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Comparison of Methods of Measuring Cardiac Output in Newborn Lambs

JAAP R. G. KUIPERS, DANIEL SIDI, MICHAEL A. HEYMANN,[18] AND ABRAHAM M. RUDOLPH

Cardiovascular Research Institute and the Departments of Pediatrics, Physiology, and Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California, USA

Summary

To define agreement between methods, we measured cardiac output (CO) in chronically instrumented lambs by four different methods. In 23 lambs we measured CO simultaneously by the Fick and microsphere methods and with an electromagnetic flowmeter over a wide range of CO (80–454 ml/kg/min) in different experimental conditions on 97 occasions. When the electromagnetic flowmeter was corrected for coronary flow (about 8% of CO) calculated from microspheres, the mean cardiac outputs were almost identical for these three methods (237, 235, and 236 ml/kg × min, respectively). Comparisons between any two of the methods showed a correlation coefficient greater than 0.89. In four lambs, 52 measurements of CO by Fick and thermodilution had a correlation coefficient of 0.94. We conclude that any of the four methods, if appropriately applied, adequately measures CO in a variety of circumstances and may be used with confidence for physiologic or other studies.

Speculation

In newborn and young animals cardiac output can be measured with equal accuracy by any of four different techniques when appropriately applied. These methods can be used with confidence in future studies of the newborn circulation.

Changes in cardiac output after birth have been studied by several groups in newborn lambs (2, 5, 7, 8, 14). Although data from these studies demonstrated a gradual decrease in cardiac output related to body weight in the first 8 wk after birth, there were differences in the actual values of cardiac output at rest. These differences could be due to variation in breed or to the experimental conditions. They could also have been related to differences in the methods used for measuring cardiac output.

To determine whether the observed differences in cardiac output were due to the various methods used, we measured cardiac output simultaneously by the Fick and microsphere techniques and with an electromagnetic flowmeter after recovery from thoracotomy in lambs of different ages. We also measured cardiac output simultaneously by the Fick and thermodilution techniques. To assess the correlations among the different methods over a wide range of cardiac output, we modified cardiac output by inducing various types of stress in the lambs.

MATERIALS AND METHODS

We studied 27 lambs of mixed western breed. The date of birth was documented. Two groups of studies were performed. In the first group of 23 lambs (ages 5–58 days, weights 3.2–14.5 kg), we measured cardiac output simultaneously by Fick and microsphere methods and with electromagnetic flowmeters following a thoracotomy performed 2–46 days after birth. In the second group of four lambs (ages 2–13 days, weights 3.5–6.4 kg), we measured cardiac output simultaneously by the Fick and thermodilution methods after inserting catheters through vessels in the neck on the second day after birth.

Preparation. In lambs in group I, a thoracotomy was performed in the third or fourth left intercostal space under general anesthesia with halothane (Fluothane$_R$) using methods we have reported previously (5). Briefly, the pericardium was incised and polyvinyl catheters were inserted through pursestring sutures directly into the main pulmonary artery and through the left atrial appendage into the body of the atrium. Closure of the ductus arteriosus was confirmed by palpation. A precalibrated electromagnetic flow transducer (C. & C. Instruments, Culver City, CA) (I.D., 7–14 mm) was selected to fit without constriction and was placed around the ascending aorta just above the coronary arteries. Polyvinyl catheters were inserted into an artery and a vein in the hind leg and advanced so that their tips lay in the mid-abdominal aorta and inferior vena cava. A third was inserted into the carotid artery. In some lambs a polyvinyl catheter (O.D., 4 mm) was inserted into the jugular vein. The lambs were allowed to recover 48 h before studies were done.

Into the four lambs in group II, under local anesthesia, a polyvinyl catheter (I.D., 1 mm) was inserted via the carotid artery into the aorta. A 5F KMA thermodilution catheter was passed into the jugular vein and advanced, while pressure was monitored, to the pulmonary artery. The lambs were allowed to recover for at least 12 h.

Procedure. For each experiment, the lamb was removed from the ewe, weighed, and placed in a sling so that it was supported in an upright position; the lambs were not sedated but were blindfolded to aid in keeping them calm. They rested quietly and often fell asleep during the course of the studies. Several manipulations were made to change cardiac output and thereby evaluate the four techniques under a wide range of conditions. These included infusion of sodium nitroprusside, volume loading, hypoxia, and beta-adrenergic blockade but not all were done in the same lambs. After control measurements had been made, nitroprusside was infused in amounts of either 5 or 10 μg/kg × min for 1–2 h. Volume loading was achieved by infusion of 0.9% NaCl solution at 40°C at a rate of 25 ml/kg × min for 2 min. Left atrial pressure was raised to levels above 15 mmHg and stayed constant for 3–5 min after the infusion. It is during this brief period of steady state that the comparisons of cardiac output were made. Volume loading studies also were done in some lambs during infusion of nitroprusside. The hypoxic studies were performed by administering 15, 12, 9, or 6% oxygen in nitrogen through a plastic bag surrounding the head and neck. Beta-adrenergic blockade was achieved by intravenous injection of 0.5 mg/kg of propranolol repeated every 30 min. Beta adrenergic blockade also was done in some lambs during hypoxia.

Measurement of cardiac output. All measurements used for the comparisons during volume loading were made during the steady state period of 3–5 min. For the other manipulations we did not measure cardiac output by the Fick or microsphere method if the arterial blood O_2 saturation, heart rate, or blood pressures were unstable. Absence of intracardiac or ductus arteriosus shunting

was confirmed by qualitative indocyanine green indicator dilution curves and by direct palpation in those animals in which a thoracotomy was performed.

Fick method. Oxygen consumption was measured by a continuous flow-through system that we have described previously (6). The face mask, placed around the mouth and nose for collection of the expired air, was enclosed within the bag surrounding the head and neck during hypoxia. The hypoxic gas was blown through the bag in an amount greatly exceeding the minute ventilation of the lamb, so that no air was drawn into the bag. Before each measurement of O_2 consumption, the fraction of inspired O_2 was checked on a sample of the inspired gas passing from the gas mixer to the O_2 analyzer. Paired blood samples were withdrawn slowly and simultaneously from the aorta and the pulmonary artery. These samples represented arterial and mixed venous blood, respectively. Oxygen content of arterial and mixed venous blood were calculated from O_2 saturation and hemoglobin concentration measured in a microoximeter (Radiometer OSM2 Hemoximeter). Oxygen capacity was calculated by multiplying the hemoglobin concentration by a factor of 1.36. We have shown previously that this method provides accurate measurements of O_2 content (7).

Microsphere method. Left ventricular output and blood flow distribution were determined with radionuclide labeled microspheres by injecting 15 μ microspheres into the left atrium while reference samples were withdrawn into preweighed syringes from the descending aorta and the carotid artery (4) for 1 or 1.25 min at a rate of 7 ml/min. At the end of the studies the lambs were killed with an intravenous injection of sodium pentobarbital. The lambs were dissected as previously described (9). Their individual organs were incinerated in an oven and counted for radioactivity in a 1000-channel (Ino-tech, Inc., Fort Atkinson, WI) pulse height analyzer. Blood flow to the various organs was calculated with the aid of a 370 IBM computer. Cardiac output was measured by determining radioactive counts of the entire animal.

Electromagnetic flowmeter. Left ventricular output minus coronary blood flow was measured with a precalibrated flow transducer connected to a Statham SP2202 flowmeter and was recorded on a Beckman dynograph. The electromagnetic flow transducer and flowmeter system had a frequency response of 100 Hz, a reproducibility of ±2%, and a 5% error. After the lamb was killed, the position of the flow transducer was checked and the calibration factor was confirmed.

In the lambs in group I, values of cardiac output were obtained from the flowmeter, O_2 consumption was read, and blood samples for O_2 content were obtained just before the injection of the microspheres.

Thermodilution method. Right ventricular output was determined by injecting 3 ml of iced solution of 0.9% NaCl into the proximal hole of the thermodilution catheter. The change in temperature of the injectate solution was sensed by the thermistor located at the tip of the catheter; cardiac output was calculated by the KMA thermodilution computer which used the Stewart-Hamilton equation.

In the lambs in group II, measurement of cardiac output by the Fick method preceeded the injection of iced saline by less than 1 min. In this group of newborn lambs the absence of intracardiac or ductal shunt during hypoxia was reconfirmed by indicator dilution curves at the end of each hypoxia experiment.

Analysis. We calculated the linear regression lines for the values of cardiac output obtained by the different methods and compared one to another. To determine if an observed regression line differed from the expected line ($y = a + bx$, where $a = o$ and $b = 1$; $r = 1$), we used analysis of covariance to compare the residual variances, the slopes, and the intercepts of the two regression lines (10). For this latter analysis, $P < 0.05$ was considered significant.

RESULTS

Group I. We obtained 97 simultaneous measurements of cardiac output by Fick and microsphere methods and by electromagnetic flowmeter. They were obtained in the following circumstances: 31 control measurements; 4 during volume loading; 16 during nitroprusside infusion, 4 of which also were during volume loading; 7 after propranolol; and 39 with various degree of hypoxia including 12 with propranolol. The cardiac output ranged from 80–454 ml/kg × min. The electromagnetic flow transducer was positioned on the aorta above the origin of the coronary arteries and thus measured left ventricular output minus coronary blood flow. Since we could calculate coronary blood flow from the microsphere studies, we have also reported the flows measured with the electromagnetic method corrected for coronary flow by adding this value.

The mean values of cardiac output measured by each of the three methods (Table 1) were almost identical when the flow transducer values were corrected for coronary blood flow (which averaged about 8% of cardiac output). The comparisons between the methods were also very good (Table 2). The mean and S.D. of the individual % differences (Table 2) demonstrate a significant scatter, particularly in those comparisons that considered the microsphere method. Four of the measurements by microspheres were more than 30% different from both the Fick method and the electromagnetic flowmeter (Table 2). The comparison of cardiac output measured simultaneously by Fick (x) and electromagnetic flowmeter (y) had a regression $y = 0.82x + 20.7$; $r = 0.93$ (Fig. 1, left panel). After correcting cardiac output as measured by the electromagnetic flowmeter for coronary blood flow, the regression line was almost the same as the line of identity, $y = 0.99x + 2.6$, $r = 0.95$ (Fig. 1, right panel). The comparison of cardiac output measured simultaneously by microspheres (x) and electromagnetic flowmeter (y) had a regression line $y = 0.76x + 38.6$; $r = 0.90$ (Fig. 2, left panel). When the correction for coronary flow was made, the regression line was $y = 0.92x + 21.7$; $r = 0.92$ (Fig. 2, right panel). The comparison of cardiac outputs measured simultaneously by Fick (x) and microspheres (y) was $y = 0.93x + 14.0$; $r = 0.89$ (Fig. 3).

Group II. Fifty-two simultaneous measurements of cardiac output were made by Fick and thermodilution methods. In 22 studies, the lambs were resting quietly in a warm (25°C, 13 studies) or a cool environment (17°C, 9 studies). In 30 studies the measurements were made during hypoxia ($FIO_2 = 0.09$) including 13 measurements in a cool environment. Values of cardiac output ranged between 156–594 ml/kg × min (840–2365 ml/min) for the measurements with the Fick method. The mean cardiac output by the Fick method was 375 ± 79 ml/kg × min (mean ± S.D.) and by the thermodilution method was 388 ± 91 ml/kg × min (mean ± S.D.). The mean and S.D. of the individual differences was 3.5 ± 9.6% of total cardiac output measured by the Fick method and 7.7% of the measurements had differences greater than 20%. Comparison of Fick (x) and thermodilution (y) measurements had a regression line $y = 1.03x + 1.3$; $r = 0.94$.

The calculated slopes for the four different methods of measuring cardiac output are shown in Figure 4.

DISCUSSION

This study shows that there is a good correlation among all the methods used in our laboratory to measure cardiac output in

Table 1. *Mean, S.D., and range of 97 simultaneous measurements of cardiac output in 23 lambs*

	(ml/kg × min)		(ml/min)	
	Mean ± S.D.	Range	Mean ± S.D.	Range
Fick	237 ± 73	92–440	1610 ± 254	634–3810
Microspheres	235 ± 76	124–454	1578 ± 277	685–3786
Flow transducer	217 ± 64	80–364	1454 ± 212	475–3100
Flow transducer + coronary blood flow	236 ± 75	85–438	1603 ± 267	523–3636

Table 2. *Mean and S.D.(s) of the individual % differences between 97 simultaneous measurements of cardiac output in 23 lambs (see text)*[1]

x	y	$\frac{[q(y) - q(x)]}{q(x)}$ %	s %	n′ %	n^2 %
Fick	Microspheres	−0.6	15.0	16.5	4.1
Fick	Flow transducer	−8.5	10.1	10.3	1
Fick	Flow transducer + coronary	−0.3	7.5	7.5	0
Microspheres	Flow transducer	−7.6	12.5	15.4	4.1
Microspheres	Flow transducer + coronary	+1.3	11.5	9.4	2.1

[1]n′, n^2 = % of observations in which the difference between two methods is greater than ± 20% (n′) or ± 30% (n^2); q(x) and q(y) = cardiac outputs obtained by the methods indicated under x and y, respectively.

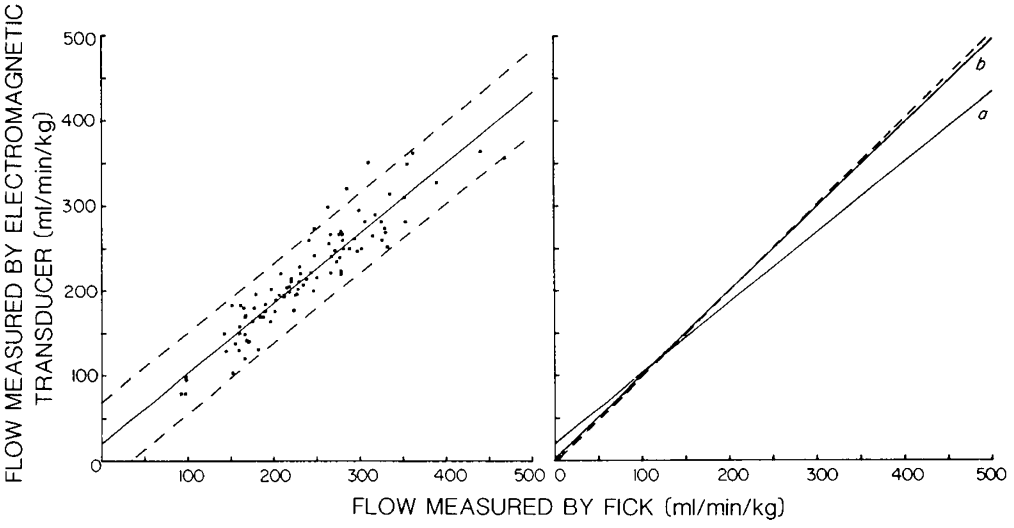

Fig. 1. Comparison of 97 measurements of cardiac outputs by electromagnetic flowmeter (y) and Fick (x) methods in 23 lambs. (*Left*) Electromagnetic flow values not corrected for coronary flow. The dashed lines show the 95% confidence limits for the data. (*Right*) The comparison of the regression line obtained before (a) and after (b) addition of coronary flow to the electromagnetic flowmeter cardiac outputs. The dotted line is the line of identity (see text).

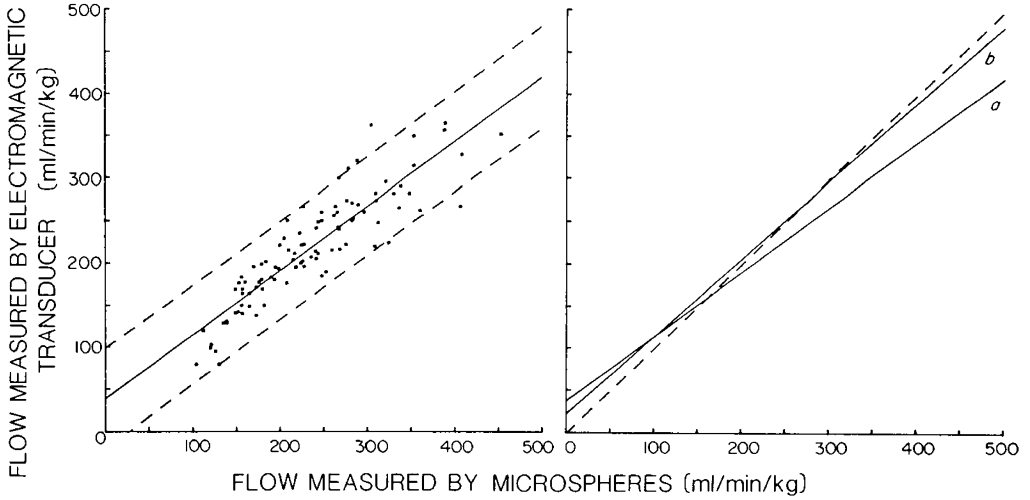

Fig. 2. Comparison of 97 measurements of cardiac outputs by electromagnetic flowmeter (y) and microsphere (x) methods in 23 lambs. (*Left*) Electromagnetic flow values not corrected for coronary flow. The dashed lines show the 95% confidence limits for the data. (*Right*) The comparison of the regression line obtained before (a) and after (b) addition of coronary flow to the electromagnetic flowmeter cardiac outputs. The dotted line is the line of identity (see text).

lambs of different ages and over a wide range of cardiac output induced by various cardiovascular manipulations. Examination of the various sets of cardiac output show that there is a random symmetric scatter of observations on either side of the line of direct proportionality among Fick, microspheres, and thermodilution methods. For the measurements by electromagnetic flow transducer, the correlation improved greatly by adding coronary blood flow (Figs. 1 and 2, right panels). Under resting conditions, coronary blood flow constitutes about 5% of left ventricular output; however, when coronary blood flow increases, it could account for a much higher % of left ventricular output. Under these circumstances, a large error can be made if cardiac output is

measured by electromagnetic flowmeter. For example, during hypoxia, coronary blood flow averaged 15%. In some instances it was 30% of left ventricular output (Sidi, unpublished observations). Most of the higher values of cardiac output were obtained during hypoxia; this explains the shift in the regression line away from the line of identity at the upper end of the range of cardiac outputs when uncorrected electromagnetic flow values were used (Figs. 1 and 2, right panels). This error, associated with failure to include coronary blood flow in the cardiac output measurement, could be avoided by placing the transducer around the pulmonary artery. But in our experience with newborn lambs, as pulmonary arterial pressure falls after birth, the electromagnetic flow signal may be interfered with and reliable flow tracings may not be obtainable for a few days until good electrode contact is established.

The distinct advantages of the electromagnetic flowmeter are that it allows continuous measurement of cardiac output without any injection or sampling of blood and even a short steady state is not required. This makes this method preferable to others when registration of instantaneous changes are important or for evaluation of beat-to-beat changes. The use of an electromagnetic flow transducer requires a thoracotomy and a recovery period of at least 2–3 days (Sidi et al, personal observations) before starting the studies. This could preclude obtaining measurements of cardiac output at a time when major cardiovascular readjustments are occurring. In addition, in a fast growing animal, the flow transducer can become obstructive after a certain period of time estimated as 2–3 wk for newborn lambs (5). The other methods have the advantage that they do not require thoracotomy, thus permitting chronic studies to be started very shortly after the instrumentation of the animal.

Since we can measure oxygen consumption continuously by the flow-through system previously described (6), we have found the Fick method most convenient. Previously, it has been technically difficult to measure oxygen consumption in conscious animals breathing low O_2 gas mixtures. We overcame this by using the technique described. One limitation of the Fick method is the requirement for a period of steady state during which oxygen consumption, blood oxygen contents and flow must be stable (12). Another limitation is that blood loss may be considerable if a large number of measurements are made in small animals.

The thermodilution method allows instantaneous measurements of cardiac output (11, 13) but frequent repeated measurements may be associated with fluid overloading, especially in small animals. Another limitation of the thermodilution method is the stiffness of the commercially-available catheters. These catheters may perforate the right ventricle, particularly in young animals. Also, in prolonged chronic studies, the tip of the catheter may become covered with fibrin and temperature recordings may be inaccurate.

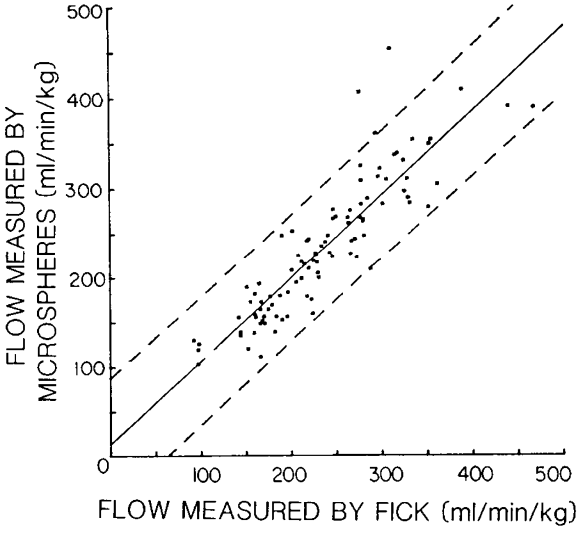

Fig. 3. Comparison of cardiac output by the microsphere (y) and Fick (x) methods on 97 measurements from 23 lambs. Dashed lines show the 95% confidence limits for the data.

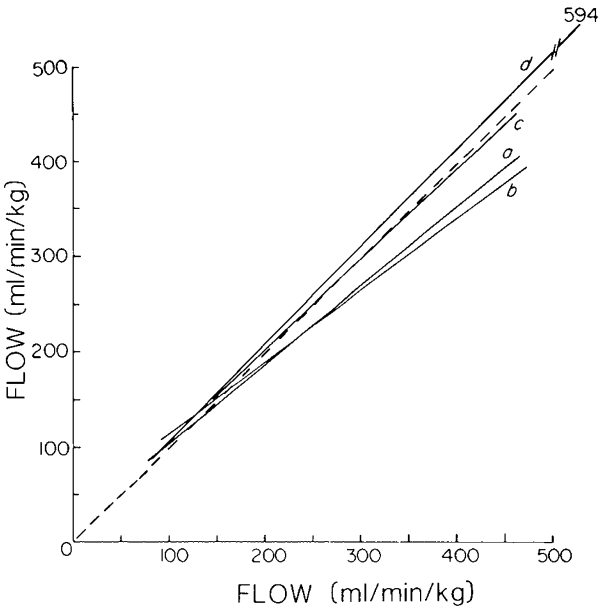

Fig. 4. Calculated slopes of the four sets of results: (*a*) comparison of electromagnetic flowmeter, not corrected for coronary blood flow (y) and Fick (x); (*b*) comparison of electromagnetic flowmeter, not corrected for coronary blood flow (y) and microsphere (x); (*c*) comparison of microsphere (y) and Fick (x); and (*d*) comparison of thermodilution (y) and Fick (x). The dotted line is the line of identity.

The microsphere method allows a limited number of measurements of cardiac output. It also requires a short steady state period during the period of injection (1). Errors may occur if changes in cardiac rhythm are induced by the injection of the microsphere into the cardiac cavity. It is possible that on the few occasions when cardiac output measured by the microsphere method differed greatly from the Fick and flowmeter recordings, cardiac arrhythmia was present. Another potential error with the microsphere method is inadequacy of mixing (3), particularly if the injection is made into the left ventricular cavity entered by retrograde passage of a catheter from a peripheral artery. The necessity to withdraw a large amount of blood is also a limitation in small animals. Despite these difficulties, the microsphere method has the distinct advantage that it can be used to measure blood flow to all organs in the body. It is also the only method by which cardiac output can be measured when there is an intracardiac or ductal left-to-right shunt, and also by which the shunt can be evaluated. This could be very useful in the neonatal period.

In conclusion, we have found excellent correlation among the four methods that we used for measuring cardiac output. The preferred method for measuring cardiac output should be based on the objectives and conditions of the studies planned.

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15. The current address of J. R. G. Kuipers: University of Groningen, Academic Hospital, Department of Pediatric Cardiology, Oestersengel 59, 9713 EZ, Groningen, The Netherlands.
16. The current address of D. Sidi: Service de Cardiologie Infantile, Hôpital Necker-Enfantes Malades, Rue Sevrès, Paris 75015, France.
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18. Requests for reprints should be addressed to: Dr. M. A. Heymann, 1403-HSE, University of California, San Francisco, CA 94143.
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