepared with an activity concentration of 8 μCi/ml/kg of body weight of the dog. One milliliter of this solution was used for injection, and the remainder was used for the preparation of standards. Three standards were made in distilled water at dilutions of 1:1000, 1:500, and 1:250.

The ^{99m}Tc, used as sodium pertechnetate, was eluted from a ^{99}Mo-^{99m}Tc generator, assayed, and prepared with an activity concentration of 6 μCi/ml/kg of body weight of the dog. This solution was used in the manner described for ^{113m}In.

Dye preparation. Powdered Cardio-Green was dissolved in diluent supplied by the manufacturer to yield 2.5 mg dye/ml solution. Calibration of the dye-detecting instrument required a dye-blood mixture and was prepared in four separate 5-ml aliquots of blood. A blank control blood sample was drawn through the tubing and cuvette at 38.2 ml/min to establish the zero baseline. The remaining three aliquots of blood were "spiked" with dye to yield concentrations of dye in blood of 0.002, 0.004, and 0.006 mg/ml, respectively, and drawn through the tubing.

Experimental procedure—animals. The animal experiments were carried out in 16 mongrel dogs weighing 12–20 kg, anesthetized with an intravenous dose of pentobarbital sodium* (35 mg/kg). The femoral artery was cannulated with a Size 14 intracatheter. One milliliter of dye solution was injected into the external jugular vein rapidly and simultaneously with a 1.0-ml volume of either ^{113m}In or ^{99m}Tc (Fig. 3).

For simultaneous sampling, the femoral arterial cannula was attached to the densitometer tubing which was connected in series with the tubing leading to the scintillation crystal. The free end of the latter

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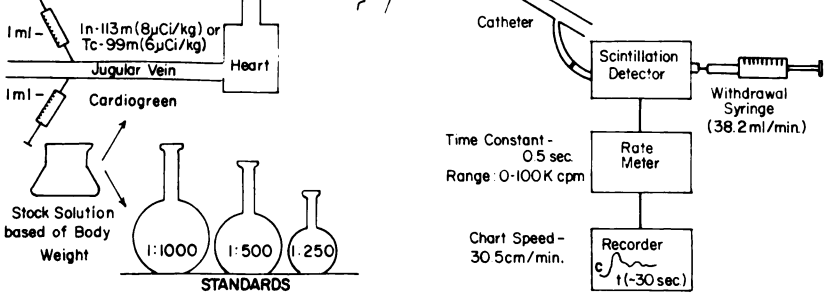

FIG. 3. Diagrammatic sketch of experimental setup showing injected solutions, standards, sampling device, and recorder.

tubing was in turn affixed to the motor-driven syringe. Blood was then withdrawn from the arterial cannula, through the densitometer, past the scintillation crystal, and into the syringe. The withdrawal syringe was started just before injection of the indicators. At the moment of injection the recorders were started, and a continuous recording was made of both activity and dye concentration changes in the arterial blood. When the output curves had been recorded, the blood was reinfused into the animal.

Experimental procedure—circulation model. To test the validity of the technique and to determine the amount of shielding and length of tubing that must be in contact with the crystal, measurement of volume flow was performed on a modified Wigger's circulation model (*3*) with a volume of approximately 800 ml; the system has a reciprocating pump with a stroke volume of approximately 20 ml when operating at 60 strokes/min.

The indicator was injected proximal to the reciprocating pump while withdrawal of blood past the scintillation probe and collection of the "measured" volume were made distally. The "measured" volume of blood was collected in a graduated cylinder for 30 sec after injection. When corrected by a factor of two, this volume equaled blood flow per minute. The amount of isotope injected into the model was 50 μCi/ml, which kept the counting rates within the order of magnitude of the animal experiments.

Calculation of cardiac output. The calculation of cardiac output can be expressed by the general equation (*4*):

$$Q = \frac{I}{\int C(t)dt} \qquad (1)$$

in which Q is flow (ml/min), I is amount of tracer injected (μCi), and $\int C(t)dt$ is total area under the dilution curve (μCi-min/ml).

The area under the cardiac output curve was determined as the sum of two areas (Fig. 4). Area A_1 was estimated by planimeter. Area A_2 was calculated from points on the descending limb of the ouput curve with the assumption that the descending limb is exponential (*4*).

In order to convert the units of area in question, two conversion factors were used, one to convert the horizontal length (cm) along the base of the curve to time (min) and another to convert the vertical height (cm) of the curve to concentration (μCi/ml).

The horizontal conversion factor, H, is the reciprocal of the chart speed. In this situation the chart speed was 30.5 cm/min; therefore the horizontal correction was 30.5^{-1} min/cm.

The vertical conversion factor, V, includes a correction for the sensitivity of the detection apparatus

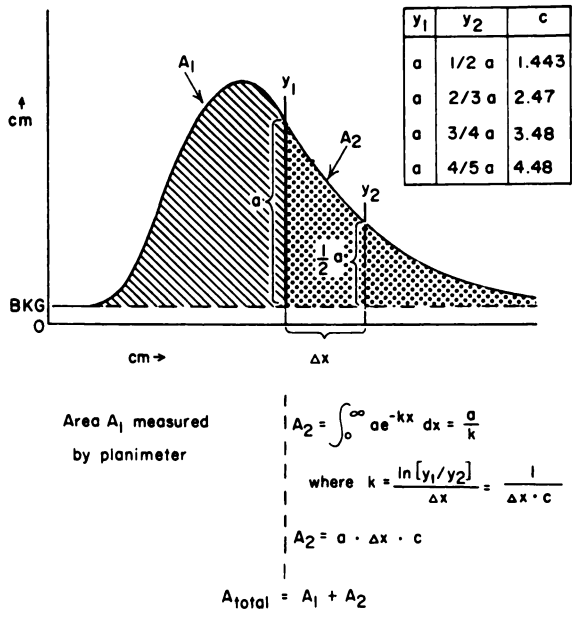

FIG. 4. Calculation of cardiac output from isotope dilution curve. See text for details.

and was determined from three standards of known concentration relative to the injected radioisotope. The vertical deflection (cm) of each of the three standards was plotted as a function of concentration (μCi/ml) and a "best-fit" straight line drawn through these points. The vertical conversion factor was determined as the reciprocal of the slope of this "best-fit" straight line; thus the units of V are μCi/ml-cm. Since the standards were made from the injected solution, the factor V is equal to Z (μCi/ml) divided by the dilution of injected solution necessary to cause a vertical deflection of 1 cm.

Equation 1 becomes

$$Q = \frac{Z(SC)}{A_{total}\,HV} \qquad (2)$$

in which Z is concentration of injected radioisotope (μCi/ml), SC is syringe calibration (ml), A_{total} is total area under the dilution curve (cm^2), H is horizontal conversion factor (cm/min), and V is vertical conversion factor (μCi/ml-cm).

For convenience H and V have been defined as reciprocals. New horizontal and vertical conversion factors are defined as follows:

$H = H^{-1}$ = Chart speed of recorder (cm/min).

$V = Z(V)^{-1}$ = Dilution of injected solution necessary to cause a vertical deflection of 1 cm. [V can be determined directly from plot of vertical deflection (cm) of standards versus concentration (μCi/ml).]

Thus Eq. 2 is converted to the following

$$Q = \frac{Z(SC)}{A_{total}\frac{1}{H}\frac{Z}{V}}. \quad (3)$$

When Z is canceled the final equation used to calculate the cardiac output becomes

$$Q = \frac{(SC)HV}{A_{total}}. \quad (4)$$

The calculation of cardiac output from the dye-dilution curve was performed according to the method outlined in the *Cardio-Densitometer Instruction Manual* (*5*).

RESULTS

The flow of blood within the circulation model was determined using both the volume collection method and the ^{113m}In-dilution method (Table 1). The comparable data indicate clearly that the shielding and length of tubing in contact with the crystal had been adjusted to give accurate estimates of volume flow (measured vs. calculated $p > 0.1$).

TABLE 1. SUMMARY OF DATA USING ^{113m}In WITH CIRCULATION MODEL

Experiment no.	Measured volume (ml/min)	Calculated volume (ml/min)
1	1,058	1,019
2	1,078	1.076
3	1,098	1,080
4	1,118	1,111
5	1,118	1,128
6	1,138	1,033
7	1,138	1,098
8	1,098	1,024
9	1,108	1,163
10	1,118	1,113

Mean difference = (Measured volume — calculated volume) = 23
Standard error of mean = 14.9
$t = 1.543$

Table 2 depicts a comparative study using dogs, showing 16 sets of values which were obtained from simultaneous injections of indocyanine green dye and ^{113m}In, or the dye and ^{99m}Tc. The Student's t test showed that there were no significant differences between the dye and the isotope output values, whether the nuclide was ^{113m}In ($p > 0.3$) or ^{99m}Tc ($p > 0.2$).

DISCUSSION

These findings indicate that reasonable estimates of cardiac outputs may be made using ^{113m}In or ^{99m}Tc as $Na^{99m}TcO_4$ with little or no processing of the eluant obtained from their respective generator. Two advantages seem obvious: first, immediate availability of tracer without the time required for additional processing such as tagging the tracer to a protein; and second, rapid disappearance of tracer from the peripheral blood, which facilitates multiple cardiac output determinations. A primary disadvantage of this method is the necessity of arterial catheterization for the withdrawal of blood through the radiation detection system. In animal studies this procedure is not as inconvenient as it would be in the clinical evaluation of cardiac output. It is suggested that carrier-free ^{113m}In or $Na^{99m}TcO_4$ might be used in conjunction with an external detection system in which cardiac output is estimated without arterial puncture (*6,7*).

Both Crane at al (*8*) and Eichling et al (*7*) have used circulation models to validate their procedures. It is also useful to emphasize the utility of a circulation model for optimizing the radiation detection system. For example, a circulation model with a known pumping rate makes it easy to determine the proper amount of shielding and length of tubing that must be in contact with the crystal. Crane et al (*8*)

TABLE 2. ANIMAL STUDIES USING DOGS (12–20 kg) WITH INJECTIONS OF CARDIOGREEN AND ^{113m}In OR ^{99m}Tc

Experiment no.	Densitometer (ml/min)	^{113m}In (ml/min)	Experiment no.	Densitometer (ml/min)	^{99m}Tc (ml/min)
1	2,000	2,228	1	1,705	1,785
2	2,705	2,757	2	1,511	1,726
3	1,455	1,377	3	2,705	2,847
4	1,695	1,360	4	1,706	1,469
5	2,304	2,580	5	1,544	1,363
6	1,749	1,870	6	1,745	2,110
7	1,655	1,635	7	2,969	3,160
8	2,215	2,520	8	2,969	2,162

Mean difference (Dens. — ^{113m}In) = —69
Standard error of mean = 75.6
$t = 0.913$

Mean difference (Dens. — ^{99m}Tc) = —96
Standard error of mean = 72.6
$t = 1.322$

had to use an electrocardiograph attached to a scaler because of problems encountered with recording ratemeters. Our results show that with careful attention to the shielding and tubing, a simple recording ratemeter of the type used clinically for renograms can be used.

SUMMARY

A study is presented of cardiac output determinations with ^{99m}Tc and ^{113m}In compared with indocyanine green dye in the dog as well as the volume flow of a circulation model. The results indicate that both nuclides can be used for accurate determination of cardiac output with little or no preparation after they have been eluted from the nuclide generator. A simple method of computation of cardiac output from curves generated by a recording ratemeter is discussed. The importance of a circulation model for "calibration" of cardiac output equipment is emphasized.

ACKNOWLEDGMENT

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