Measurement of Cardiac Output by an Indicator-Dilution Method

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IN PREPARATION for hemodynamic studies in anesthetized man, a dye-dilution method for the measurement of cardiac output has been evaluated in dogs. This seemed necessary in view of previous reports suggesting a systematic error in the dye-dilution method which limited interpretation of observations to change within the individual observed.[1, 2] In the present study, error was assessed by comparing values for cardiac output measured by the dye-dilution method with those obtained by the direct Fick method.

Procedure

Eight dogs (17 to 39 kg. in weight) were anesthetized (pentobarbital, 30 mg./kg.), heparinized (3 mg./kg.), paralyzed (succinylcholine, 1 to 2 mg./minute), and ventilated with 99.4 per cent oxygen for 40 minutes without rebreathing. Then the system, including cuffed endotracheal tube, directional valves, Harvard respiration pump (30 cycles/minute) and recording spirometer with carbon dioxide absorber, was closed and oxygen added intermittently. Thereafter, at approximately hourly intervals, oxygen uptake was measured by appropriate closed-circuit spirometric techniques over a period of 10 to 15 minutes. Midway in each period, blood was removed via catheters simultaneously from the pulmonary artery and the aorta for analysis of oxygen and carbon dioxide content with Van Slyke apparatus. At the end of the period of recording oxygen uptake, sampling was begun from the aorta through the densitometer (Waters XC-100A) at 0.5 ml./second using the Harvard Withdrawal Pump. The internal volume of the sampling system from the tip of the aortic catheter to the distal end of the densitometer was 0.5 ml. and the 90 per cent response time to a step change of dye concentration was measured as 1.0 second. The galvanometer (densitometer) was set to the base line (C.E.C. Oscillographic Recorder). Then a measured volume (about 1 ml.) of solution of indocyanine green* (2.5 mg./ml.) was rapidly injected from a calibrated syringe into the pulmonary artery via a second catheter that was filled previously with dye solution and was separate from the blood-sampling system. This technique removed the need for flushing the dye from the catheter with saline solution. Injection was made without regard to the phase of the respiratory cycle. After each sample of blood was removed, citrated canine blood was given in equal amount via the femoral vein.

For calibration of the densitometer, blood was removed prior to each injection of dye and an aliquot was set aside as the blank, along with an aliquot of the dye solution used for injection. The several concentrations of dye in blood were prepared by the method of Sinclair and associates,[3] whereby the maximal desired concentration is prepared and then progressively diluted with blood, or by a method that is more convenient and of comparable accuracy, in which multiple microliter syringes (10, 20, 30, 40, 50-microliter delivery—Hamilton†) are used for dye solution and a calibrated 10-ml. syringe for blood. In either procedure, dilution of the solution with distilled water[4, 5] is avoided. Solutions

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* Indocyanine green (trade name, Cardio-Green) was supplied for these studies by Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.

† Hamilton Syringe Co., Whittier, California.

TABLE 1. Comparison of Canine Cardiac Output by Fick and Indicator-Dilution Methods

Dog	Comparison	Cardiac Output				
		Fick Method, L./min.	Dye-Dilution Method			
			Individual Calibration Curve		Initial Calibration Curve	
			L./min.	$\frac{\text{Fick-Dye}}{\text{Fick}}$, %	L./min.	$\frac{\text{Fick-Dye}}{\text{Fick}}$, %
1	1	3.50	3.20	+8.6	3.20	+8.6
	2	3.36	3.23	+3.9	3.36	0.0
	3	2.50	2.45	+2.0	2.61	−4.4
2	4	4.54	5.28	−16.3	5.28	−16.3
	5	3.34	3.88	−16.2	3.45	−3.3
	6	2.40	2.40	0.0	2.06	+14.2
3	7	4.06	3.68	+9.4	3.68	+9.4
	8	3.94	3.66	+7.1	3.54	+10.2
4	9	2.32	2.49	−7.3	2.49	−7.3
	10	2.63	2.85	−8.4	2.95	−12.2
	11	2.97	3.35	−12.8	3.17	−6.7
	12	2.79	2.77	+0.7	2.86	−2.5
5	13	2.97	2.92	+1.7	2.92	+1.7
	14	2.67	2.53	+5.2	2.50	+6.4
	15	2.65	2.40	+9.4	2.30	+13.2
6	16	2.12	1.88	+11.3	1.88	+11.3
	17	1.60	1.40	+12.5	1.34	+16.3
	18	1.07	1.07	0.0	1.04	+2.8
	19	0.72	0.65	+9.7	.63	+12.5
7	20	3.06	2.68	+12.4	2.68	+12.4
	21	3.23	3.42	−5.9	3.15	+2.5
	22	3.29	2.89	+12.2	2.83	+14.0
8	23	2.45	2.61	−6.5	2.61	−6.5
	24	2.27	2.23	+1.8	2.24	+1.3
			Mean	+1.4		+3.2
			S.D.	±9.1		±9.2
			S.E.	±1.9		±1.9

containing blood were stirred during the removal of aliquots. Each microliter syringe was rinsed four times with dye solution before final filling and delivery of dye to the blood. The calibration samples were prepared in 20-ml. test tubes, which were stoppered and stored in a water bath maintained at 37° C. Calibration with blood at room temperature (or less than body temperature) was avoided in order to approach conditions that existed during inscription of the curve, as electrical compensation for the altered optical density of blood at room temperature produced a change of sensitivity to the indicator dye. After thorough mixing, the sample was passed through the densitometer at the same flow rate (0.5 ml./second) and in the same direction that were used for the recording of the dye-dilution curve. The blank was run first, at which time the galvanometer was set to the same base line used for inscription of the curve. The samples then were run through in the sequence of increasing dye concentration. The calibration curve was nonlinear over

the range of dye concentrations (0 to 15 mg./liter) generally used. About 30 minutes elapsed between removing the blood and completing the calibration curve.

Cardiac output by the direct Fick method and by the dye-dilution method was calculated in the usual manner including, in the latter, a semilogarithmic replot of the disappearance slope and linear extrapolation to 2 per cent of peak dye concentration[6, 7] (an arbitrary cut-off point). The individual dye-dilution curves were analyzed in two ways: (1) by means of a calibration curve prepared with blood drawn just prior to the recording of each dye-dilution curve (individual calibration curve), and (2) by means of the calibration curve prepared with blood drawn from each dog just prior to the study (initial calibration curve). The initial calibration curve, therefore, is the same as the first individual calibration curve for each dog.

Results

In table 1, results obtained in 24 observations by the Fick method are compared with those obtained by the dye-dilution method using the data from 24 *individual* calibration curves (fig. 1) and the eight *initial* calibration curves. Cardiac output (Fick method) varied among dogs from 0.72 to 4.54 liters/minute, with a mean of 2.75 liters/minute. Differences between Fick and dye values (using both individual and initial calibration curves) expressed as percentage of the Fick value, varied from −16.3 to +16.3. With the individual calibration curve, the mean of the differences (expressed as percentage of the Fick value) was +1.4 and the standard deviation was 9.1 or 304 ml./minute. Changes of 10 per cent or more between consecutive measurements were indicated by Fick values on nine occasions. On all of these occasions the dye values also indicated changes of the same sign greater than 10 per cent, and they deviated from the Fick changes by an average of 4 percentage points. Similar results were obtained with the initial calibration curve.

Discussion

Hamilton and co-workers,[8] considering the estimated errors of the direct Fick and the dye-dilution method using T-1824 and multiple plasma samples, and possible physiologic variables, concluded that a deviation as high as 25 per cent between the results of the two methods is to be expected. Dow[9] has indicated some additional problems associated with continuous photometry of flowing blood, but our results confirm recent reports,[4, 10] based on the use of Colson-Gilford densitometer and indocyanine green, that a standard deviation of differences between values obtained by the direct Fick and the dye-dilution method of about 10 per cent can be achieved. In our study, this achievement was possible by attention to several details that are necessary to minimize nonspecific changes in optical density of flowing blood.[3] These details included the elimination of flushing the dye from the catheter with saline solution and the calibration with dye-blood samples that were maintained at 37° C. rather than at room temperature and that were constituted solely of blood and of a dye solution similar to that used for injection. Problems of background dye affecting the calibration were minimized by the rapidity with which indocyanine green leaves the circulation (half-time, 10 minutes).[11]

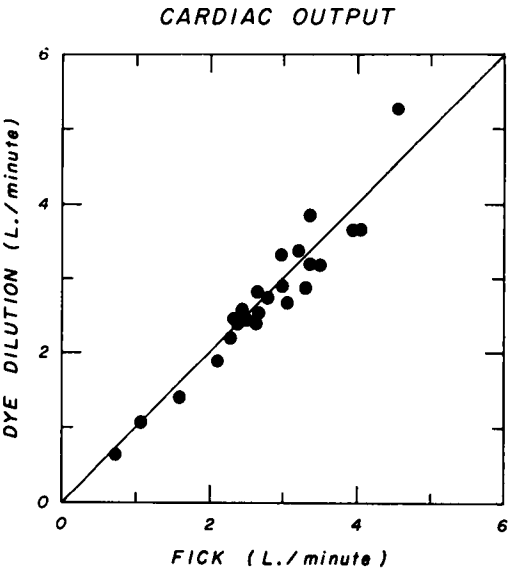

FIG. 1. Comparison of values for cardiac output measured by the Fick method and the dye-dilution method. A diagonal line of identity and the results of 24 individual observations in eight dogs are plotted.

The use of the individual calibration curves for each dye curve constructed with blood removed just prior to injection of the dye did not seem to improve the results materially.

Summary

A dye-dilution method using indocyanine green as the indicator and a Waters XC-100A densitometer for the measurement of cardiac output is described. Results obtained by this technique in dogs are satisfactory when compared with those obtained by the Fick method. A convenient means of calibrating the densitometer is described wherein calibrated microliter syringes are used for the dye solution and calibrated 10 ml. syringes are used for the blood.

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EMPHYSEMA In patients with emphysema and without respiratory failure as shown by blood gas changes, the disease was usually preceded by chronic bronchitis. Though loss of lung elasticity was a prominent feature, ventilation was much less markedly reduced than in patients with respiratory failure with blood gas changes where loss of elasticity was minor as compared to expiratory obstruction. (*Kahana, L. M., and others: A Comparative Study of the Clinical and Functional Pattern in Emphysematous Patients With and Without Chronic Respiratory Failure, Amer. Rev. Resp. Dis. 87: 699 (May) 1963.*)