COMPARISON OF THE CARDIAC OUTPUT MEASUREMENTS WITH ELECTROMAGNETIC FLOWMETER AND DYE-DILUTION TECHNIQUE IN DOGS, WITH A NOTE ON THE COMPARISON BETWEEN RADIOCARDIOGRAPHY AND EAR-DYE METHOD IN MAN

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There are relatively few studies and opinions are still divided as to the agreement between the electromagnetic flowmeter and dye-dilution technique in measurements of cardiac output in animals. Of 22 pairs of cardiac output measurements performed with an electromagnetic flow probe applied to the root of aorta in open-chest, anesthetized dogs and with peripheral venous injection of indocyanine green dye and an arterial cuvette, the measured points fell within the range of $\pm 20\%$ on both sides of the line of identity in 19 instances.

Studied on 8 human subjects with radiocardiography and ear-dye method performed simultaneously with peripheral venous injection of a mixture of R^{131} ISA and indocyanine green, cardiac output given by ear-dye method was higher than that given by radiocardiography by an average of 9 ± 11 (SD)%.

Agreement and disagreement in cardiac output measurements given by electromagnetic flow probe, dye-dilution method with arterial cuvette, dye-dilution method with ear-piece densitometer and radiocardiography were discussed.

CARDIAC output measured with direct Fick principle¹ and that measured with indicator dilution technics² have been in good agreements.^{3-6,15} As to the agreement between the dye dilution method and the electromagnetic flowmetry in measuring cardiac output, there are relatively few studies.^{5,7-9} In this report, we will describe the results of simultaneous measurements of cardiac output in anesthetized dogs with dye dilution method using an arterial cuvette and electromagnetic flowmeter.

We will also discuss the results of our simultaneous measurements of cardiac output in human subjects with radiocardiography and

dye dilution technic with ear-piece densitometer, not using the usual 'end-tail calibration' but employing, instead, a new method for the calibration of the ear-dye curves.

METHODS

Cardiac output of 4 anesthetized mongrel dogs, weighing 13.0 – 15.5 Kg, was measured simultaneously, in a total of 22 pairs, by dye dilution method with arterial cuvette and by electromagnetic flowmeter. The electromagnetic flow probe (Model MF-5, Nihonkohden Kogyo Co., abbreviated hereafter as NKK), of non-cannulating type, was placed around the root of

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Fig.1. A typical record of the relationship between the blood concentration of indocyanine green-dye and recorder deflection.

the aorta, after dog's chest was opened at the left 4th intercostal space, under anesthesia with 25–30 mg/Kg sodium pentobarbital. Instantaneous aortic flow (AF) was integrated electronically, giving stroke volume (SV), and from this, the cardiac output. Heart rate was monitored by electrocardiograms (ECG). The right carotid artery was ligated and cannulated, to record the arterial blood pressure (ABP) with an electro-manometer (Model MP-24, NKK). Faithful recording of the phasic change in blood pressure was not attempted in this study.

For dye dilution studies, 1.0 ml of indocyanine green at a concentration of 2.5 mg/ml was injected into a femoral vein as a bolus, followed by a saline flush. The femoral artery of the same hindlimb was cannulated and the arterial blood was drawn into the cuvette densitometer (Model PWA-5, Elma Optics, Co., Tokyo) at a constant speed of 53 ml/min. The area beneath the dye-dilution curves during the

Fig.2. A system used to calibrate the electromagnetic flow probes with saline solution. The time required for saline to fill up the space between A and B was measured with a stop-watch.

Fig.3. Typical records of the calibration, using the system of Fig.2, showing a lower (left) and higher (right) rate of flow. Saw-like records below show the output of an electronic integrator, reset twice (left) and 3 times (right) during the calibration.

Fig.4. A typical record of the relationship between the flow rate of saline and the output of an electromagnetic flowmeter.

first circulation was measured with the hypothesis of a single exponential decay, i.e., with Hamilton's method.¹⁰ Since multiple dye dilution studies were made in one and the same dog, the blood concentration of the dye gradually built up with time. Lest this effect should produce any error in the calculation of the area beneath the dye curve, blood samples were drawn into the cuvette densitometer at appropriate intervals during a run of experiment, and the densitometer output was recorded before and

Fig.5. Typical records of a pair of dye dilution curves obtained with the injection into the femoral vein (upper) and right atrium (lower).

after adding a known amount of dye to the blood, in order to make the blood concentration of dye to increase by known amount. In this way the cuvette densitometer was calibrated, nearly constantly, against the rising background concentration of the dye in blood during the course of

Fig. 6. The rate of flow of saline or blood, at two levels of hematocrit, plotted against the electromagnetic flowmeter deflection.

an experiment.

After several dye dilution curves were recorded in a dog under the prevailing blood pressures, another series of dilution studies were made, in the same dog, at the higher as well as lower end of the arterial blood pressure scale. For this purpose, noradrenaline was used to raise the blood pressure, and sodium pentobarbital was used to lower it.

Fig. 1 is a typical record of the relationship between the blood concentration of indocyanine green and recorder deflection. For blood concentrations of dye in excess of 10 mg/l, the concentration-deflection relation was non-linear.

In a separate study on one dog, dye-dilution curves obtainable with the femoral venous injection of dye were compared with those obtainable with the right atrial injection of dye, with less than 2 minutes elapsing within a pair of such recordings. A femoral vein and artery were cannulated, the former for the injection of dye and the latter for connection to an arterial cuvette. A catheter was advanced through a jugular vein and under fluoroscopic control until the tip reached the right atrium. The femoral venous cannula and the right atrial catheter were each connected to a polyethylene tubing system of identical diameter and length, filled with indocyanine green dye, 1 ml and 2.5 mg/ml in concentration. With saline flush, the dye could be injected rapidly either into the femoral vein or the right atrium, in exactly equal amounts. As soon as the dye-dilution curve with the femoral

venous injection was recorded and the blood was returned to the animal, the following dye-dilution study with the right atrial injection was performed, and, in this way, 3 pairs of such determinations were made.

Every electromagnetic flow probe was calibrated in vitro at the end of each experiment, using the same segment of the aorta as it measured flow in vivo, against known rates of steady volume flow of 0.9% NaCl.

Fig. 2 shows our system for the calibration of electromagnetic flow probes. A segment of the aorta, cannulated at both ends with a pair of glass tubes in continuity with a conduit and a reservoir of 0.9% NaCl solution is shown. The saline was made to flow at known rates of steady flow and the electrical output of the electromagnetic flow probe, riding such a segment of the aorta, was recorded (Fig. 3, 4).

The relative sensitivity of the electromagnetic flow probes to the flow of blood and that of saline was determined in a separate study, where a flow probe was mounted on an excised segment of dog's aorta and various rates of flow was produced, with saline and blood at 2 levels of hematocrit, with a roller pump, Model C-16, Tokyo-Rikakikai Co., Tokyo.

RESULTS

In 3 paired determinations, there was no consistent variation in the measured cardiac output with the two injection sites, i.e., whether the dye was injected in the femoral vein or right

Fig. 7. Typical records of a study for the simultaneous measurement of cardiac output with dye-dilution method with arterial cuvette (A) and an electromagnetic flowprobe applied to the aorta. In (B) are shown, from above downwards, electrocardiogram (ECG), aortic flow (AF), arterial blood pressure (BP) and integrated aortic flow, each step representing stroke volume (SV).

Fig. 8. Cardiac output determined simultaneously with electromagnetic flowmeter (EMFM) and indocyanine green dye-dilution method with arterial cuvette.

atrium, although the shape of the dilution-curves was more satisfactory when dye was injected into the right atrium than when it was injected in the

femoral vein. Fig. 5 shows typical records of one of such paired dilution studies. Cardiac output determined with the dye injection in the femoral vein ranged within 1.45 ± 0.12 l/min and that determined with the dye injection in the right atrium ranged within 1.52 ± 0.25 l/min. The difference between the two tests was not statistically significant ($0.8 > p > 0.7$).

Given a rate of volume flow, the electrical output of the electromagnetic flowmeter was clearly a function of hematocrit, as shown in Fig. 6. It was therefore necessary to correct the flow values for hematocrit, whenever the electromagnetic flow-probe was calibrated with saline only. Where hematocrit values were not measured, the flow signals were corrected for an assumed hematocrit of 31%. Although this formed a source of error in the measured cardiac output, errors of this origin were probably small, because hematocrit values ranged 30–35% in most of the measured dogs.

Fig. 7 shows typical records of an experiment in which cardiac output was measured simultaneously with electromagnetic flowmeter and indicator dilution technic with dye-injection in

Fig.9. Typical records of a study for the simultaneous determination of cardiac output with ear-dye method (A) and radiocardiography (B). In (A), the deflection at the end of 1 minute after the dye injection, not shown here, was identified with $0.85 \cdot (m/BV) \cdot (H_i/H_f)$, where H_i and H_f are the height of the radiocardiographic deflection shown in (B).

the femoral vein. Records of the aortic flow, shown in this figure, are slightly distorted, as evidenced by the lack of horizontal base-line during the ventricular diastole, but records of this kind were not excluded from this study.

Results of such studies, repeated in a total of 22 times in 4 anesthetized dogs, are shown in Fig. 8 in which abscissa gives cardiac output as measured by dye-dilution technic with arterial cuvette and ordinate gives that measured with electromagnetic flowmeter. Cardiac output measured with electromagnetic flowmeter averaged $1.60 \pm 0.73(\text{SD})$ l/min and that measured with dye-dilution technic averaged $1.46 \pm 0.65(\text{SD})$ l/min. The difference between the two tests was statistically significant ($0.02 > p > 0.01$), the electromagnetic flow probe giving a slightly higher values of cardiac output than dye-dilution method. The difference, electromagnetic probe minus dilution method, averaged $0.12 \pm 0.21(\text{SD})$ l/min, or, in per cent of the average dye-cardiac-output, $8.1 \pm 14.3\%$. On the other hand, the measured points

fell within the range of $\pm 20\%$ on both sides of the line of identity, as shown in Fig. 8, except in 3 of 22 cases.

DISCUSSION

Dye-dilution method continues to be one of the most actively studied subjects of cardiovascular research,^{11,14,16} and its studies include comparison with other techniques, such as ultrasound¹⁷ and thermal dilution and fiberoptic cardiac output measurements¹⁸ as well as the use of new indicators, such as radio-iodinated sodium hippurate¹⁹ and a non recirculating indicator, dissolved hydrogen²⁰

As to the agreement between the indicator dilution method with arterial cuvette and electromagnetic flowmetry in measuring cardiac output in dogs, cardiac output measured with the two methods differed within $\pm 20\%$ in 19 of 22 determinations (Fig. 8). This result compares favorably with the result of *Hamilton et al.*⁵ where 75 paired determinations of the cardiac output, made with indocyanine green dye-dilu-

Fig.10. Cardiac output determined simultaneously with radiocardiography (RCG) and ear-dye method.

tion method with injection into the superior vena cava and made with chronically implanted probes of the electromagnetic flowmeter, gave a coefficient variation of $\pm 20.4\%$. In another study on acute preparations, cardiac output measured with electromagnetic flowmeter and the dye-dilution technic differed within $\pm 25\%$ in all but 12 of 95 determinations.⁷

Several reports have described the existence of a systematic difference between dye cardiac output and electromagnetic probe flow. Thus, with chronically implanted electromagnetic flow probe and dye-dilution method, using cardio green dye injected into the right atrium and blood sampling from the aorta, a study on dogs revealed that the dye-dilution technique gave results averaging 45–65% greater than the flowmeter technique.⁸ Based on their earlier study,^{2,1} in which the accuracy of the flowmeter technique was “confirmed”, it was concluded that the cardio-green dye gave higher than true flow. That a period of a few seconds is required for the dye to form a stable complex with the blood before it passes through the densitometer was considered as one of the possible sources of errors.

With indocyanine green injected into either the inferior vena cava or the left atrium, and blood sampling from the femoral artery, *Weaver et al.*⁹ recorded the left and right dye cardiac outputs and the results were compared with aortic and pulmonary probe flow. A good agreement was obtained between the dye cardiac output and the pulmonary artery flow, but the

aortic probe ‘underestimated’ the cardiac output by 14–24%; the authors⁹ ascribed these findings to the difficulty of zero estimation with the aortic flow probe.

If it is the case that the aortic flow probe underestimates the cardiac output by 14–24%⁹ or 10%,^{2,2} we should expect a probe cardiac output considerably lower than the dye cardiac output, because we used aortic flow probes in this study. However, this was not seen in our study (Fig. 8). As to the possibility that we have underestimated the cardiac output by injecting the dye into the femoral vein, our preliminary study showed that the femoral vein injection did not produce any substantial error (Fig. 5).

As an extension of the above study, we performed simultaneous measurements of cardiac output in humans with radio cardiography and ear-piece dye method; the results to be described below may be of some interest, because they suggest that radiocardiography is a valid method for cardiac output measurements and that the ear-dye method overestimates the cardiac output slightly.

For comparing dye-dilution technic with ear-piece densitometer with radiocardiography in human subjects, 9 human subjects, resting in supine position, were injected with a mixture of indocyanine green (Dai-ichi Seiyaku Co.), 10 mg in a volume of 2 ml, and 1–2 ml of $R^{131}ISA$, 20 to 30 μCi , rapidly at the antecubital vein, followed by a saline flush. Dye dilution curves of indocyanine green were recorded with an ear-piece densitometer (Erma Optics, Tokyo) applied to an ear-lobe and securely fixed by bandages, and, simultaneously with this, a radiocardiogram was recorded with a scintillation counter placed over the precordium.

With a radiocardiograph (Metro, Kyoto), precordial dilution curves were recorded externally in compliance with the original method.^{2,3,24}

The methods of radiocardiography used in this study were essentially the same as described by *Kinoshita*.^{2,5} Briefly, blood volume was first measured with 5 μCi of $R^{131}ISA$ injected intravenously and with sampling of the venous blood from the contralateral antecubital vein after 8 minutes. Then a scintillation counter was placed over the precordium and a bolus of fluids containing 20 μCi of $R^{131}ISA$ was injected into an antecubital vein, followed by a saline flush. Precordial dilution curve of the radioactivity was recorded during the first circulation of the

Fig. 11. Reproducibility of the measurements of cardiac output with radiocardiography, a result comparing the 1st measurement (abscissa) with the immediately following 2nd measurements (ordinate).

indicator and shortly afterwards, and the height of the precordial dilution curve at the end of 1 minute after the injection of $R^{131}ISA$ was determined. This was termed the H_i , meaning the initial height. At the end of 8 minutes after the injection of $R^{131}ISA$, 'equilibrium' radioactivity was recorded from over the precordium, and the height of the dilution curve at this 'equilibrium' state was termed the H_f , meaning the final height.

In calibrating the ear-piece densitometer, we did not employ the usual "end-tail calibration". Instead, at the end of 1 minute after the injection of a mixture of indocyanine green and $R^{131}ISA$, the ear-piece densitometer deflection was calibrated against the calculated blood concentration of the dye, calculated, as follows, in consideration of 4 factors, (a) the amount of indocyanine green injected, (b) loss of the dye from blood stream that is expected to have occurred by the end of 1 minute, (c) blood volume and (d) the ratio of the initial to final volume of dilution for the injected substances. The ratio measurable from radiocardiogram, H_i/H_f , is an index of the dilution volume ratio, initial to final, for the capillary-impermeable $R^{131}ISA$.

The initial height of the dilution plateau (H_i) is higher than the final height of plateau (H_f) primarily because the volume of blood with

which the injected dose of $R^{131}ISA$ is mixed is smaller initially than it is finally. Therefore the 'functional' dilution volume at the initial stage of mixing is not BV (blood volume measurable with $R^{131}ISA$ prior to the determination of cardiac output), but $BV \times (H_f/H_i)$. If this consideration applies to the indocyanine green-dye as recorded by ear-piece densitometer, the initial 'functional' dilution volume for the indocyanine green-dye should also be $BV \times (H_f/H_i)$. Since the amount of the dye existing in the circulating blood is a fraction (α) of the dose injected (m), it follows that the initial blood concentration of the dye as recorded by the ear-piece densitometer (C) should be

$$C = \alpha \cdot m / BV(H_f/H_i) = (\alpha \cdot m / BV) \cdot (H_i/H_f)$$

With a degree of arbitrariness, α was chosen to be 0.85, because the blood concentration of indocyanine green-dye is known to decay exponentially with a decay constant (k) of normally $0.16-0.20 \text{ (min.)}^{-1}$ in the absence of the diseases of the liver. For a decay constant $k = 0.18 \text{ (min.)}^{-1}$, α is calculated to be 0.83. Therefore, $\alpha = 0.85$, assumed in this study, is a reasonable rounded figure for normal human subjects.

Fig. 9 shows typical records of a study with the simultaneous cardiac output determinations with ear-piece dye method and radiocardiography. Results of this kind of studies, made in 8 human subjects, are shown in Fig. 10. Although the number of measurements is too small to permit a final conclusion, ear-piece curves gave cardiac output higher than radiocardiography by an average of $9 \pm 11 \text{ (SD)\%}$.

As shown in Fig. 11, cardiac output measurements in men with radiocardiography was reproducible with errors of such degree that standard deviation of the percentage difference between the 1st and 2nd measurements was $\pm 6\%$. The coefficient of variation, i.e., standard deviation of the difference between the 1st and 2nd measurements given in absolute values, divided by the mean cardiac output, was $\pm 9\%$.

This may imply either that the radiocardiography consistently underestimated the cardiac output or that ear-dye curves consistently overestimated the cardiac output.

Although a certain investigator has cast doubt on the validity of radiocardiography as a cardiac output measuring technique,^{2,6} it is unlikely that the cardiac output determined by radiocardi-

graphy is systematically in error, in view of a good agreement reported between the cardiac output determined by radiocardiography and that measured with indicator-dilution method with arterial blood sampling.^{2,4-27} In measurements of cardiac output and pulmonary blood flow, both in the presence and absence of intracardiac shunt, radiocardiography and direct Fick method gave closely similar values according to Hirakawa, Kuwahara *et al*.^{28,29} who described the transport of the injected isotope through chambers and trunk vessels of the cardiopulmonary circulation, and the total heart radioactivity (radiocardiogram), with a series of mathematical equations. Solution of these mathematical equations, using an analog computer in such a way that there may be the best fit between the time-course of the total heart activity and the recorded radiocardiogram, gave values of cardiac output and volume of different chambers and circuits of the cardiopulmonary circulation.^{28,29}

It is therefore more likely that ear-dye curves overestimated cardiac output, and this inference is in agreement with the opinion of most other investigators. Thus measurement of cardiac output with dilution method, using Evans blue dye T-1824 and an ear oximeter calibrated with an arterial blood samples withdrawn 5 minutes after the injection of the dye into an antecubital vein, yielded values which averaged about 9% greater than the values calculated from simultaneous arterial cuvette oximeter curves.^{1,5} Difficulties inherent to an ear-dye curve in cardiac output measurements have been well documented.^{1,30} That the ear-dye curves tend to overestimate the cardiac output was also a conclusion from simultaneous measurements of dye-cardiac output with cuvette whole blood method and ear-piece method.³¹ Parenthetically, with an ear-densitometer which does not require the withdrawal of blood samples to calibrate the instrument for each individual subject, a good agreement was found among ear-dye cardiac output and those measured with cuvette curves and direct Fick method.³²

Finally, merits and demerits of our method of calibrating ear-dye curves may deserve a mention. We employed a new method of calibrating the ear-dye curves as described in 'Method'. Thus the dye-curves were 'calibrated' at the end of 1 minute after the injection of the dye, and it was quite easy to be certain that we are measuring the height of dye-curves exactly at the end of 1 minute after the dye injection. If blood levels of

the dye show a considerable fluctuation during the first few minutes, as shown to be the case with T-1824 in human subjects,¹ a minor time-delay between the dye curve recording and blood sampling will introduce a large error in the end-tail calibration of dye-curves. But there couldn't be any time-delay in our method of calibration. One drawback in our method was that we assumed that 85% of the injected indocyanine green-dye remained in the blood stream at the end of 1 minute after the injection, an assumption that can be a source of errors in calculating the cardiac output, especially in the presence of an impaired liver function.

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