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Noninvasive determination of cardiac output in a model of acute lung injury [Laboratory Investigation]

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Abstract

Objective: To examine the utility of single breath CO_2 analysis as a noninvasive measure of cardiac output in a model of acute lung injury.

Setting: An animal laboratory in a university-affiliated medical center.

Design: A prospective, animal cohort study comparing 21 parameters derived from single breath CO_2 analysis with cardiac output determined by an ultrasonic flow probe.

Subjects: Six adult sheep with saline lavage-induced acute lung injury.

Interventions: Animals were treated with repetitive saline lavage to achieve a uniform degree of acute lung injury (PaO_2 of <100 torr [<13.32 kPa] on an FIO_2 of 1.0). Cardiac output was manipulated by successive injections of an hydraulic constrictor placed around the inferior vena cava and measured using an ultrasonic flow probe. Twenty-one derived components of the CO_2 expirogram were evaluated as predictors of cardiac output.

Measurements and Main Results: Thirty-eight measurements of cardiac output were available for comparison with derived variables from the CO_2 expirogam. Stepwise linear regression identified four variables for the equation predicting cardiac output: a) PaO_2/FIO_2 ratio; b) the angle between the slope lines for phases II and III divided by the tidal volume; c) mixed expired CO_2 tension; and d) physiologic deadspace to tidal volume ratio. The multivariate equation was highly statistically significant and explained 80% of the variance (adjusted R^2 = .80, p < .0001). The bias and precision of the calculated cardiac output were .00 and .38, respectively. The mean percent difference for the cardiac output estimates derived from the single breath CO_2 analysis station was -0.01%.

Conclusions: Our results indicate that changes in cardiac output can be determined using

components of the CO_2 expirogram with a high degree of reliability in animals with induced acute lung injury. Specifically, the use of four parameters derived from a plot of expired CO_2 concentration vs. expired volume predict changes in cardiac output in adult sheep with induced lung injury with an adjusted coefficient of determination of .80. Prospective application of this technology in the clinical setting with the rapidly changing physiology that is characteristic of the acutely ill patient will be essential in determining the clinical usefulness of single breath CO_2 analysis as a noninvasive measure of cardiac output. (Crit Care Med 1997; 25:864-868)

KEY WORDS: CO_2, elimination; cardiac output; deadspace; gas exchange; mechanical ventilation; respiration disorders; ventilators, mechanical; ventilation perfusion ratio

Noninvasive determination of cardiac output offers the potential to provide meaningful information regarding hemodynamics, oxygen delivery, and cardiopulmonary interaction during mechanical ventilation without the risks of pulmonary artery catheterization. Single breath CO_2 analysis provides breath to breath information regarding the efficiency of gas exchange and the relationship between pulmonary blood flow and alveolar ventilation [1]. We have previously described a recently developed device for single breath CO_2 analysis [2] and reported our initial experience with the noninvasive determination of cardiac output using single breath CO_2 analysis in a healthy animal model [3]. In the present study, we extend our previous observations in a saline-lavaged animal model of acute lung injury.

MATERIALS AND METHODS

The hardware and software utilized in the analysis of the CO_2 expirogram have been previously described [2]. The derived components of the CO_2 expirogram that were evaluated in the present study included 21 parameters previously described in the prediction of cardiac output in healthy animals [3], as well as the PaO sub 2/FIO_2 ratio.

Animal Preparation.

This protocol was approved by the Animal Care and Use Committee of Children's Hospital and the animals were handled according to the Guidelines for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Council (DHHS Publication No. [National Institutes of Health] 85-23, 1985). Adult sheep were induced with intramuscular ketamine (20 to 30 mg/kg) and intubated orally with a 7.5-mm inner diameter endotracheal tube (Mallinckrodt, Glenn Falls, NY). After the establishment of adequate intravenous and arterial access, maintenance anesthesia was provided by halothane (0.5% to 1.0% inspired) and muscle relaxation by pancuronium (0.2 mg/kg/hr). Controlled ventilation was delivered throughout the protocol at standardized ventilator settings, using a volume-cycled ventilator (Emerson 3MV-Ped, Emerson Equipment, Cambridge, MA): FIO_2 = 1.0, tidal volume 10 to 12 mL/kg, with rate adjusted to achieve $PaCO_2$ between 35 and 45 torr (4.66 and 5.99 kPa).

In order to provide a stable model of acute lung injury, the animals underwent repetitive lung lavage using warmed physiologic saline, as has been previously described [4]. During lavage, the animals were ventilated with an FIO_2 of 1.0 and 35 to 40 mL/kg of warmed normal saline was instilled in 60-mL aliquots via the endotracheal tube. Instillation lasted [approximately]3 to 5 mins and the lavage fluid was then allowed to drain passively with the animal placed in a 10 degrees head down tilt. The animals were then ventilated with an FIO_2

of 1.0 at the same rate and tidal volume as pre-lavage for a period of 5 mins. Lavage was repeated until the PaO_2 was <100 torr (<13.32 kPa) with an FIO_2 of 1.0 (usually two or three repetitions).

After the induction of lung injury, a left thoracotomy was performed at the 5th to 6th intercostal space using sterile surgical technique. A hydraulic constrictor (Hazen Everett, Teaneck, NJ) was placed around the inferior vena cava at the atrial-caval junction. The arterial pressure waveform and electrocardiogram were continuously displayed throughout the protocol. A previously calibrated, 14-mm ultrasonic flow transducer (T108, Transonic Systems, Ithaca, NY) was placed around the main pulmonary artery and blood flow was continuously measured. Cardiac output was manipulated by successive injections of the hydraulic constrictor with normal saline. Incremental injections of 0.2 mL were made until the animal manifested systemic hypotension or metabolic acidosis (usually four to six injections totaling 0.8 to 1.2 mL). Expired tidal volumes were continuously measured and the delivered tidal volume was adjusted to maintain a constant expired tidal volume of 10 mL/kg.

The protocol included co-calibration of the CO_2 analysis station and the blood gas analyzer to a standard calibration gas (10% CO_2). This calibration procedure was repeated at the beginning of each testing sequence. Fifteen minutes after each injection, arterial blood gas tensions were measured using a standard laboratory blood gas analyzer (278 Blood Gas System, Ciba Corning, Medfield, MA), and a 5-min recording of the single breath CO_2 expirogram was saved to disk for subsequent off-line analysis.

Data Analysis.

The statistical methods used to derive a predictive equation for cardiac output have been previously described [3]. Derived components from the CO_2 expirogram were evaluated as predictors of cardiac output using stepwise multiple linear regression analysis. Before creation of the multivariate model, a set of bivariate analyses was performed to determine which of the potential predictor variables was associated with the criterion measure, cardiac output. In each of these analyses, the relationship was examined using linear regression with the effects of the subjects removed by including dummy variables to represent the individual sheep. The results from these analyses were used to select the subset of potential predictors for the multivariate analysis. The effect of the subject was also accounted for in the multivariate model. The Durbin-Watson statistic was computed on the residuals for the model to test for autocorrelation. The analysis included a test of the assumption of slope homogeneity for each predictor variable, as well as a test of the assumption of homogeneity of variance for each predictor variable. The residuals were tested for normality and excessive skewness. The results of all such analyses indicated that the data met the underlying assumptions required for the multivariate analysis used in deriving a predictive equation for the criterion measure. Statistical significance was assumed at $p < .05$.

In our previous study in a healthy animal model [3], stepwise multiple linear regression of 21 variables derived from analysis of the CO_2 expirogram identified two variables which predicted cardiac output changes with a high degree of accuracy: a) the angle between the slope lines for phases II and III divided by the volume of CO_2 per breath (angle/mL CO_2); and b) the slope of phase II. The data from the present study were analyzed using a series of four separate analyses. These analyses were intended to build on the models developed on the healthy animals while allowing for the possibility that the injured animals had a very different

relationship between cardiac output and the predictor variables. Therefore, in the series of analyses, the first analysis was a pure replication in which the predictive equation for the injured sheep was constrained to be identical to that developed for the healthy sheep. These constraints were progressively relaxed until the final analysis, which was completely independent of the analysis performed in the earlier study.

Specifically, in the first three analyses, we utilized the two variables previously determined to predict cardiac output changes in healthy adult sheep. In the first analysis, the slope coefficients derived from our previous data in healthy animals were used in the multivariate predictive equation for cardiac output changes. In the second analysis, we utilized the same two variables. However, the slope coefficients were estimated from an analysis of the present data set in injured animals using stepwise linear regression. In the third analysis, we used the same predictor variables and slope coefficients as in the second analysis, but the PaO_2/FIO_2 ratio was added to the regression equation in order to account for the degree of lung injury in the predictive equation. Finally, in the fourth analysis, we repeated the stepwise multiple linear regression analysis de novo using the data set from the injured animals. Before creation of the multivariate model, a set of bivariate analyses was performed to determine which of the potential predictor variables was associated with the criterion measure, cardiac output.

The bias and precision were evaluated using the mean and SD of the differences between the measures. The differences between the methods of cardiac output measurement (bias) were plotted against the average of the two methods. The bias measures sytematic error between the methods, and the precision quantifies the random error or variability [5]. The limits of agreement were defined as the mean difference +/- two SD and describe the range that includes 95% of the differences between the measures. The percent difference was calculated from the following formula: percent difference (%) = 100 x (difference between the methods)/mean cardiac output measurement.

RESULTS

Six adult sheep (mean weight 44.2 kg, range 40.0 to 48.0) were anesthetized and underwent repetitive lavage. Baseline arterial blood gases and CO_2 expirograms were obtained 30 mins after completing the surgical preparation. Incremental injections of the constrictor were performed as described above.

A total of 38 separate measurements of cardiac output were available for comparison with derived variables from the CO_2 expirogam. The cardiac output measured by ultrasonic flow probe ranged between 0.95 and 4.79 L/min (mean 2.51).

Using the variables previously identified in normal animals as the most accurate predictors of cardiac output changes (the angle between the slope lines for phases II and III divided by the volume of CO_2 per breath, and the slope of phase II) [3], we performed three separate analyses of the data acquired in animals with acute lung injury. In model 1, the slope coefficients derived from our previous data in healthy animals were used in the multivariate predictive equation for cardiac output and were found to predict cardiac output with a coefficient of determination of 0.38. In model 2, we derived the slope coefficients from the present data set and were able to predict cardiac output with a coefficient of determination of 0.66. In model 3, we added the PaO_2/FIO_2 ratio to the predictive equation and were able to increase the accuracy of the cardiac output prediction to yield a coefficient of determination of

0.74 (Table 1). The increase in the value for R^2 obtained by adding the PaO_2/FIO_2 ratio to the predictive equation was determined to be statistically significant ($p < .004$). The bias and precision of the calculated cardiac output, using model 3, were .00 and .49, respectively. The limits of agreement were -.98 and .98. The mean percent difference for the cardiac output estimate derived using the variables in model 3 was 0.00%.

Model/Variable	Slope Coefficient	*p* Value	R for Model	R^2 for Model
1) Fixed Slopes			.62	.38
Angle/mL CO_2	–0.408			
Slope phase II	0.044			
2) Estimated Slopes			.81	.66
Angle/mL CO_2	–0.214	.0179		
Slope phase II	0.032	.4541		
3) Estimated Slopes with Pao_2/Fio_2			.86	.74
Angle/mL CO_2	–0.255	.0024		
Slope phase II	0.031	.4073		
Pao_2/Fio_2	–0.006	.0044		

Angle/mL CO_2, angle between the slope lines for phases II and III divided by the volume of CO_2 per breath.

Note that there are no *p* values for model 1 because the slope coefficients were fixed prior to the analysis.

Table 1. Summary of model predictions of cardiac output in acute lung injury, using variables derived from healthy animals

When we repeated the stepwise multiple linear regression analysis de novo using the data set from the injured animals (model 4, Table 2), four variables were selected for the predictive equation for cardiac output: a) PaO_2/FIO_2 ratio; b) the angle between the slope lines for phases II and III divided by the tidal volume; c) mixed expired CO_2 tension; and d) physiologic deadspace to tidal volume ratio (Table 3). The multivariate equation derived from model 4 predicted cardiac output with a coefficient of determination of 0.80 (adjusted R^2 = .80, $p < .0001$). The predicted cardiac outputs derived from models 3 and 4 are compared in Figure 1 and Figure 2. The bias and precision of the calculated cardiac output using model 4 were .00 and .38, respectively (Figure 2). The limits of agreement were -.76 and .76. The mean percent difference for the cardiac output estimate derived using the variables in model 4 was -0.01%.

Variable	Partial Correlation	t Statistic	*p* Value
P_{ECO_2}	.79	7.18	.0000
V_{ECO_2}	.77	6.81	.0000
Angle/cc CO_2	–.74	–6.19	.0000
Angle/P_{ECO_2}	–.73	5.99	.0000
V_{CO_2}	.69	5.38	.0000
Slope phase II	.69	5.24	.0000
Angle	–.62	–4.37	.0001
Slope phase III	.57	3.85	.0006
V_D/V_T	–.37	–2.19	.0363
V_D/V_T alv	–.34	–2.03	.0516
Volume phase I	–.31	–1.80	.0819
V_D alv	–.30	–1.74	.0923
V_D air	–.21	–1.20	.2400
Slope phase III/ P_{ECO_2}	.20	1.11	.2745
Angle/Vt	–.18	–1.03	.3109
Vd/Vt air	–.18	–1.02	.3156
Slope phase II/ P_{ECO_2}	.17	.95	.3473
P_{AO_2}/F_{IO_2}	–.08	–.45	.6587
Efficiency	.06	0.36	.7217
V_T alv	.03	.16	.8749
Volume phase III	.03	.15	.8829
Volume phase II	.02	.12	.9084

P_{ECO_2}, mixed expired CO_2 tension; V_{ECO_2}, volume of CO_2 per breath; Angle/cc CO_2, angle between the slope lines for phases II and III divided by the volume CO_2 per breath; Angle/P_{ECO_2}, angle between the slope lines for phases II and III divided by the mixed expired CO_2 tension; V_{CO_2}, minute CO_2 production; Angle, angle between the slope lines for phases II and III; V_D/V_T, physiologic deadspace/tidal volume ratio; V_D/V_T alv, alveolar deadspace/alveolar tidal volume ratio; V_D alv, alveolar deadspace; V_D air, airway deadspace; Slope phase III/P_{ECO_2}, slope of phase III divided by the mixed expired CO_2 tension; Angle/V_T, angle between the slope lines for phases II and III divided by the tidal volume; V_D/V_T air, airway deadspace/tidal volume ratio; Slope phase II/P_{ECO_2}, slope of phase II divided by the mixed expired CO_2 tension; V_T alv, alveolar tidal volume.

The partial correlation coefficient is the standard Pearson Product Moment correlation computed after the effects of the

Table 2. Bivariate relationships of potential predictors of cardiac output (model 4)

Variable	Slope	Standard Statistic	t Error	*p* Value
Pa_{O_2}/F_{IO_2}	–0.004	0.002	–2.336	.0269
Angle/V_T	0.026	0.010	2.545	.0167
Pe_{CO_2}	3.576	0.389	9.185	.0000
V_D/V_T	5.143	2.288	2.248	.0326

Angle/V_T, angle between the slope lines for phases II and III divided by the tidal volume; Pe_{CO_2}, mixed expired CO_2 tension; V_D/V_T, physiologic deadspace/tidal volume ratio.

Table 3. Coefficients obtained from stepwise regression analysis (model 4)

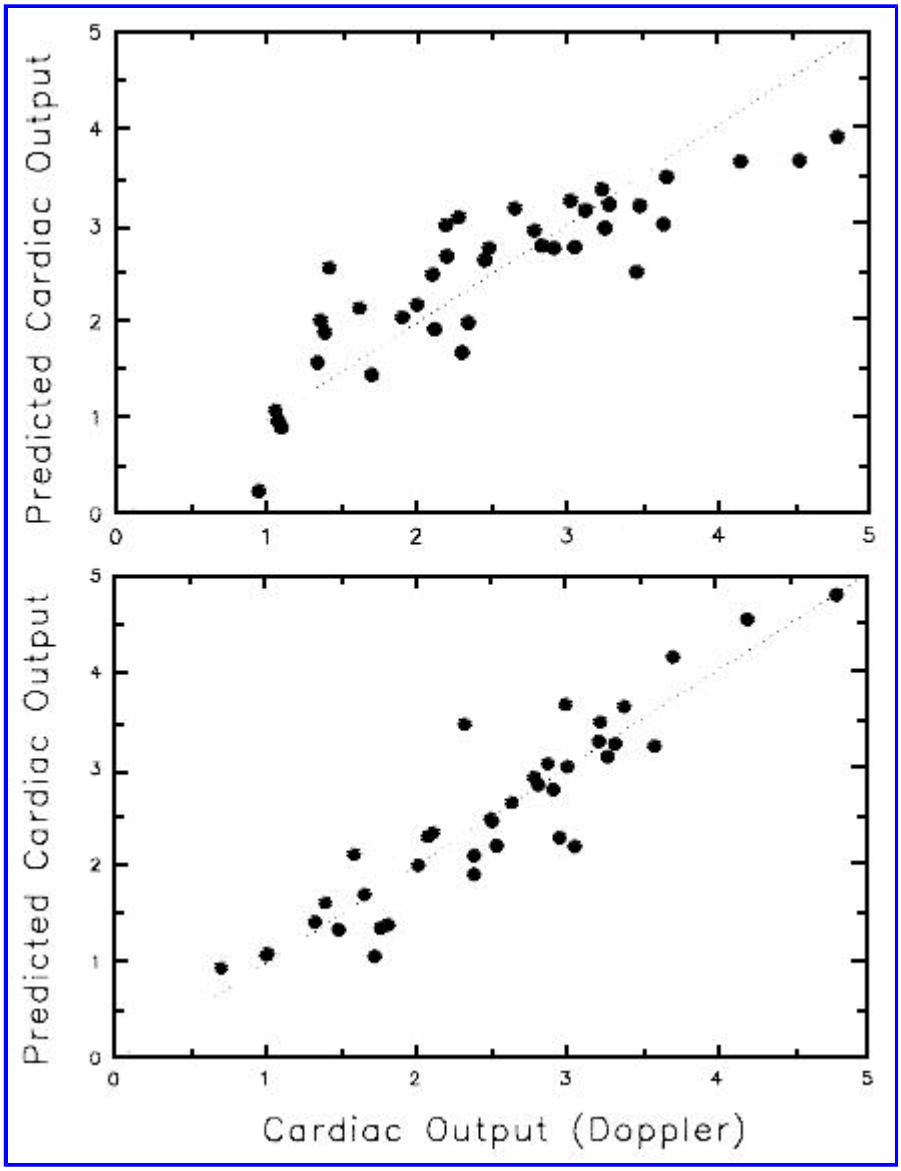

Figure 1. Cardiac output predicted by the multivariate equation plotted against the cardiac output measured by ultrasonic flow probe. Top panel: Model 3: Predicted cardiac output = b + ([-0.255]X_1 + [0.031]X_2 - [0.006]X_3), where b is a constant representing the baseline measure of cardiac output, X_1 is angle/mL CO_2, X_2 is slope phase II, and X_3 is PaO_2/FIO_2 ratio. The adjusted R^2 was 0.74. Lower panel: Model 4: Predicted cardiac output = b + ([-0.004]X sub 1 + [0.026]X_2 + [3.576]X_3 + [5.143]X_4), where b is a constant representing the baseline measure of cardiac output, X_1 is PaO_2/FIO_2 ratio, X_2 is angle/Vt, X_3 is mixed expired CO_2 tension, and X_4 is physiologic deadspace/tidal volume ratio. The adjusted R^2 was .80. The dashed line represents the line of identity, y = x.

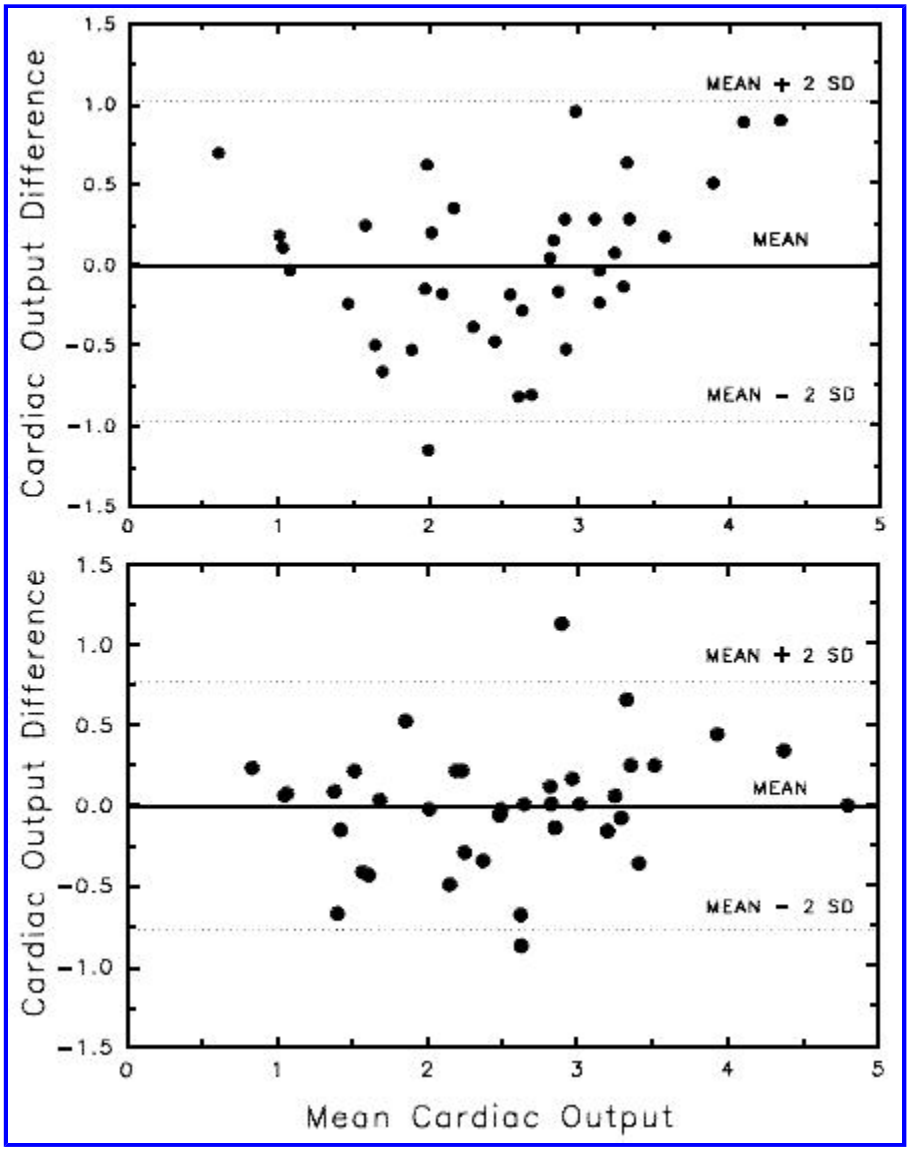

Figure 2. Bias of the predicted cardiac output plotted against the average cardiac output ([predicted cardiac output - measured cardiac output]/2). The bias and precision of the calculated cardiac output, using model 3 (top panel), were .00 and .49, respectively. The limits of agreement were -.98 and .98. The mean percent difference for the cardiac output estimate derived using the variables in model 3 was 0.00%. The bias and precision of the calculated cardiac output, using model 4 (bottom panel), were .00 and .38, respectively. The limits of agreement were -.76 and .76. The mean percent difference for the cardiac output estimate derived using the variables in model 4 was -0.01%.

DISCUSSION

Our results indicate that changes in cardiac output can be determined with a high degree of reliability using components of the CO_2 expirogram in animals with induced lung injury. Specifically, the use of three parameters-two of which were identified as the most reliable predictors of cardiac output in normal animals-predicts changes in cardiac output with an adjusted coefficient of determination of .74 and a mean percent difference of 0.00% (model 3). Furthermore, the use of four parameters-one of which is included in model 3 (PaO_2/FIO_2 ratio), and one of which is altered slightly from model 3 (the angle between the slope lines for phases II and III divided by the tidal volume)-predicts changes in cardiac output with an adjusted coefficient of determination of .80 and a mean percent difference of -0.01% (model 4).

Previous attempts to derive information about cardiac output noninvasively have yielded mixed results. There have been a number of previous [6-9] attempts to utilize the Fick equation to provide noninvasive determination of cardiac output. The accuracy of the measurement is critically dependent on an adequate period of equilibration during partial CO_2 rebreathing given the small absolute value of the arterial-venous CO_2 content difference. Furthermore, values derived from the CO_2 Fick equation are generally not precise enough to be accepted as a substitute for data derived from thermodilution. There has been some recent progress in attempts to improve the precision of cardiac output data derived from the CO_2 Fick method. Neviere and colleagues [10] examined a partial CO_2 rebreathing system with 20 secs of equilibration in adult patients with obstructive lung disease and demonstrated an R^2 of .92, a mean bias of -0.06 L/min/m^2, and a precision of 0.028 L/min/m sup 2 when compared with thermodilution. Gedeon and colleagues [11] proposed a mathematical model incorporating both the CO_2 Fick equation and the shunt equation to improve the precision of their measurement. In animals with induced abnormalities of both gas exchange and cardiovascular function, their technique predicted cardiac output obtained by thermodilution with an R^2 of .85 and a precision of 15%. However, when applied to adults following cardiac surgery, the algorithm performed considerably worse with an R^2 of .64, a mean bias of -0.14 L/min, and a precision of 0.77 L/min [12].

Measurements of thoracic electrical bioimpedance, first described in the 1960s [13], have also been developed as a noninvasive method of cardiac output estimation. The performance of the technology in the critical care setting was initially less than satisfactory [14]. However, a recent modification of the impedance cardiography system has shown promising results. Shoemaker and colleagues [15] reported a multicenter experience with thoracic electrical bioimpedance in 68 critically ill adults with a variety of diagnoses. Compared with cardiac outputs determined by thermodilution, thoracic electrical bioimpedance yielded values for cardiac output with an R^2 of .74, a mean bias of -0.013 L/min, and a precision of 1.4 L/min with a mean percentage difference of 16.6%. By comparison, model 4 in our study yielded values for cardiac output with an R^2 of .80, a mean bias of 0.00 L/min, and a precision of 0.38 L/min with a mean percentage difference of -0.01%.

We acknowledge that our data have several potential limitations. Our model included induced changes in cardiac output by successive inflation of an occluder around the inferior vena cava. It is possible that the changes in the CO_2 expirogram that we observed may not be applicable to settings of increased cardiac output that arise spontaneously or are produced pharmacologically. Our model also included placement of the ultrasonic flow probe around the pulmonary artery, which required a thoracotomy, and the animals were studied with an open hemithorax. The open hemithorax may have produced alterations in ventilation/perfusion relationships, particularly in the nondependent lung, that are not applicable to patients with an intact chest. The lung injury model chosen for this study, a saline-lavaged preparation, has been demonstrated to provide a uniform degree of impairment of lung mechanics and gas exchange [4,16]. However, in the clinical setting with nonuniform degrees of lung injury as well as changing ventilation/perfusion relationships over time, the reliability of our technique to predict cardiac output may be challenged. Finally, we allowed a 15-min period for equilibration and stabilization of measured parameters in deriving our predictive equation, which is different from the rapidly changing clinical setting in which precise determination of cardiac output is most helpful. However, our analysis of the CO_2 expirogram offers the potential to provide breath-to-breath information about cardiac output which can be updated continuously and

without the need for an arterial blood gas. Prospective application of this technology in the clinical setting with the rapidly changing physiology that is characteristic of the acutely ill patient will be essential in determining the clinical usefulness of single breath CO_2 analysis as a noninvasive measure of cardiac output.

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