for 30 min. To the mixture was added 3.2 g of anhydrous sodium sulfite, and this mixture was extracted twice with 10-ml portions of benzene (13).

The benzene extract was evaporated to dryness in a liquid scintillation vial at 50° under a nitrogen stream. Twenty milliliters of Bray's scintillation solution (14) was added, and tritium and carbon 14 were determined simultaneously in a liquid scintillation counter[5]. Counting efficiency was determined by the external standard method. Some variability in the inhibition data was noted between tubes of microsomes (even from the same liver preparation). For this reason, a standard inhibitor, 1-(4-biphenylyl)pentyl hydrogen succinate (IX), was utilized routinely.

RESULTS AND DISCUSSION

The activity of IIIa–IIId and IVa–IVd as inhibitors of rat liver β-hydroxy-β-methylglutaryl-CoA reductase is shown in Table II. Unfortunately, the low solubility of these compounds in the enzyme assay prevented the determination of I/S values required for 50% inhibition. Thus, no definite conclusions can be made concerning the effect of increasing the size of the alkyl group at the C-3 position of the glutaric acid moiety with or without a C-3 hydroxyl group. However, the limited data do indicate that no substantial changes in inhibitory activity resulted from these modifications [compare 3-hydroxy-3-methyl (X) to 3-hydroxy-3-*n*-propyl (IVa) and the similar degree of inhibition shown by the analogs when assayed at identical I/S values].

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Comparison of Dye Dilution Method to Radionuclide Techniques for Cardiac Output Determination in Dogs

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Abstract □ A study was undertaken to identify the most accurate ^{99m}Tc-labeled radiopharmaceutical and to determine the accuracy of a noninvasive radionuclide technique (antecubital injection and precordial detection) for cardiac output determinations. Phase I employed sodium pertechnetate, stannous pyrophosphate with sodium pertechnetate, technetium-99*m* red blood cells, and technetium-99*m* human serum albumin as radionuclide tracers. Cardiac output was determined by the dye dilution method and then by the invasive radionuclide technique. The radiopharmaceutical was injected into the same intracardiac catheter used in the dye dilution method. Seven to 10 mongrel dogs were used to test the accuracy of each radiopharmaceutical. A paired *t* test and regression analysis indicated that technetium-99*m* human serum albumin was the most accurate radiopharmaceutical for cardiac output determinations, and the results compared favorably to those obtained by the dye dilution method. In Phase II, technetium-99*m* human serum albumin was used as the radionuclide tracer for cardiac output determinations with the noninvasive technique. The results compared favorably to those obtained by the dye dilution method. Regression analysis indicated a correlation coefficient of 0.91. A paired *t* test demonstrated that the difference between the two methods was not statistically significant ($p > 0.05$). The data suggest that a noninvasive radionuclide technique using an intravascular radiopharmaceutical may be safe and nontraumatic for cardiac output determinations in humans.

Keyphrases □ Cardiac output—determination, comparison of dye dilution method and radionuclide techniques, dogs □ Dye dilution method—determination of cardiac output, comparison to radionuclide techniques, dogs □ Radionuclides—use in determination of cardiac output, comparison to dye dilution method, dogs

Measurement of cardiac output using readily detectable tracers such as indocyanine green[1] or suitable radionuclides is based on the principle of conservation of mass (1–3). The direct Fick method involves measuring the amount of oxygen extracted from the inspired air by the lungs and the arteriovenous oxygen difference (4–6). The Stewart–Hamilton dye dilution method is analogous to the direct Fick method (7–9). The validity and reproducibility of this method were verified by several investigators (10–14). The relative ease of detection and quantitation of radioactive tracers have resulted in the use of radiopharmaceuticals for cardiac output determinations (15–29). However, the necessity for cardiac catheterization and cannulation usually limits their usefulness.

[1] Cardio-green, Hynson, Westcott and Dunning, Baltimore, Md.

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Table I—Data Pairs Obtained by the Radionuclide Method Using Sodium Pertechnetate as the Tracer and the Dye Dilution Method

Dog	Cardiac Output, liters/min: Dye Dilution Method	Cardiac Output, liters/min: Radionuclide Method (Sodium Pertechnetate)
1	2.27	1.51
2	1.62	1.37
3	2.83	1.98
4	1.91	1.32
5	3.94	2.64
6	2.02	1.14
7	1.68	1.41
8	2.39	1.88
Mean	2.33	1.66
SD	0.71	0.46
Paired *t* test		
mean of difference = 0.67		
standard deviation of difference = 0.35		
t test = 5.49 (statistically significant)		

BACKGROUND

Technetium-99*m* as the pertechnetate ion and ^{99m}Tc-labeled human serum albumin and red blood cells have been investigated as tracers for cardiac function determinations. Technetium-99*m* was used in its pertechnetate form for cardiac output studies (30). Invasive arterial cannulation was used to inject pertechnetate into the external jugular vein, and blood samples were drawn at a constant rate from the femoral artery. This technique may distort the radionuclide dilution curve and render the results inaccurate due to the distance between the injection and sampling sites.

Schelbert *et al.* (31) reported a correlation coefficient of 0.94 for the left ventricular ejection fraction between the radionuclide method and cineangiocardiography. Although precordial recording was utilized, technetium-99*m* human serum albumin was injected into a central venous catheter at the superior vena cava. Antecubital injection and precordial recording of dilution curves for cardiac function determinations have been studied (32–34); however, the validity of this technique has not been established.

In radionuclide cardioangiography, intravascular agents are preferred. Technetium-99*m* human serum albumin and technetium-99*m* red blood cells have been the two most commonly studied intravascular agents. In this study, sodium pertechnetate was used because the leakage of pertechnetate ions from the vascular compartment was not thought to be significant. Stannous pyrophosphate plus sodium pertechnetate was selected as a tracer following reports on the *in vivo* labeling of red blood cells (35, 36).

Four technetium-99*m* radiopharmaceuticals were studied to determine which one correlated best with the dye dilution method for cardiac output determination. The superior radiopharmaceutical, technetium-99*m* human serum albumin, then was used to determine the reliability of a relatively noninvasive radionuclide technique.

EXPERIMENTAL

Technetium-99*m* was eluted from a molybdenum-99–technetium-99*m* generator[2] as sodium pertechnetate. Technetium-99*m* human serum albumin was prepared by the electrolytic method (37, 38). Technetium-99*m* red blood cells were prepared by pretinning red blood cells with stannous glycoheptonate and then were mixed with technetium-99*m* as the pertechnetate (39).

In Phase I, 37 mongrel dogs were anesthetized with pentobarbital, 35 mg/kg, by intravenous bolus injection. The injection catheter was inserted *via* the right femoral vein to the right ventricle, and the sampling catheter was inserted *via* the right femoral artery to the aorta. Catheter placement was verified by radiological examination. A 25-mg vial of indocyanine green was reconstituted aseptically with 10 ml of diluent to yield a solution of 2.5 mg/ml.

The densitometer[3] was calibrated with a known concentration of indocyanine green in 10 ml of mongrel dog blood. After calibration, a bolus of 2.5 mg (1.0 ml) of indocyanine green was injected *via* the injection catheter using a 1.0-ml syringe[4], a three-way stopcock, and a 5-ml saline flush. The dilution was traced on the densitometer, and the computed cardiac output was displayed at the lighted digital window.

Table II—Cardiac Output Obtained by the Dye Dilution Method and the Radionuclide Method Using Stannous Pyrophosphate plus Sodium Pertechnetate for *In Vivo* Labeling of Red Blood Cells

Dog	Cardiac Output, liters/min: Dye Dilution Method	Cardiac Output, liters/min: Radionuclide Method (Stannous Pyrophosphate and Sodium Pertechnetate)
1	1.92	1.67
2	2.36	1.39
3	2.01	1.13
4	3.18	3.05
5	2.18	2.03
6	3.32	2.65
7	2.45	1.09
8	2.40	1.57
9	2.16	0.67
10	1.79	1.04
Mean	2.38	1.63
SD	0.48	0.71
Paired *t* test		
mean of difference = 0.75		
standard deviation of difference = 0.47		
t test = 0.53 (statistically significant)		

Immediately following the determination of cardiac output by the dye dilution method and while the animal was still anesthetized, the dog was placed in the supine position with its four extremities held toward the four corners of a stretcher. The detector of the mobile radioisotopic camera[5] was positioned at a left anterior oblique view with a 60° angle for proper recording of cardiac anatomy and bolus passage through the cardiopulmonary circulation. Before the radiopharmaceutical injection, the videotape system of the mobile camera was activated. A 5–10-mCi dose of a ^{99m}Tc-radiopharmaceutical was injected *via* the injection catheter in the identical manner as the dye dilution method.

The bolus passage, which gives the radionuclide dilution curve, was recorded by the videostorage system of the camera. Five minutes after the ^{99m}Tc-radiopharmaceutical bolus injection, an equilibrium count rate, C_e, was recorded. Then ^{125}I-radioiodinated serum albumin was injected *via* a peripheral vein for blood volume determination (40). The data from individual videotapes were transferred to a large magnetic storage tape through the computer-attached recording unit.

After individual animal data were fed to the computer[6] for analysis, the bolus passage through the cardiopulmonary circulation was framed by the computer into multiple 1-sec frames; the equilibrium study appeared as a single frame. For each set of animal data, four regions of interest were selected using a light pen and the oscilloscope of the computer. In the flow study and the equilibrium study, the left ventricle was labeled as Regions 1 and 3, respectively. The backgrounds surrounding the left ventricle in the flow study and in the equilibrium study were labeled Regions 2 and 4, respectively. The criteria for the selection were that there should be no overlap between regions of interest of the left ventricle and the background and that the point area of the background should be half that of the left ventricle on integration.

Once the four regions were selected and the data were entered into the computer, the computer utilized these data to calculate the area under the total dilution curve. The area of the background curve subsequently was subtracted from the total dilution curve to give the actual radionuclide dilution curve. The computer program excluded secondary recirculation from the primary dilution curve by extrapolation. It converted the points of the original curve to their semilog counterparts that were shown at the computer oscilloscope. The slope of each individual point was printed on a computer sheet. After the investigators selected the points that gave the best semilog extrapolation, the computer integrated the area under the radionuclide dilution curve. The blood volume was entered, and the offset for the curve was selected to eliminate interference by counts derived from the passage of radiopharmaceuticals through the injection catheter. The computer calculated the cardiac output of each animal using:

[2] Mallinckrodt, St. Louis, Mo.
[3] COR-100, Water Instruments, Rochester, Minn.
[4] Cornwall.
[5] Series 120, Ohio Nuclear Corp., Solon, Ohio.
[6] Model 5407A scintigraphic data analyzer, Hewlett-Packard, Palo Alto, Calif.

Table III—Cardiac Output Obtained by the Radionuclide Method Using Technetium-99*m* Red Blood Cells as the Tracer and the Dye Dilution Method

Dog	Cardiac Output, liters/min: Dye Dilution Method	Cardiac Output, liters/min: Radionuclide Method (Technetium-99*m* Red Blood Cells)
1	2.43	2.92
2	1.68	2.15
3	2.00	3.44
4	2.14	3.03
5	2.94	2.21
6	2.71	2.91
7	2.07	1.98
8	2.48	2.62
9	2.24	2.67
10	3.67	3.59
Mean	2.44	2.75
SD	0.54	0.51

Paired *t* test
mean of difference = 0.32
standard deviation of difference = 0.59
t test = −1.70

Table IV—Cardiac Output Obtained by the Radionuclide Method Using Technetium-99*m* Human Serum Albumin as the Tracer and the Dye Dilution Method

Dog	Cardiac Output, liters/min: Dye Dilution Method	Cardiac Output, liters/min: Noninvasive Radionuclide Method (Technetium-99*m* Human Serum Albumin)
1	2.96	2.49
2	1.89	1.80
3	2.02	2.34
4	1.99	2.18
5	2.97	2.85
6	2.21	2.51
7	2.43	2.39
8	2.20	1.97
9	1.48	1.25
Mean	2.24	2.20
SD	0.46	0.44

Paired *t* test
mean of difference = 0.04
standard deviation of difference = 0.26
t test = 0.48

$$Q_r = \frac{C_e BV}{A} \qquad \text{(Eq. 1)}$$

where A is the area under the radionuclide dilution curve, Q_r is the cardiac output in liters per minute, C_e is the equilibrium in counts per minute, and BV is the total blood volume.

Subsequent to the selection of the most appropriate radiopharmaceutical, seven mongrel dogs were anesthetized with pentobarbital, and the cardiac output was determined by the dye dilution method as in Phase I. Immediately following the determination of cardiac output by the dye dilution method, technetium-99*m* human serum albumin was injected *via* an antecubital vein, and the radionuclide dilution curve was traced precordially by the radionuclide camera and recorded onto the videotape. The data then were analyzed as described.

RESULTS AND DISCUSSION

In Phase I, cardiac output determinations were obtained in 37 mongrel dogs. In Group I, the cardiac output measurements determined by the dye dilution method had a mean of 2.33 ± 0.71 liters/min (mean ± *SD*); results of the pertechnetate radionuclide method had a mean of 1.66 ± 0.46 liters/min (Table I). For individual data pairs, the radionuclide cardiac output values were consistently lower than those obtained by the dye dilution method. This result might have been due to the rapid extravascularization of the pertechnetate ions after injection. On regression analysis, cardiac output data determined by the radionuclide method, Q_r, were assigned as the independent variable, and the data obtained by the dye dilution method, Q_d, were assigned as the dependent variable. The regression line of best fit was $Q_d = -0.08 + 1.46Q_r$. The correlation coefficient was 0.93, which may be due to the consistently lower radionuclide determinations. A paired *t* test indicated that the difference between the radionuclide method and the dye dilution method was statistically significant ($p < 0.05$).

In Group 2, stannous pyrophosphate was injected 10 min prior to the sodium pertechnetate injection to pretin the erythrocytes and to facilitate subsequent *in vivo* labeling of erythrocytes by the pertechnetate. The mean cardiac output value obtained by the radionuclide method (1.63 ± 0.71 liters/min) again was consistently lower than that obtained by the dye dilution method (2.38 ± 0.48 liters/min) (Table II). This result may have been due to the incomplete *in vivo* labeling of erythrocytes. Consequently, part of the injected sodium pertechnetate escaped to the extravascular compartments. This loss resulted in low equilibrium counts and low cardiac output determinations. The regression line of best fit was $Q_d = 1.51 + 0.53Q_r$. The correlation coefficient was lower ($F = 0.79$), possibly because of greater intrapair variations. A paired *t* test also indicated that the difference between the two methods was statistically significant ($p < 0.05$).

For Group 3, data obtained by using technetium-99*m* red blood cells as the tracer in the radionuclide method were compared to those obtained by the dye dilution method (Table III). Although there was a small difference between the mean cardiac output value determined by the radionuclide method (2.75 ± 0.51 liters/min) and the dye dilution method (2.44 ± 0.54 liters/min), individual data pairs varied greatly. Therefore, the correlation coefficient ($F = 0.43$) was significantly lower than that of the previous two groups, and the regression line of best fit was $Q_d = 1.19 + 0.45Q_r$. A paired *t* test indicated that the difference between the two methods was not statistically significant ($p > 0.05$).

In Group 4, the mean cardiac output obtained by using technetium-99*m* human serum albumin as a tracer in the radionuclide method (2.20 ± 0.44 liters/min) was close to the value of the dye dilution method (2.24 ± 0.46 liters/min). The difference between the individual data pairs also was very small (Table IV). Regression analysis gave a correlation coefficient of 0.85 and a regression line of best fit of $Q_d = 0.31 + 0.88Q_r$. The difference between the values in cardiac output by the two methods was not statistically significant ($p > 0.05$).

When all of the results from Phase I of the study were examined, cardiac output determinations using technetium-99*m* human serum albumin as the radionuclide tracer compared favorably to the dye dilution method. The correlation coefficient between the two methods was 0.85, and a paired *t* test indicated that the difference between these two methods was not statistically significant ($p > 0.05$). Sodium pertechnetate and stannous pyrophosphate plus sodium pertechnetate gave significantly different results when compared to the dye dilution method ($p < 0.05$). Even though cardiac output determinations using technetium-99*m* red blood cells were not significantly different from the cardiac output determined by the dye dilution method, regression analysis of the data gave a correlation coefficient of 0.43. Therefore, technetium-99*m* red blood cells appeared to be an inferior tracer.

In Phase II of the study, technetium-99*m* human serum albumin was injected antecubitally, and the dilution curve was recorded precordially. The mean cardiac output by the noninvasive radionuclide method was 2.22 ± 0.57 liters/min and that of the dye dilution method was 2.24 ± 0.54 liters/min. The intrapair differences (Table V) were small and could be explained as physiological occurrences.

Regression analysis gave a correlation coefficient of 0.91 and a regression line of best fit of $Q_d = 0.31 + 0.87Q_r$. A paired *t* test also revealed that the difference in cardiac output determinations between the noninvasive radionuclide method, using technetium-99*m* human serum albumin as the tracer, and the dye dilution method was not statistically significant ($p > 0.05$).

Various investigators reported favorable results using the radionuclide technique for cardiac flow studies when compared to the currently accepted methods. Zekert *et al.* (19) reported a correlation coefficient of 0.80 between the dye dilution method and the radionuclide method, and the difference between the pairs was not statistically significant. Campione and Steiner (20) observed good correlation between cardiac indexes determined simultaneously by the Fick method and the radionuclide technique after antecubital injections and precordial recording using ^{131}I-radioiodinated serum albumin as the tracer. Falch and Norman (28) reported a correlation coefficient of 0.96 between the dye dilution technique and the radionuclide technique using indium-113*m* as the tracer. Van Dyke *et al.* (41) also reported that cardiac output determined by the radionuclide method using technetium-99*m* human serum albumin showed good agreement with cardiac output determined by the Fick method. In the determination of the left ventricular ejection fraction, Strauss *et al.* (34) and Groch *et al.* (42) found that the correlation coef-

Table V—Cardiac Output Obtained by Noninvasive Radionuclide Technique Using Technetium-99*m* Human Serum Albumin as the Tracer and the Dye Dilution Method

Dog	Cardiac Output, liters/min: Dye Dilution Method	Cardiac Output, liters/min: Noninvasive Radionuclide Method (Technetium-99*m* Human Serum Albumin)
1	2.16	2.14
2	3.38	3.44
3	2.06	1.78
4	2.62	2.45
5	1.88	1.55
6	1.93	2.02
7	1.75	2.19
Mean	2.24	2.22
SD	0.54	0.57

Paired *t* test
mean of difference = 0.02
standard deviation of difference = 0.25
t test = 0.20

ficients between contrast angiocardiography and the radionuclide technique were 0.92 and 0.90, respectively.

The radionuclide technique employed by most of these investigators used intracardiac catheters for the injection of radiopharmaceuticals. The data from this animal model clearly demonstrated that noninvasive peripheral injection of an intravascular radiopharmaceutical yields results that are not significantly different from the widely used dye dilution method for cardiac output determinations. Although additional investigations are necessary, this study suggests that a noninvasive radionuclide technique may be safe, relatively nontraumatic, and accurate for cardiac output determinations in humans.

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