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THE DETERMINATION OF CARDIAC OUTPUT BY THE DYE DILUTION METHOD: MODIFICATIONS, COMPARISON WITH THE FICK METHOD, AND APPLICATION DURING ANESTHESIA * †

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THE determination of cardiac output by the Fick method during general anesthesia in human beings presents technical difficulties and numerous sources of error (1, 2). The dye dilution technique (3-14) involves neither the problem of obtaining accurate determinations of oxygen consumption nor the technical difficulty and complications of cardiac catheterization for sampling mixed venous blood from the pulmonary artery. The advantages of the dye dilution technique are: simplicity of the procedure and safety of application on patients during general anesthesia. It also offers a wider range of usefulness in measuring cardiac output during various stress situations (14).

The dye technique was therefore evaluated in anesthetized dogs and human beings, and thiopental was chosen to produce and maintain a steady basal state. The purpose of this paper is to report the applications of the dye technique for the determination of cardiac output in man during anesthesia, with some modifications of the dye method, and to substantiate further the validity of the dye dilution method by comparing it with the Fick method in anesthetized dogs.

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GENERAL METHODS

Dogs (weight 12 to 28 kg.): Thirty determinations of cardiac output comparing the Fick and dye methods were obtained in 11 mongrel dogs.

After anesthesia was induced and maintained by the intravenous administration of 2.5 per cent pentobarbital (25 mg. per kilogram of body weight), a number 38 Magill endotracheal tube with an inflatable cuff was inserted into the trachea with the aid of a laryngoscope. The cuff was inflated to insure an airtight fit between the tube and trachea. A number 15 needle was inserted into the right external jugular vein and connected in series with a three-way stopcock. One arm of the stopcock was attached to an intravenous drip of heparinized normal saline solution and the other arm of the stopcock was used for the

PRESSURE TRACINGS—CATHETERIZATION OF PULMONARY ARTERY

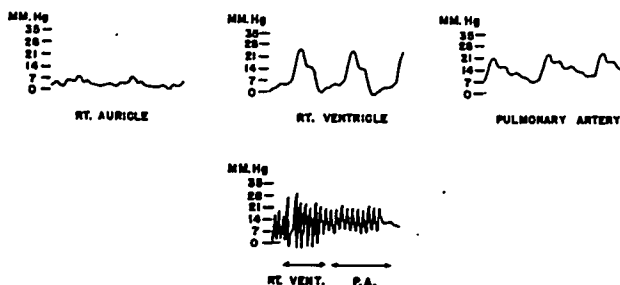


FIG. 1. The tracing on the top row was recorded at a paper speed of 3 cm. per second, showing the contour of the pressure waves in the right auricle, right ventricle, and the pulmonary artery. The tracing on the lower row was taken at a paper speed of 0.3 cm. per second, showing the change in the diastolic pressure as the polyethylene catheter passed from the right ventricle into the pulmonary artery.

injection of the dye. A polyethylene tube was placed centrally into the right femoral artery for the purpose of collecting arterial blood samples. A number 10 French cardiac catheter (15, 16) was introduced into the right femoral vein and slowly advanced until the tip of the catheter was in position in the main pulmonary artery. Pressure tracings were obtained during the introduction of the cardiac catheter with a Sanborn electromanometer and recorded on a Sanborn Viso-Cardiette. The pattern of the pressure tracings indicated at all times the position of the catheter tip (fig. 1). The dye method was started one minute after the arterial and mixed venous blood was drawn. The time interval between repeated experiments in any one animal varied from one to three hours. The surface area of dogs was

computed according to the formula given by Marshall (17, 18) and Benedict (19), using Rubner's constant for dogs in Meeh's formula.

Human Beings: Forty cardiac output determinations by the dye dilution method were obtained in 26 surgical patients. These subjects were in good physical condition and had normal cardiopulmonary function. They were brought to the anesthesia preparation room ninety minutes after the administration of morphine (5.4 to 8.0 mg.) and scopolamine (0.26 to 0.43 mg.). The dosage varied according to the age, weight, and psychic status. The term "resting state" is used synonymously with the "postsedated state," because it has been demonstrated that morphine and scopolamine in the dosage range used in these patients does not significantly alter the cardiac output or affect the circulation (8, 20). The subjects were placed in the supine position with one arm resting on a pillow elevated above the angle of Louis. A number 15 gauge needle was placed in the median basilic vein of the elevated arm for the administration of either the dye or thiopental. A thin walled number 18 needle with stylet was inserted into the brachial artery of the other arm for the collection of arterial blood samples. The dye dilution method was started after the patients rested for at least one hour after the intravenous and arterial needles were appropriately placed.

Three groups of patients were studied. *Group 1:*—Eight duplicate cardiac output determinations were obtained in 6 patients during pentothal® anesthesia to evaluate the precision of the method. *Group 2:*—Twelve cardiac output values were determined in 10 patients during the sedated state. *Group 3:*—Twenty determinations were obtained in 10 patients. In this group the cardiac output values during the sedated state were compared with those during thiopental hypnosis.

Electro-encephalographic patterns were recorded throughout the entire procedure on an eight channel Grass direct writing machine. The level of thiopental anesthesia was precisely ascertained by this method (21). An intravenous drip of 0.2 per cent thiopental was administered slowly. The rate of flow was adjusted to maintain the patients in a drowsy state but responsive to extraneous stimuli. The infusion was decreased or stopped when the electro-encephalographic pattern indicated the onset of a deeper level of narcosis. A steady state of hypnosis was maintained for five minutes before starting the dye dilution method.

TECHNICAL METHODS

Fick Method: Oxygen consumption was determined by connecting a balanced Benedict-Roth spirometer to the endotracheal tube. Samples of mixed venous and arterial blood and an oxygen consumption tracing were simultaneously obtained during a two minute period. The blood samples were collected by siliconed and slightly heparinized syringes and transferred to oxalated tonometers over mercury. The

oxygen content was analyzed by the method of Van Slyke and Neill (22).

Dye Dilution Method: Previous to the cardiac output determinations, 25 ml. of arterial blood were collected in a heparinized Erlenmeyer flask and subsequently centrifuged for thirty minutes at 3500 r.p.m. A stock solution of 1 Gm. to 20,000 dilution of dye in the control sample of plasma was made from 0.5 per cent solution of T-1824. Four different concentrations of this dye plasma stock solution (5 mg. per 100 ml.) were then obtained in the following manner:

- 0.8 ml. stock solution + 1.2 ml. plasma
- 0.6 ml. stock solution + 1.4 ml. plasma
- 0.4 ml. stock solution + 1.6 ml. plasma
- 0.2 ml. stock solution + 1.8 ml. plasma

A standard dye plasma concentration curve was constructed from the optical densities of these four samples of different concentrations, equivalent to 20, 15, 10, and 5 mg. per liter respectively, read against a plasma blank in a Coleman junior spectrophotometer at a wave length of 625 m μ . A precise amount of T-1824 (0.5 per cent concentration) was injected into either the external jugular vein in dogs or the median basilic vein in human beings by a special pipet followed by 10 ml. of saline washout (23).

Samples of arterial blood were collected (at the conclusion of the intravenous injection of the dye) in 32 small glass tubes attached to a circular plastic disk. The disk was then rotated by a motor in clockwise fashion at a speed of one tube per second. The arterial blood samples were centrifuged and the plasma transferred to individual microcuvettes. The cuvettes were made into 12 cm. lengths from soft glass tubes (I.D. 3.5 mm.—E.D. 5.5 mm.). The optical density of each cuvette was previously determined and only those cuvettes within the range of 0.001 to 0.005 were used.

The contents of each micro-cuvette were read on a Coleman spectrophotometer at a wave length of 625 m μ against the plasma control of the first tube. The optical densities were translated into dye concentrations in milligrams per liter from the previously prepared plasma dye curve. These dye concentrations were plotted against time in seconds on semilogarithmic paper (fig. 2). The cardiac output was calculated from the dye concentration curve according to the method of Hamilton *et al.* (4) and Eliasch (11):
$$F = \frac{60 \times 1}{S} \times \frac{100}{100 - H}$$
 F is the cardiac output in liters per minute, 1 the amount of injected dye in milligrams, H the hematocrit (not corrected for trapped plasma) and S the sum of all the dye concentrations in the primary circulation. The value of S is obtained in the following manner: $S = A + B$. A equals the sum of all except the last concentration on the descending limb of the primary curve (fig. 2). B equals the sum of the concentra-

tions obtained from the area of the exponential portion of the descending limb of the curve. The slope of the extrapolated descending limb is projected from the last 2 to 4 concentrations of the primary curve. The area of this exponential slope is computed by the formula of geometric series $s = \frac{a}{1-r}$ and it is added to the sum of A.

RESULTS

Dogs: The results are summarized in tables 1 to 3. The mean cardiac index by the dye technique is 4.31 ± 0.26 L./min./m.², S.D. ± 1.02 (table 1), and by the Fick method is 4.57 ± 0.29 L./min./m.², S.D. ± 1.12 (table 2).

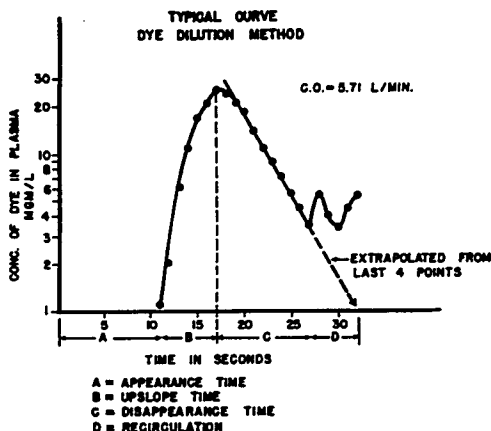


FIG. 2. A typical curve obtained by the dye dilution method in human subjects, showing time relationship and extrapolation from the descending limb.

The results of the Fick and dye methods are compared in table 3. The mean difference between the two methods is 6.2 per cent and the determinations by the Fick method averaged higher than those by the dye. The standard deviation for the difference of the two methods is 12.7 per cent. A t-test applied to the two sets of measurements of cardiac index shows that the difference between the mean values is not significant, $t = 0.67$ and $P > 0.5$. The values of the cardiac indexes of the two methods are compared in a scatter diagram (fig. 3). All except three are within the range of 12.5 per cent.

Human Beings: Group 1:—Duplicate determinations of cardiac output by the dye method were made during pentothal anesthesia. The

TABLE 1
DYE DILUTION METHOD: CARDIAC OUTPUT AND INDEX IN DOGS

No.	Sex	Body Weight Kg.	Surface Area m. ²	Cardiac Output, l./min.	Cardiac Index, l./min./m. ²
1	M	23.60	0.922	3.00	3.26
2	M	23.60	0.922	4.20	4.55
3	F	16.36	0.722	3.56	4.93
4	F	16.36	0.722	2.76	3.82
5	M	16.36	0.722	4.02	5.56
6	M	16.36	0.722	2.56	3.56
7	M	16.36	0.722	2.72	3.78
8	F	20.90	0.850	4.27	5.02
9	F	20.90	0.850	2.95	3.47
10	F	20.90	0.850	2.08	2.45
11	M	18.20	0.774	4.87	6.30
12	F	27.30	1.015	4.67	4.60
13	M	18.20	0.774	4.23	5.46
14	M	20.40	0.838	3.31	3.95
15	F	21.80	0.874	3.37	3.86

Mean = 4.31

S.D. = ± 1.02 S.E. = ± 0.26

standard deviation for the difference of the paired values of cardiac indexes is 2.44 per cent (table 4). Group 2 (postsedation):—The mean cardiac index is 3.29 ± 0.127 (table 5). Group 3:—The mean cardiac index of the sedated state is 3.39 ± 0.204 . During thiopental hypnosis in the same patients the mean cardiac index is 3.27 ± 0.184 (table 6).

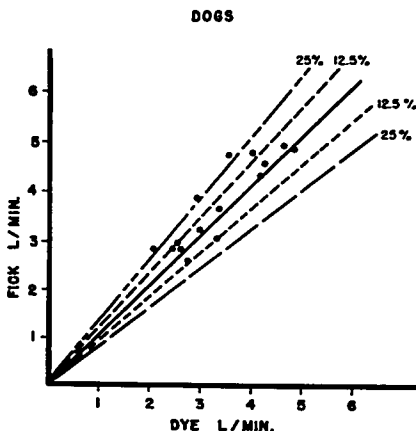


FIG. 3. Relationship of the cardiac indexes of the Fick and the dye methods.

There is no statistically significant difference between these two conditions. $P > 0.6$ ($t = 0.4326$).

Modifications

Several modifications of the dye injection method were instituted. A precision pipet was constructed for the purpose of injecting an accurate amount of dye rapidly and smoothly. The precision of the pipet is $1.67\% \pm .07$ (2, 23). The results of this precision pipet in dogs warranted its use in man. Other improvements in the human experiments with human subjects include the following: elevation of the subject's arm above the level of the angle of Louis during the

TABLE 2
FICK METHOD: CARDIAC OUTPUT AND INDEX IN DOGS

No.	Oxygen Consumption cc./min.	Oxygen Content vol. %		A/V Difference vol. %	Cardiac Output l./min.	Cardiac Index l./min./m. ²
		Arterial	Venous			
1	137.0	18.21	13.79	4.41	3.10	3.39
2	139.0	20.29	16.99	3.30	4.21	4.61
3	120.0	18.04	15.46	2.58	4.65	6.44
4	95.0	15.76	11.95	3.81	2.49	3.45
5	124.0	15.41	12.77	2.64	4.68	6.51
6	139.9	17.34	12.40	4.93	2.83	3.93
7	129.6	14.54	9.78	4.76	2.72	3.78
8	138.0	20.51	19.42	3.09	4.49	5.28
9	160.6	23.38	19.79	4.25	3.78	4.45
10	171.0	23.54	17.38	6.16	2.77	3.26
11	228.0	18.80	14.03	4.47	4.78	6.19
12	143.0	22.75	19.78	2.97	4.81	4.74
13	114.0	16.23	13.30	2.89	3.94	5.09
14	114.0	18.80	14.90	3.90	2.93	3.50
15	120.0	15.70	12.20	3.50	3.54	4.06

Mean = 4.57

S.D. = ± 1.12

S.E. = ± 0.20

intravenous injection of the dye, injection of the appropriate amount of dye per kilogram of body weight, and extrapolation of the exponential portion of the descending slope of the concentration curve by the aid of the formula of geometric series.

The rapid intravenous administration of a precise amount of dye permits the injected marking substance to ascend to the heart and lungs in the form of a bolus. Complete mixing takes place in the largest central volume, namely the pulmonary vascular bed (9). The importance of a smooth and uninterrupted injection in order to permit instantaneous mixing was pointed out by Newman *et al.* (9).

Hetzel and Swan (24) have reported no significant difference in the cardiac output values between the administration of the dye into an

TABLE 3
STANDARD DEVIATION OF PAIRS OF DETERMINATIONS OF THE DYE AND FICK METHODS

No.	C.I. L./min./m. ²		Fick - Dye	Fick + Dye	$\frac{2(\text{Fick} - \text{Dye})}{\text{Fick} + \text{Dye}} \times 100$ Per cent
	Fick	Dye			
1	3.39	3.26	0.13	6.65	3.91
2	4.61	4.55	0.06	9.16	1.31
3	6.44	4.93	1.51	11.37	26.60
4	3.45	3.82	-0.37	7.27	-10.20
5	6.51	5.56	0.95	12.07	15.70
6	3.93	3.56	0.37	7.49	9.90
7	3.78	3.78	0	7.56	0
8	5.28	5.02	0.26	10.30	5.10
9	4.45	3.47	0.98	7.92	24.78
10	3.26	2.45	0.81	5.71	28.40
11	6.19	6.30	-0.11	12.49	-1.76
12	4.74	4.60	0.14	9.34	3.00
13	5.09	5.46	-0.37	10.55	-7.00
14	3.50	3.95	-0.45	7.45	-12.10
15	4.06	3.86	0.20	7.92	5.05

Mean difference between Fick and Dye + 6.18% \pm 3.3%
S.D. 12.7%
P > 0.5

antecubital vein or pulmonary artery. Our experiences with the results from the different sites of injection are in agreement with these authors (25).

Some experiments were discarded because of the decreased blood flow owing to clotting or malposition of the arterial catheter. The patency of the arterial cannula should be tested with heparinized saline solution before injecting the dye to ensure free blood flow. Irregular dye dilution curves were obtained occasionally because of

TABLE 4
DUPLICATE DETERMINATIONS OF CARDIAC OUTPUT IN HUMAN BEINGS
DURING THIOPENTAL ANESTHESIA

Patient	Sex	Age Years	Body Surface Area m. ²	E.E.G. Level	Cardiac Output	
					I L./min.	II L./min.
R. L.	F	59	1.64	2	6.11	6.20
A. B.	F	49	1.53	2	4.33	4.31
E. M.	M	50	1.75	1	4.55	4.64
I. R.	F	49	1.74	0	5.50	5.83
I. R.	F	49	1.74	0	5.83	5.75
N. B.	M	51	1.71	2	3.95	3.96
N. B.	M	51	1.71	2	3.96	3.72
Z. C.	F	66	1.75	2	4.01	3.99

S.D. for differences of pairs: 3.46 per cent.

S.D. for single observations: 2.44 per cent.

arterial hypotension or because of delayed circulation time. When this occurred, concentration values of paired tubes were averaged and plotted every two seconds. A straight line on the descending slope of the dilution curve is thus obtained. Experiments were discarded when recirculation appeared too early and particularly when recirculation appeared during the proximal portion of the descending slope. It was observed that the use of the formula of geometric series for computing the exponential portion of the downward slope of the dye curve will account for the change of cardiac blood flow during an actual determination. In 10 per cent of the experiments the washout slope changed in shape at the lower portion of the descending limb and was always deflected to the left (fig. 4). This inward deflection of the curve may be due to an alteration of blood flow.

TABLE 5
CARDIAC OUTPUT IN HUMAN SUBJECTS: SEDATED STATE

Patient	Sex	Age, Years	Body Surface Area m. ²	Amount of Dye Injected	Cardiac Output L./min.	Cardiac Index L./min./m. ²
J. G.	M	55	1.77	3.75	6.28	3.55
A. L.	F	64	1.65	3.35	5.78	3.50
R. J.	M	24	1.90	6.76	6.51	3.43
R. L.	F	59	1.64	9.36	5.87	3.58
J. C.	F	58	1.78	8.80	7.19	4.04
I. R.	F	49	1.74	6.66	5.50	3.16
I. R.	F	49	1.74	6.66	5.83	3.35
I. R.	F	49	1.74	6.66	5.75	3.30
J. S.	M	55	1.73	8.04	4.07	2.36
S. D.	F	68	1.71	6.57	5.81	3.40
C. E.	M	41	2.04	8.69	4.92	2.65
B. A.	M	48	1.88	11.25	5.90	3.14

Mean

51.6

3.29

S.D. = + 0.438 (13.3%)

S.E. = + 0.127 (3.8%)

Comparison between the Dye and Fick Methods

The comparison between the Fick and Dye methods in our series shows a close agreement with the results reported from other laboratories (4, 7, 8, 10, 11). Our values of the cardiac index by the dye method are not consistently higher and indeed in most instances are lower than those by the Fick method as reported by others, (4, 7, 8). This discrepancy may be explained in part by the different sources of error inherent in each method (8, 14). Other factors that may account for the difference are as follows: the dye method measures the blood flow from the left ventricle over a period of twenty to thirty seconds, whereas the Fick measures the flow from the pulmonary capillary bed over a period of two to three minutes. These two methods therefore do not necessarily estimate the same circulatory factors.

TABLE 6
CARDIAC OUTPUT IN HUMAN SUBJECTS DURING THE SEDATED STATE
AND THIOPENTAL HYPNOSIS

Patient	Sex	Age, Years	Body Surface Area, m. ²	Cardiac Output L./min.		Cardiac Index L./min./m. ²	
				Sedated	Thiopental Hypnosis	Sedated	Thiopental Hypnosis
R. L.	F	59	1.64	5.87	6.11	3.58	3.73
C. M.	M	56	1.88	6.95	7.06	3.69	3.76
A. B.	F	49	1.53	7.49	5.86	4.89	3.83
T. C.	M	24	1.77	5.25	5.97	2.96	3.37
E. P.	M	39	1.95	5.13	5.72	2.63	2.93
J. B.	M	30	1.92	6.60	6.79	3.44	3.54
T. D.	M	14	2.00	5.48	5.50	2.74	2.75
A. N.	M	47	1.77	5.42	5.19	3.06	2.93
A. L.	F	64	1.65	5.78	3.44	3.40	2.08
R. L.	F	59	1.64	5.87	6.20	3.58	3.78
Mean		44.1	1.775			3.39	3.27
						S.D. ± 0.645	± 0.581
						S.E. ± 0.204	± 0.184
						P > 0.6	

Duplicate determinations of cardiac output by the dye method during a steady state of thiopental narcosis revealed a standard deviation for the difference of the paired observations of 2.44 per cent (table 4). Kopelman and Lee (26) reported a coefficient of variation of 6 per cent obtained with the dye dilution method in 10 nonsedated unanesthetized

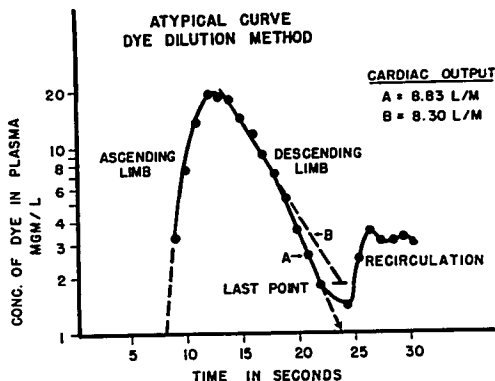


FIG. 4. A dye dilution curve in human subjects showing the change in contour of the descending limb: (A) indicates extrapolation from the distal portion of the changed slope, (B) indicates the extrapolation from the proximal portion of the descending limb. Calculation of the cardiac index by slope (A) is 5 percent higher than (B) in this instance.

human beings. The maintenance of a steady state of thiopental hypnosis during the repeated procedure, the use of the precision syringe, the introduction of a precise amount of dye according to body weight, and the determination of the exponential portion of the curve by the use of the geometric series may in part explain our lower percentage of error of the method.

The standard deviation of the mean values of the cardiac index during the resting state of 12 patients (table 5) is 13.3 per cent and the standard error of the mean is 3.8 per cent. These results compare favorably with the standard deviation of 12.8 per cent of the cardiac

TABLE 7
MEAN CARDIAC INDEX IN HUMAN SUBJECTS DURING THE RESTING STATE
Dye Dilution Method

Cardiac Index L./min./m. ²	S.E.	S.D.	No. of Patients	Authors	Year
3.29	±0.13	±0.44	12	Elsten and Li	1953
3.39	±0.20	±0.64	10		
3.27	±0.18	±0.58	10*		
3.20		±0.20	53	Doyle <i>et al.</i> (14)	1953
3.30		±0.50	9	Ball <i>et al.</i> (27)	1952
3.40		±0.30	6	Beard and Wood (28)	1951
3.70			15		
Fick Method					
3.50		±0.30	53	Doyle <i>et al.</i> (14)	1953
3.37			10	Sancetta <i>et al.</i> (29)	1952
3.74			13	Lagerlöf and Werkö (30)	1948
3.12		±0.40	13	Cournand <i>et al.</i> (15)	1945
3.30			18	Stead <i>et al.</i> (31)	1945
3.10			17	McMichael and Sharpey-Schafer (32)	1944

* Thiopental Hypnosis.

index by the Fick method in 13 determinations reported by Cournand (15) (table 7).

Thiopental Hypnosis

Cardiac output determinations were performed in a series of patients during the postsedated state and thiopental hypnosis. Thiopental hypnosis was used to maintain a uniform steady state in surgical patients. We believe that this technique is of particular importance in producing a basal state in patients for evaluating resting hemodynamics before operation. This degree of thiopental narcosis as compared with the postsedated period (table 6) does not significantly alter cardiac output. The cardiac index in this series is in close agreement with those reported by other investigators (table 7).

Application During General Anesthesia

These studies indicate the usefulness of the dye method for the measurement of cardiac output during general anesthesia. Control evaluations may be adequately obtained during thiopental hypnosis in surgical patients. The dye method may appropriately be employed for the study of cardiac output and related hemodynamics in the following conditions: (1) during pentothal, nitrous oxide, ether, or cyclopropane anesthesia; (2) during the use of combinations of anesthetic agents, that is, pentothal plus nitrous oxide, cyclopropane plus ether, and curare plus cyclopropane or ether; (3) changes of position of the patient in light and deep levels of anesthesia, and (4) intermittent positive pressure breathing during general anesthesia. These studies are now in progress.

SUMMARY

The results of the dye injection technique are compared with those of the Fick method. The mean cardiac index in dogs is 4.57 ± 0.29 L./min./m.² (Fick) and 4.31 ± 0.26 (dye). The standard deviation of the difference of the two methods is 12.7 per cent. The modifications of the dye method are described.

The precision of this method in human beings is 2.44 per cent. The mean cardiac index of 12 determinations in human subjects during the postsedated state is 3.29 ± 0.127 L./min./m.². The mean cardiac index during the postsedated state and that of thiopental hypnosis are compared in another group of 10 patients showing no statistically significant difference between the two conditions.

It is proposed that a steady basal state can be maintained by the slow intravenous administration of thiopental (0.2 per cent). This technique, especially in apprehensive patients, is useful in obtaining resting values of cardiac output.

The satisfactory agreement of the results of the dye method as compared with the Fick method, the reasonable precision, and advantages of the dye technique over the Fick method indicate its usefulness for the determination of cardiac output during the anesthetized state in human subjects.

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