PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 167, 279–283 (1981)

Cardiac Output Determination by Thermodilution Technique: The Method of Choice in Low Flow States[1] (41164)

BARRY A. LEVINE* AND KENNETH R. SIRINEK*,†

Departments of Surgery,† and Physiology,† Audie L. Murphy Memorial Veterans Administration Hospital and The University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284*

Abstract. The purpose of this study was to investigate the validity of the thermodilution technique of determining cardiac output in low flow states. We compared the simultaneous determinations attained by the thermodilution method to those made by microsphere dilution and electromagnetic flow transducer methods. Measurements were carried out in five awake miniature swine (10–14 kg) by means of chronically implanted ascending aortic flow transducer and left atrial catheters. A Swan–Ganz thermodilution catheter and a femoral arterial catheter were placed on the morning of the study. Four simultaneous cardiac output determinations were carried out in each animal using the three techniques. The first two measurements were made during normotension and the last two during graded, stable hypovolemic shock (mean arterial pressure, 75 and 50 mm Hg). In addition, 34 simultaneous measurements of cardiac output were carried out using thermodilution and flow transducer methods. No significant difference occurred among the cardiac outputs derived by any of the three methods used, either during normotension or shock. Linear regression analysis showed excellent correlation between thermodilution and each of the other methods. The results of this study show thermodilution to be an accurate, repeatable technique for measurement of cardiac output in low flow states, including shock, thus widening its applicability in experimental models.

The thermodilution technique for determining cardiac output (CO), first described by Fegler (1) in 1954, has gained widespread acceptance as a simple and accurate method for repeated measurements in laboratory animals and man. Investigators have compared this technique to other methods, including indocyanine green dye dilution (2–6), microsphere dilution (7), and electromagnetic flow transducer (8). Although all of these studies demonstrated good correlation with existing methods, application of the thermodilution technique in small experimental animal models in normotensive as well as shock states has not been fully investigated or validated.

Several aspects of the few studies in which the low flow state was used are problematic. Mathur *et al.* (9) did not make concomitant measurements of cardiac output by methods other than thermodilution in most of their subjects. Moodie *et al.* (4) used a mechanical pumping system to compare measurements by thermodilution and flow meter. This type of system may not accurately reflect either the mixing capabilities or pulsatile characteristics of an organism's intact central and peripheral cardiovascular system. Finally, many studies validating the thermodilution technique compared cardiac output determinations to those derived by the indocyanine green dye dilution technique (2, 4, 6, 9). While indocyanine dilution was the standard method for many years, serious doubt about its accuracy in both very high and low flow states has been raised (10–13).

The purpose of this study was to investigate the accuracy of the thermodilution method of cardiac output determination in an awake small animal model in which cardiac output was generally below 2 liters/min. Thermodilution cardiac outputs were compared with values obtained by micro-

---

[1] Supported by a grant from the Veterans Administration Medical Research Service. In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences–National Research Council.

0037-9727/81/060279-05$01.00/0

sphere dilution and flow transducer techniques. Comparisons were made at normotension as well as during graded levels of hypovolemic shock.

Materials and Methods. Five miniature swine (University of Texas Laboratory Animal Facility, Bastrop, Tex.) weighing 10–14 kg each were used. Each animal was anesthetized (chloralose, 100 mg/kg) and underwent a left thoracotomy. A precalibrated electromagnetic flow transducer (Zepeda Company, Seattle, Wash.) was placed around the ascending aorta, just above the aortic valve, and the connectors brought out at neck level. After coupling the transducer to a dual-channel flow meter (Zepeda), electronic and mechanical zero flow states were correlated. A heparinized silastic catheter was then placed directly into the left atrium again exiting at neck level. The animals were allowed to recover for at least 14 days, during which they were trained to stand in a modified Pavlov restraint with ventral support.

Each animal was fasted 48 hr before the experiment began. On the morning of the experiment each animal was lightly anesthetized (pentobarbital, 10 mg/kg) and a No. 5 French Swan–Ganz thermodilution catheter (Edwards Model 93-132-5F) was placed, with pressure monitoring, from the right femoral vein into the pulmonary artery. The catheter was then coupled to an Edwards 9520A cardiac output monitor. A distal aortic catheter was placed via the right femoral artery for both pressure monitoring and blood withdrawal. The aortic and pulmonary arterial catheters were coupled via Statham P 23Db transducers (Statham Instruments, Oxnard, Calif.) to a multichanneled recorder for continuous monitoring.

The flow transducer leads were connected to the dual-channel flow meter, and the left atrial catheter was cleared so that blood could be aspirated easily. The animal was then heparinized and allowed to awaken and stabilize in the Pavlov stand for at least 3 hr before the experiment began.

Thermodilution technique. Cardiac output determination. A 2-ml injection of iced D_5W (0–1°) was removed from its ice bath and rapidly injected (<1 sec) through the central venous pressure (CVP) port of the No. 5 French Swan–Ganz catheter at the end of a respiratory cycle. The temperature change from the CVP port 15 cm distal to the thermistor at the tip of the catheter was then registered by the Edwards 9250A computer; cardiac output was derived by standard equations integrated into the computer's circuitry (10). The time–temperature curves of each injection were monitored on a strip recorder. These curves were inspected for return to near baseline levels and rejected if this did not occur.

Electromagnetic flow transducer technique. Each transducer was calibrated prior to being placed in the animal as well as after completing each experiment. Calibration was accomplished by placing the transducer snugly around a piece of porcine aorta in a pump circuit and constructing a curve of flow meter readings (microvolts) versus known flow rates through the porcine artery.

Radioactively labeled microsphere technique. Microspheres (3-M Company, St. Paul, Minn.) 15 ± 3 μm in diameter, labeled with ^{125}I, ^{141}Ce, ^{85}Sr, or ^{46}Sc, were suspended in 10% dextran and a sorbitan polyoxyalkalene derivative (Tween) (one drop/10 ml). Aliquots of each sphere injection solution were drawn into five preweighed microhematocrit tubes, reweighed, and counted in a Packard auto-gamma scintillation spectrometer (Packard Instruments, Downers Grove, Ill.) for 5 min. An average of counts per minute per gram (cpm/g) of spheres of the five microhematocrit tubes was then taken to determine the counts per minute per gram of sphere injectate. After determining the total weight of the injectate (the syringes were weighed before and after the addition of the labeled spheres), the total counts in each sphere-containing syringe could be derived by the formula: total counts injected = (weight of injectate × cpm/g). For each microsphere cardiac output determination, 1 ml of the radiolabeled suspension containing approximately 800,000 spheres was injected into the left atrial catheter. The suspension was then immediately flushed into the atrium with 5 ml of 5% dextrose and water at body temperature. Residual radioactivity in the spent syringe was counted, and this amount was subtracted from the total counts to yield the amount injected.

Ten seconds before each microsphere injection, reference aortic samples were withdrawn at a constant rate of 6 ml/min by a monostaltic pump. The use of a single, distal aortic, reference catheter had been validated in our laboratory prior to this study. The withdrawal lasted for 70 sec, with collecting tubes being changed every 10 sec. The tubes were then counted for 5 min in the scintillation spectrometer. Determination of the true count for each isotope with accommodation for overlapping spectra from each radiolabel, was done by the methods described by Heymann (14). The cardiac output for each sphere injection was derived by the formula: cardiac output (ml/min) = reference flow rate (ml/min) × total counts injected (cpm) divided by reference sample counts (cpm).

Experimental design. In each animal cardiac output was determined simultaneously by the three techniques with thermodilution and electromagnetic readings taken at the time of microsphere injection. Four sets of determinations were made. The first determination was made 45 min after the start of the experiment during normotension. The second determination was carried out 30 min later, again at normotension. The animal was then bled to a mean systemic arterial pressure of 75 mm Hg. After a 30-min stabilization at this pressure, the third cardiac output determination was obtained. Finally, the animal was bled to a mean systemic arterial pressure of 50 mm Hg, stabilized for 30 min, and the fourth determination was made. The animal was then sacrificed and the heart was removed, sectioned, and counted to establish the fraction of the total injected radioactivity (and thereby the fraction of cardiac output) going to the heart via the coronary arteries. The lack of shunting via the coronary circulation was assumed in accordance with pilot studies in our laboratory. The electromagnetic flow transducer determinations of cardiac output were corrected for this since the flow transducers were placed distal to the coronary arteries.

In addition, 34 simultaneous measurements of cardiac output by thermodilution and flow transducer were carried out in the course of the experiments. Each electromagnetic transducer flow was corrected for the animal's assumed coronary flow at that mean arterial pressure by the method described above.

Values obtained by the thermodilution, microsphere dilution, and flow transducer techniques were compared by an analysis of variance and linear regression. Significant differences were those with a P value of less than 0.05.

Results. The mean arterial pressure of the five animals during the first cardiac output determination was 107 ± 3 mm Hg; and was 100 ± 2 mm Hg during the second, 75 ± 0 mm Hg during the third, and 50 ± 0 mm Hg during the fourth determination period. The cardiac output determinations using each of the three methods are noted in Table I.

The mean cardiac outputs ranged from a high of 1390 ± 322 ml/min during the first determination (normotension), to a low of

TABLE I. SIMULTANEOUS DETERMINATIONS OF CARDIAC OUTPUT USING THREE SEPARATE METHODS[a]

Time after onset of experiment	Mean arterial pressure[b] (mm Hg)	Methods			Statistical comparison[c]
		Thermodilution	Flow transducer	Microsphere	
45 min	107 ± 3	1348 ± 282[d]	1343 ± 275	1390 ± 322	NS
1 hr 15 min	100 ± 2	1010 ± 156	979 ± 137	1053 ± 176	NS
2 hr 15 min	75 ± 0	942 ± 149	890 ± 140	801 ± 134	NS
3 hr 15 min	50 ± 0	764 ± 83	713 ± 80	755 ± 97	NS

[a] Cardiac output measured in ml/min.

[b] All values represent the mean of measurements in five animals.

[c] By analysis of variance.

[d] (×SEM).

713 ± 80 ml/min during the fourth period (hypotension) and showed a progressive decrease as the mean arterial pressure was lowered during the study. Cardiac outputs in the individual animals ranged from a high of 2490 ml/min during the first period to a low of 435 ml/min during hypotension.

Analysis of the timed aortic withdrawal after each microsphere injection showed that during normotensive periods, counts in the blood returned to background levels within 30 sec. During severe hypotension, however, background levels of radioactivity in the withdrawn blood were not reestablished until 50 sec after injection. The percentage of injected radioactivity found in the heart substance varied from 3.5% during normotension to 9% during severe hypotension.

When the electromagnetic flow transducers were removed and recalibrated at the conclusion of each experiment, it was found that no changes in the electromagnetic characteristics had occurred.

Duplicate cardiac output determinations by both thermodilution and flow transducer techniques varied 3–5%.

The thermodilution cardiac output determinations were then compared to values obtained by both the flow transducer and microsphere methods. Figure 1 depicts the comparison of the 54 simultaneous cardiac outputs by thermodilution (y) method with those determined by the electromagnetic flow transducer (x). The equation defining this relationship is $y = 1.0x + 39.6$ with $r = 0.96$ ($P < 0.001$). The mean difference between the two methods was 6.0%. Figure 2 depicts the same type of comparison for thermodilution (y) versus microsphere withdrawal (x)-derived simultaneous cardiac outputs. This relationship is represented by the equation $y = 1.07x - 81.2$ with an $r = 0.96$ ($P < 0.001$). The mean difference between these two methods was 11.4%.

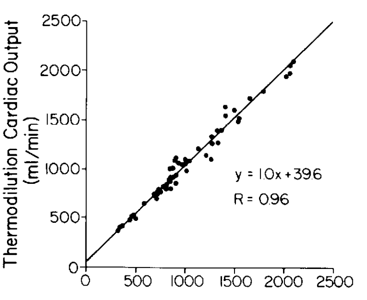

FIG. 1. Comparison of cardiac outputs derived by both thermodilution and flow probe methods.

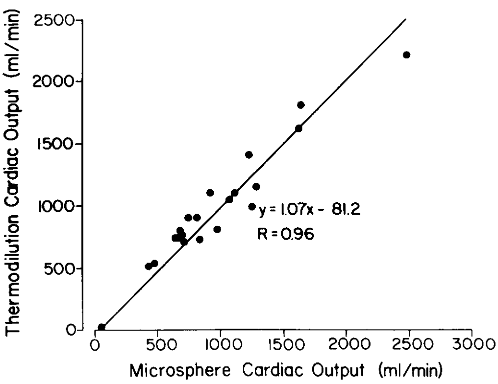

FIG. 2. Comparison of cardiac outputs derived by both thermodilution and microsphere techniques.

Comparison of the mean cardiac output determinations for each of the four time periods failed to show any significant differences among the three methods employed (Table I).

Discussion. Much of the experimental hemodynamic work in our laboratory is based on a small animal model, the miniature swine. It is necessary therefore to have an accurate, repeatable, and easy method for determination of cardiac output in this model. Both electromagnetic flow transducer and radiolabeled microsphere withdrawal are excellent methods of cardiac output measurement and have been used in the past, both in our own models (7) as well as those of others (14–17). The former method requires implantation of the transducer on the ascending aorta via thoracotomy which, in chronic models, is related to a significant degree of mediastinitis and formation of aneurysm. The latter method is limited by the number of separate isotope labels available. Thus, only four or five measurements of cardiac output can be made over the course of a long experiment. Furthermore, each measurement requires withdrawal of an arterial blood sample.

Indocyanine green dye dilution is another method widely used in experimental models to determine cardiac output. However, because of the toxicity and slow dissipation of the dye, it, too, is limited to a given number of determinations during an experiment and also requires arterial blood withdrawal. Other disadvantages include lack of dye stability and dye recirculation, making continuous readjustment of baseline levels necessary.

The thermodilution technique affords several advantages. It uses an indicator (temperature) which is nontoxic and can be carried in a small volume of physiologic solution. The indicator is dissipated rapidly without recirculation, permitting repeated measurements at short time intervals without either deleterious effects or changes in baseline indicator blood levels. No blood sampling is necessary because the thermostatic detector is placed within the vascular compartment. Thus, the effects associated with depletion of the intravascular volume are avoided. Finally, the method is technically simple to perform, allowing application in many different situations.

The results of the present study demonstrate the applicability of the thermodilution technique in the low flow state. The large proportion of the determinations were below the 2 liter/min level (96%) and many were below 1 liter/min (48%). In the miniature swine model, at both normotension and graded levels of hypotension, measurements of cardiac output were statistically identical to those obtained by the microsphere dilution method and electromagnetic flow transducer. Although on the average, the thermodilution method yielded a value slightly higher than either of the other techniques, these differences were not statistically significant. It would seem then that the thermodilution technique of cardiac output determination is well suited to monitor cardiac output in situations where low flow states are expected.

---

1. Fegler, G., Quart. J. Exper. Physiol. **39**, 153 (1954).
2. Callaghan, M. L., Weintraub, W. H., and Coran, A. G., J. Ped. Surg. **11**, 629 (1976).
3. Ganz, W., Donoso, R., Marcus, H. S., Forrester, J. S., and Swan, H. J. C., Amer. J. Cardiol. **27**, 392 (1971).
4. Moodie, D. S., Feldt, R. H., Kaye, M. P., Strelow, D. A., and Van Der Hagen, L. J., J. Surg. Res. **25**, 305 (1978).
5. Solomon, H. A., San Marco, M. A., Ellis, R. J., and Lillehei, C. W., Surg. Forum **20**, 28 (1969).
6. Vliers, A. C. A. P., Visser, K. R., and Zijlstra, W. G., Cardiovasc. Res. **7**, 133 (1973).
7. Levine, B. A., Schwesinger, W. H., Sirinek, K. R., Jones, D., and Pruitt, B. A., Surgery **84**, 113 (1978).
8. Merjavy, J. P., Hahn, J. W., and Barner, H. B., Surg. Forum **25**, 145 (1974).
9. Mathur, M., Harris, E. A., Yarrow, S., and Barrat-Boyes, B. G., J. Thorac. Cardiovasc. Surg. **72**, 221 (1976).
10. Weisel, R. D., Berger, R. L., and Hechtman, H. B., N. Engl. J. Med. **292**, 682 (1975).
11. Jacobs, R. R., Heyden, W. C., Williams, B. T., Schmitz, U. T., and Schenk, W. G., J. Surg. Res. **10**, 25 (1970).
12. Jacobs, R. R., Schmitz, U. T., Heyden, W. C., Roding, L. B., and Schenk, W. G. Jr., Surg. Forum **19**, 113 (1968).
13. Jacobs, R. R., Williams, B. T., and Schenk, W. G., Arch. Surg. **102**, 199 (1971).
14. Heymann, M. A., Payne, B. D., Hoffman, J. I. E., Rudolph, A. M., Prog. Cardiovasc. Dis. **20**, 55 (1977).
15. Archie, J. P., Fixler, D. E., Ullyot, D. J., Hoffman, J. I. E., Utley, J. R., and Carlson, E. L., J. Appl. Physiol. **35**, 148 (1973).
16. Hoffbrand, B. I., Forsyth, R. P., Cardiovasc. Res. **3**, 426 (1969).
17. Segadal, L., and Svanes, K., Scand. J. Clin. Lab. Invest. **39**, 415 (1979).

Received September 25, 1980. P.S.E.B.M. 1981, Vol. 167.