An In Vitro Calibration of the Thermodilution Method of Cardiac Output Determination

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Abstract

***(J. Extra-Corpor. Technol.* 19[2] p. 221-227 Summer 1987, 13 refs.) The accuracy of cardiac output ($\dot{Q}$) determinations by the indicator dilution method will depend, amongst other things, upon the precision of the instruments used to make the measurements. Using an in vitro calibration we determined the accuracy and reproducibility of the measured flow from three different thermodilution computer-catheter systems in our institution. The regression equation describing the relationship between computed and true flow, Computed Flow = M (True flow) + B where M = the slope and B = the intercept of the regression line, was determined for each system. These equations defined the extent to which the system departed from 100% accuracy in the idealized environment of a flow-bench model. As such, they quantify the minimum error that is likely to be encountered when the same measurement is made in vivo.**

Introduction

The determination of cardiac output by the indicator dilution technique has gained wide acceptance. When a known quantity of dye such as indocyanine green is injected into the central veins and sampled from a systemic artery through a densitometer, the concentration/time curve may be analyzed for average concentration during the time of sampling. When corrected for recirculation by logarithmic extrapolation of the initial downslope of the dye curve to zero concentration, cardiac output may be calculated.[1] Two major developments have advanced this methodology. First, computers have been programmed to make all the calculations necessary to determine flow by the indicator dilution technique. Second, the availability of thermistor tipped catheters having an inflatable balloon to guide them into the pulmonary artery has disposed of the need for both an arterial access and an indicator that recirculates.

Recent investigations have been directed at establishing the reliability and reproducibility of thermodilution cardiac output determinations in the clinical setting.[2,3] These data have helped define the limitations of this methodology. One report [3] states that when using commercial thermodilution computers to make the necessary calculations, there must be a minimum difference of 12-15% among three consecutive measurements to suggest clinical significance. Such problems with reliability usually result from difficult-to-reverse procedural difficulties and signal errors attendant upon making these measurements in critically ill and unstable patients. [2,3] Examples are:

a) the slow migration of the catheter such that the proximal (injectate) port is no longer proximal to the right ventricle.

b) the induction of arrhythmias by the cold indicator, leading to the performance of a reduced number of injections.

c) the development of pulmonary hypertension and increased right heart pressures, leading to tricuspid regurgitation or a right to left shunt through a patent foramen ovale—both of which result in a measurement error.

However, the extent to which thermodilution mea-

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surements are unreliable because of computer-catheter inaccuracy or technique alone is usually not known. It is assumed that if the measurements were being made in an ideal system—i.e., perfect mixing, no loss of indicator, perfect thermistor position, absence of respiration induced thermistor movement or temperature fluctuation, absence of the time-variation of flow caused by respiration and other factors—then the computer-catheter unit would reliably report the actual flow. This assumption may not be valid if the system, or technique itself, is inaccurate.

To determine the precision of the instruments and technique these systems may be calibrated in an ideally stable and controlled in vitro environment. The most sophisticated in vitro unit is the one designed by Powner and Snyder and reported in *Medical Instrumentation*.[4] A less elaborate, but more accessible, flow-bench unit has been reported by Davis.[5] Here we present our experience with a refined version of the Davis model, in calibrating three different thermodilution cardiac output computer and catheter systems in our institution.

Materials and Methods

The bench model was designed to permit simultaneous determinations of flow by both the thermodilution technique and by timed volume collection. Tap water at body temperature, 37 ± 0.5 °C, was pumped from a warm water bath[a] through a simulated right ventricular conduit, into a 5 liter graduated cylinder. The "ventricle" consisted of a 3-port, 200 cc, glass distilling flask.[b] In order to produce mixing analogous to that in vivo the flask was placed upon a magnetic stirrer.[c] The flask and stirrer were then firmly clamped to a ring stand. Large bore, (25 mm, ID, length 12 cm), tubing[d] was connected to the outflow port of the "ventricle" to simulate the outflow tract and pulmonary artery. The middle port was fitted with a one holed rubber stopper.

A glass rod was passed through the stopper to allow for the escape of trapped air during priming. The inflow port and the large bore outflow tube were connected to appropriate lengths of tubing (1/2 in OD x 3/8 in ID).[d] The proximal piece of conducting tubing was fed through an occlusively set roller pump[e] used to drive the system (Figure 1). A thermistor-tipped flow-directed catheter[f], appropriate for the computer being tested, was then passed through a small hole in the proximal conducting tubing. This hole was situated such that when the catheter was in its final position, 60-

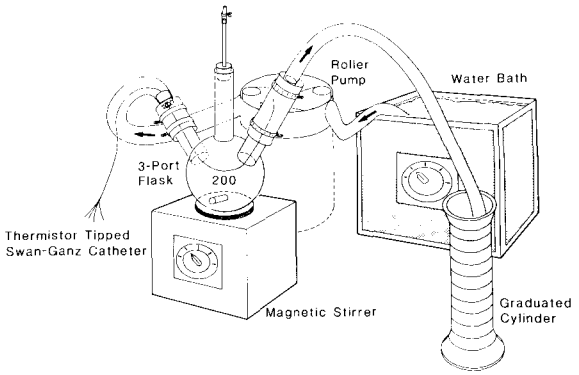

Figure 1: Schematic diagram of bench model.

70 cm of its length would be immersed in the circuit. The catheter was threaded through the "ventricle" until its thermistor lay well into the outflow tract. Care was taken to ensure that, in its final position, the thermistor did not contact the wall of the tubing. The hole was sealed with 100% silicone rubber.

All cardiac output determinations were done during the time that the water bath was not in its active heating phase. Thermodilution curves were recorded on a Grass®, model 7D, polygraph.[g]

Although adequate mixing is not thought to be a problem in vivo, provided the catheter is positioned well—injectate lumen proximal to the right ventricle—uniform mixing of the indicator with blood over the whole vascular cross section is a basic assumption for the validity of the thermodilution method.[6] In our model, adequacy of mixing was determined by sampling the temperature-time curves at several points across the stream. The sampling thermistor was moved by rotating the catheter at its point of insertion. At high flow rate and stirrer speed the temperature-time record was found to be similar regardless of the sampling points. This was considered proof of adequate mixing.

Because the circulating medium was not blood but tap water, it was necessary to correct the thermodilution cardiac outputs by a factor which allowed for the different specific gravity (SG) and specific heat (SH) of these two liquids. The formula for calculation of cardiac output in these computers is:[7]

$$Vb = \frac{Vi \times (Tb-Ti) \times 60 \times 1.08}{A}$$

where

Vb = cardiac output in ml/60 sec

Vi = volume of injectate in ml

Tb,Ti = temperature of blood and indicator respectively

a Lab-Line®, magnestir bath; Melrose Park, IL 60160
b Lab Glass®, Vineland, NJ 08360
c Fisher®, model 120M, Itasca IL 60143
d Tygon®, Akron, OH 44309
e Sarns®, model 7000 MDX; Ann Arbor, MI 48106
f Swan-Ganz®, American Edwards Laboratory, Anasco, Puerto Rico, 60610
g Grass Instruments, Quincy, MS 02100

A = area under the temperature-time curve in °C x seconds

The number 1.08 in the numerator of the equation is equal to:

$$\frac{\text{Specific Gravity x Specific Heat (Indicator)} = .98}{\text{Specific Gravity x Specific Heat (Blood)} = .91}$$

and assumes the indicator is 5% dextrose in water, or normal saline, and that it is being injected into blood. When using tap water as the circulating medium this ratio becomes equal to $\frac{.98}{1}$.

Thus all cardiac outputs were multiplied by a correction factor, .91 equal to .98/1.08.

We tested the thermodilution cardiac output signal from three different computers. The test injectate for a given instrument was the same as the one we had been accustomed to using in day-to-day practice. The computer and quantity of indicator used were:

Computer A) Columbus Instruments® , Cardiotherm-500;[h] 6 cc 5% D/W at room temperature, delivered manually over a period of 3 or 4 seconds.

Computer B) Edwards® cardiac output computer, model 9520,[i] 5 cc 5% D/W at 0-5 °C, delivered manually over a period of 3 or 4 seconds.

Computer C) Edwards® lung water computer, model 9310;[i] 10 cc isotonic saline at 0-4 °C, delivered by a pneumatic autoinjector.*

Each computer was appropriately adjusted for the catheter and injectate used. A temperature probe sat in the injectate liquid used by computer A and B and constantly reported injectate temperature to its respective computer. Computer C was not equipped with such a probe and it assumed injectate temperature.

When all of the above preparations were satisfactorily completed, five determinations of flow measured by thermodilution were made at any true flow by timed volume collection. The duration of time between each injection was standardized at 90 seconds. With the graduated cylinder and observer eye at the same level, the time required for volume to increase by 1-5 liters, depending on flow rate, was measured by stop watch. Accuracy of flow by the thermodilution technique was defined to be the difference between the average of 3 timed collections and the average of 5 determinations of flow by indicator dilution. Each difference represented the error of the thermodilution technique relative to the true flow. For a given computer these differences were tested for significance using a paired t-test (two tailed). Regression equations further defined the relationship between computed and true flow for each computer. The slope and intercept of these lines were compared to the line of identity.

*The syringe in the injector, Columbus Instruments®, thermodilution injector 500, [h] filled automatically from a 500 cc bag of iced saline after each injection. To minimize any error due to warming of the injectate between a series of measurements, the syringe was filled with iced saline immediately prior to a new series of measurement.

h Columbus, OH 43204

i American Edwards Laboratory, Irvine, CA 92701

Results

The response of each computer was reproducible and relatively accurate (Table 1). The best reproducibility (coefficient of variation) was seen in computer A, where room temperature injectate was used. In general, however, the average coefficient of variation remained stable at 7% or less. The error at each flow rate is given in column 4. In one computer, C, the error of the thermodilution technique relative to the true flow was significant.

Although the displayed cardiac output of each computer was linear ($r > .99$), they all departed somewhat from the line of identity (Figure 2). Computer A

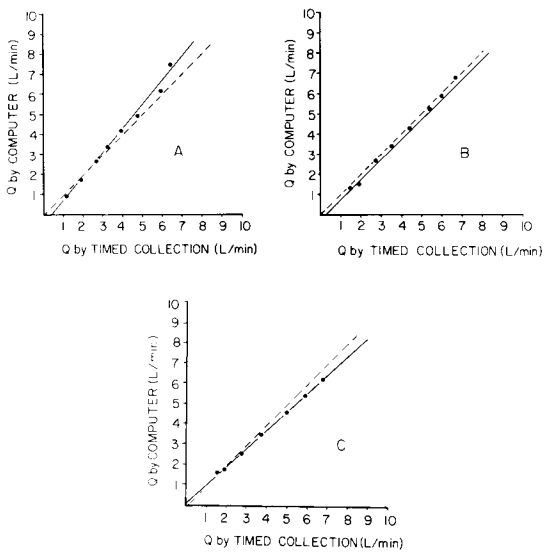

Figure 2: Individual regression lines. Interrupted line is line of identity.

slightly underestimated at low flows and slightly overestimated at high flows. Computer B systematically underestimated true flow by 280 cc/min. Computer C increasingly underestimated flow above 1.5L/min. In none of the computers did the 95% confidence limits around both the estimated slope and intercept include the slope and intercept of the line of the identity (Table 2).

Discussion

We have presented our experience with a bench model designed for calibration of thermodilution car-

Table 1
Computed and True Flows ($\dot{Q}$)

$\dot{Q}$ by Computer (L/min)		True Q (L/min)	Error	
Mean ± SD	SD/Mean x 100+	Mean ± SD	$\dot{Q}$(True)-$\dot{Q}$(Comp)	
Computer A				%
.86 ± .05	5.8%	1.10 ± .01	.24	(22)
1.73 ± .06	3.5	1.81 ± .07	.08	(4)
2.57 ± .08	3.1	2.59 ± .08	.02	(1)
3.37 ± .13	3.9	3.22 ± .06	-.15	(5)
4.15 ± .15	3.6	3.94 ± .15	-.21	(5)
4.86 ± .14	2.9	4.14 ± .05	-.12	(3)
6.15 ± .51	8.3	5.86 ± .03	-.29	(5)
7.44 ± .22	3.0	6.36 ± .04	-1.08	(17)
Mean	4.3 ± 1.9		-.19 ± .40	(7.8 ± 7.5)
Computer B				
1.28 ± .11	8.6%	1.44 ± .02	.16	(11)
1.55 ± .16	10.3	1.91 ± .01	.36	(19)
2.64 ± .06	2.3	2.72 ± .09	.08	(3)
3.43 ± .23	6.7	3.42 ± .06	-.01	(0)
4.24 ± .29	6.8	4.42 ± .06	.15	(3)
5.25 ± .52	9.9	5.38 ± .11	.13	(2)
5.84 ± .33	5.7	5.97 ± .06	.13	(2)
6.76 ± .40	5.9	6.63 ± .07	-.13	(2)
Mean	7.03 ± 2.6		.11 ± .14	(5.3 ± 6.5)
Computer C				
1.43 ± .10	7.0%	1.46 ± .04	.03	(2)
1.79 ± .14	7.8	1.91 ± .03	.12	(6)
2.57 ± .12	4.7	2.87 ± .04	.30	(10)
3.46 ± .20	5.8	3.77 ± .03	.31	(8)
4.50 ± .31	6.9	4.96 ± .03	.46	(9)
5.33 ± .40	7.5	5.87 ± .01	.54	(9)
6.10 ± .34	5.6	6.65 ± .09	.55	(8)
Mean	6.5 ± 1.1		.33 ± .20*	(7.4 ± 2.7)

All values are mean ± SD
+ Coefficient of variation; * Significant error by paired t-test ($p < .005$)

Table 2
Regression Equations; True $\dot{Q}$ = $\frac{\text{computed } \dot{Q}\text{-B}}{\text{M}}$

Computer	Slope (M)	Intercept (B)	R^2	Difference from slope = 1	95% Confidence interval of slope	Difference from intercept = 0	95% Confidence interval of intercept
A	1.18	-.48	99.1%	$p < .01$	± .170	$p < .05$	± .380
B	1.04	-.28	99.7	NS	± .087	$p < .05$	± .011
C	.90	+.06	99.9	$p < .001$	± .035	NS	± .117

Regression equations describing the relationship between computed and true flow. The confidence intervals provide information about the accuracy of our calibration. In effect they are saying that if we were to repeat the calibration one hundred times, we would expect to fall within the confidence interval ninety-five times.

diac output computer and catheter systems. The model that has been used is a modified version of one originally designed by Joel Davis and reported in *The Journal of Extra-Corporeal Technology*.[5] Our system differs from his in three respects: 1) tap water, rather than blood, is used as the circulating medium, 2) true flow is measured directly by timed volume collection rather than by electromagnetic flowmeter, 3) a magnetic stirrer rather than an in-line prosthetic heart valve is used to effect mixing. These modifications were intended to simplify the methodology, thus rendering it more accessible, without compromising on any theoretical considerations. The interpretation of the results of this in vitro comparison of true flow versus thermodilution measured flow is dependent upon the acceptance of the model as a satisfactory simulator of cardiac function as related to the thermodilution method.

Our analysis revealed small inaccuracies in each of our computer-catheter systems. These inaccuracies might have had their source(s) in the computer, the catheter, the signal, i.e.: the volume and temperature of the injectate, or the model itself. Although no attempt was made to pinpoint the source(s)—the error described is that which resulted when the measurements were carefully conducted exactly according to instructions but in an unnaturally stable and controlled environment—it is nevertheless very unlikely that a significant error existed in either the catheters or computers, as the catheters themselves were new and the computer electronics always checked out. Likewise, limitations of the model are unlikely to account for a significant portion of the measured error. See later discussion. In keeping with what is widely held to be true, it is much more probable that unavoidable inaccuracies in the signal itself best explain our results. To overcome these inaccuracies it would be necessary to design a catheter that could instantly report to the computer the exact amount of indicator delivered to the circulation. Until such a catheter is available, signal errors can only be minimized by carefully following the "instructions for use" suggested by the instrument manufacturer.

Although the reproductibility of serial measurements with each system tested was good, it was not as good as the more precise calibration done by Powner and Snyder.[4] Using their much more sophisticated model the standard deviation of 5-10 serial measurements at the same flow rate was between .02 and .20 versus .05 and .52 in our own study. These differences in reproducibility could be explained by their practice of routinely discarding the first measurement of any series as a means of preventing bias from the initial temperature equilibration of the catheter—a practice that we neglected to incorporate, but in retrospect we recommend.

In order to relate the calibration to our in vivo measurements, the injectate delivery techniques and the size of the signals that we used in vitro were the same as those we were accustomed to using in vivo. Because it was not our intention to compare systems, these were not standardized. Using the regression equations from Table 2, which relate computed to true flow, the computed flows from each system could be corrected for error. For example, if computer A registers a flow of 5.50 L/min the true flow

$$= \frac{5.50 - (-0.48)}{1.18}$$

$$= 5.07 \text{ L/min}$$

If true $\dot{Q}$ in vivo were 5.07 L/min, and the clinical circumstances were relatively stable, eg: the cardiac

catheterization laboratory, where the patient is breathing spontaneously and catheter position is verified fluoroscopically, the error of the in vivo measurement is likely to approximate the error quantitated by the in vitro calibration. However, under less stable circumstances, for example in critically ill patients receiving mechanical ventilation, the error of the in vivo measurement is likely to exceed that anticipated from the in vitro calibration.[8,9,10] Under these circumstances one could not use the in vitro error to estimate the in vivo error and the utility of the calibration would lie in assuring the operator of the accuracy and reproducibility of his instruments and technique. With regard to the effect of injectate's volume and temperature on accuracy and reproducibility in the critically ill patient, Elkayam et al have found that the use of 10 ml at room temperature and 5 ml of iced injectate is comparable in reproducibility and accuracy to the standard technique (using 10 ml of iced injectate)[2] The use of 5 ml at room temperature and 3 ml of iced injectate is associated with a marked decrease in reproducibility but it provides accurate results, especially when cardiac output is reported as a mean value of five consecutive or the three middlemost determinations.[2]

Three characteristics of the model require special comment:

a) Catheter constant. It was assumed that the use of water instead of blood as the circulating medium would have a neglible effect on the "catheter constant"—a factor dialed into the computer at the time of use that corrects for the amount of indicator lost during passage through the injection lumen.

b) Weakly pulsatile flow. It is important to note that flow within this model is more constant than it is pulsatile. In fact, this is an advantage, because the formula used in these computers (the Stewart-Hamilton equation) is a constant flow equation.[13] It is fortunate that the washout curve recorded distal to an effective mixing region is essentially exponential for steady and pulsatile flow, provided the stroke volume and rate of pulsatile flow remain unchanged. This has been shown to be true for pulsatile flow in models and in heart-lung preparations. Therefore, the Stewart-Hamilton equation can give satisfactory mean flow measurements under appropriate conditions for both types of flow. It is acknowledged, however, that this study does not address the sensitivity of each computer to error from time-varying flow.

c) A constant and unidirectional temperature drift. Before any simultaneous determinations of flow were made, the rate of fall of temperature at the thermistor during a very low flow state (1 L/min) was measured and found to be .06 °C/min. This was identical to the rate of fall of temperature in the water bath during the time that the normothermia unit of the bath was not in its active heating phase (during the active heating phase thermodilution determinations are not possible). Since a thermodilution cardiac output determination at a flow of 1 L/min would take 30 seconds or less, it would be occurring on a drift of .03 °C. Although cyclical temperature variations of .01-.02 °C are seen in the pulmonary artery during spontaneous ventilation, these fluctuations are associated with a stable mean temperature.[11,12] The temperature drift seen in this bench model is analogous to that seen in a patient or laboratory animal whose whole body temperature is falling. It is capable of causing a small underestimate of flow by shifting upward the temperature-time curve (Figure 3) and thus increasing the area below it—which is the denominator of the Stuart-Hamilton equation.* Thus, a very small systematic underestimate of flow was expected in this model. Although on the one hand this error may be avoided by a constant temperature reservoir, it may be increased if cold-injectate-containing fluid is recirculated back into a small (< 3-4 gallon) reservoir.

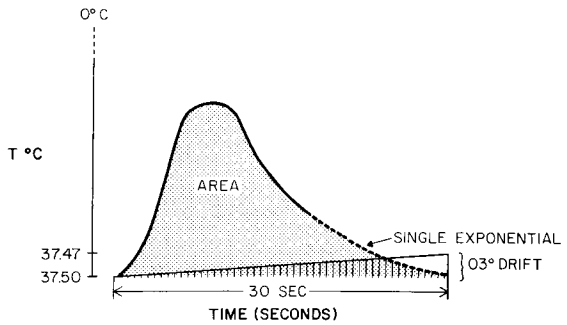

Figure 3: Error due to temperature drift.

In conclusion, the computer-catheter systems and technique used at our institution to measure cardiac output by the thermodilution method were calibrated in vitro with a relatively simple flow-bench model. The inaccuracies described in this idealized environment

*The situation is not perfectly analagous, in that our circuit was surrounded by air at room temperature. To isolate any error due to differences in thermal conductivity between our system and the in vivo state, we immersed our flask in water at 37 °C and pumped this water through the circuit. With the circulating water and the water jacket at the same temperature and falling at the same rate, .06 °C/min, the flow was measured by thermodilution technique. For the same true flow, we found no difference between the computed flow with this system as compared to the system surrounded by air. To ensure that the amount of indicator lost between the site of injection and the site of detection is negligible, it is advisable that the catheter-bearing portion of the circuit be surrounded by an insulator, such as bubble wrap.

are a quantification of the minimum error that is likely to be encountered when $\dot{Q}$ is measured in vivo by thermodilution technique. This calibration added to our ability to interpret what were often suspect measurements of flow in vivo.

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