

Cardiac Output Measurement Using a Modified Carbon Dioxide Fick Method: A Validation Study in Ventilated Lambs

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ABSTRACT: Cardiac output can be measured using a modified carbon dioxide Fick (mCO_2F) method. A validation study was performed comparing mCO_2F method-derived cardiac output (Q^{mCO_2F}) with invasively measured pulmonary blood flow. In seven randomly bred ventilated newborn lambs, cardiac output was manipulated by creating hemorrhagic hypotension. When steady state was reached, Q^{mCO_2F} was measured. Gas analysis was performed in simultaneously obtained arterial and venous blood samples (right atrium [RA], superior vena cava [SVC], and inferior vena cava [IVC]). Carbon dioxide exchange and pulmonary blood flow was measured continuously using a CO_2 SMO Plus monitor and a pulmonary ultrasonic flow probe (Q^{ufp}), respectively. Mean bias, defined as $Q^{mCO_2F} - Q^{ufp}$, was small (respectively, $-0.082 L \cdot min^{-1}$, $-0.085 L \cdot min^{-1}$ and $-0.183 L \cdot min^{-1}$ for venous sampling from RA, SVC, and IVC). The limits of agreement were -0.328 to $0.164 L \cdot min^{-1}$ (RA), -0.335 to $0.165 L \cdot min^{-1}$ (SVC), and 0.415 to $0.049 L \cdot min^{-1}$ (IVC). In conclusion, measurement of cardiac output with the mCO_2F method is reliable and easily applicable in ventilated newborn lambs. For clinical use, the site of venous blood sampling is of minor importance. (*Pediatr Res* 61: 279–283, 2007)

Monitoring cardiac output is essential in the treatment of critically ill patients. It may improve the indication and choice of treatment in a hemodynamically unstable patient. Furthermore, the response to the intervention can be monitored and evaluated.

Bedside cardiac output monitoring is feasible in adult and pediatric patients, but remains complicated in the newborn. Several techniques for cardiac output monitoring in children are available (1–3). Most techniques for cardiac output measurement are not feasible in newborns. In critically ill neonates, cardiac output is usually estimated from the interpretation of several clinical variables, such as blood pressure, urine output, blood gas analysis, and capillary refill. Tibby and colleagues (4) showed that clinicians using these indirect parameters of cardiac performance were unable to predict the actual cardiac output in ventilated children and infants. The same was shown in ventilated adults (5). Nonetheless, this clinical estimation of cardiac output is nowadays still the most frequently used method. This emphasizes the need for a

reliable, (semi)continuous, preferably noninvasive, accurate method of cardiac output monitoring in critically ill newborns. Only in this way can objective hemodynamic parameters be obtained on which a rational therapeutic regimen can be based.

Theoretically, cardiac output can be measured in ventilated patients using a mCO_2F method. We performed a validation study of this technique in a lamb model.

METHODS

We compared the Q^{mCO_2F} with measured pulmonary blood flow using a perivascular ultrasonic flow probe (ufp) positioned around the common pulmonary artery (Q^{ufp}).

mCO_2F method. The mCO_2F method is based on the principle that in steady state, carbon dioxide production in tissue (CO_2P) equals pulmonary carbon dioxide exchange ($\dot{V}CO_2$). $\dot{V}CO_2$ can be measured in a ventilated patient using a computer-aided analysis of expiratory airflow (Q_{exp}) and carbon dioxide fraction in expiratory air ($FeCO_2$).

$$\dot{V}CO_2 = \left\{ \int_0^T Q_{exp}(t) \cdot FeCO_2(t) \cdot dt \right\} \cdot T^{-1} \quad (1)$$

where $\dot{V}CO_2$ = carbon dioxide exchange (L/min); Q_{exp} = expiratory airflow (L/min); $FeCO_2$ = carbon dioxide fraction in expiratory air (gradient); T = time (min).

CO_2P is the product of cardiac output (Q) and the venoarterial difference in carbon dioxide concentration ($C_{(v-a)}CO_2$).

$$CO_2P = Q \cdot (C_vCO_2 - C_aCO_2) \quad (2)$$

where CO_2P = carbon dioxide production (mL/min); Q = cardiac output (L/min); C_vCO_2 = venous carbon dioxide concentration (mL/L); C_aCO_2 = arterial carbon dioxide concentration (mL/L).

Carbon dioxide concentration in blood can be measured using different methods, depending on the calculation method of carbon dioxide concentration in the erythrocyte (6–10). In this study, we used the Douglas equation (10):

$$c_bCO_2 = c_pCO_2 \cdot \left[1 - \frac{(0.0289 \cdot Hb)}{(3.352 - 0.456 \cdot sO_2) \cdot (8.142 - pH)} \right] \quad (3)$$

where c_pCO_2 = total carbon dioxide concentration in plasma (mL/100 mL); c_bCO_2 = total carbon dioxide concentration in blood (mL/100 mL); Hb = hemoglobin concentration (g/dL); sO_2 = oxygen saturation (gradient).

Total carbon dioxide concentration in plasma is calculated using the Henderson-Hasselbalch equation:

$$c_pCO_2 = 2.226 \cdot s \cdot pCO_2 \cdot (1 + 10^{pH-pK}) \quad (4)$$

where c_pCO_2 = total carbon dioxide concentration in plasma (mL/100 mL); 2.226 = conversion factor mEq to mL/100 mL; s = solubility coefficient of

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Abbreviations: IVC, inferior vena cava; mCO_2F , modified carbon dioxide Fick; Q^{mCO_2F} , mCO_2F method-derived cardiac output; Q^{ufp} , cardiac output determined by pulmonary ultrasonic flow probe; RA, right atrium; SVC, superior vena cava; $\dot{V}CO_2$, pulmonary carbon dioxide exchange

carbon dioxide in plasma (mEq/mm Hg); pK' = apparent pK ; pCO_2 = partial carbon dioxide pressure (mm Hg).

$$s = 0.0307 + 0.00057(37 - T) + 0.00002(37 - T)^2 \quad (5)$$

where s = solubility coefficient of carbon dioxide in plasma (mEq/mm Hg); T = temperature ($^{\circ}C$)

$$pK' = 6.086 + [0.042 \cdot (7.4 - pH)] + \{(38 - T) \cdot [0.0047 + 0.00139 \cdot (7.4 - pH)]\} \quad (6)$$

For use in calculations, CO_2P and $\dot{V}CO_2$ need to be converted to standard temperature pressure, dry (STPD) conditions.

$$CO_2P^{STPD} = CO_2P^{BTPS} \cdot \left\{ \frac{T_0}{T^{BTPS}} \right\} \cdot \left\{ \frac{(P^{BTPS} - pH_2O)}{P_0} \right\} \quad (7)$$

where CO_2P^{STPD} = carbon dioxide production under STPD conditions; CO_2P^{BTPS} = carbon dioxide production under BTPS conditions; $BTPS$ = body temperature pressure, saturated; T_0 = standard temperature (273 K); T^{BTPS} = temperature under BTPS (K); P^{BTPS} = pressure under BTPS conditions (kPa); pH_2O = partial pressure of water vapor at T^{BTPS} (kPa); P_0 = standard pressure (101.4 kPa).

$$\dot{V}CO_2^{STPD} = \dot{V}CO_2^{ATPS} \cdot \left\{ \frac{T_0}{T^{ATPS}} \right\} \cdot \left\{ \frac{(P^{ATPS} - pH_2O)}{P_0} \right\} \quad (8)$$

where $\dot{V}CO_2^{STPD}$ = pulmonary carbon dioxide exchange under STPD conditions; $\dot{V}CO_2^{ATPS}$ = pulmonary carbon dioxide exchange under ATPS conditions; $ATPS$ = ambient temperature pressure, saturated; T_0 = standard temperature (273 K); T^{ATPS} = ambient temperature (K); P^{ATPS} = pressure under ATPS conditions (kPa); pH_2O = partial pressure of water vapor at T^{ATPS} (kPa); P_0 = standard pressure (101.4 kPa).

Then, cardiac output can be calculated using the following equation.

$$Q = \frac{(\dot{V}CO_2)^{STPD}}{(C_{(v-a)}CO_2)^{STPD}} \quad (9)$$

Q = cardiac output (L/min); $(\dot{V}CO_2)^{STPD}$ = pulmonary carbon dioxide exchange under STPD conditions (mL/min);

$(C_{(v-a)}CO_2)^{STPD}$ = venoarterial difference in carbon dioxide concentration under STPD conditions (mL/L).

Animal preparation. The study was approved by the Ethical Committee on Animal Research of the Radboud University Nijmegen and performed in seven randomly bred newborn lambs (2.9–6.4 kg). After anesthesia induction using midazolam (2.0 mg·kg⁻¹) and pentobarbital (15–20 mg·kg⁻¹), the lambs were orotracheally intubated with a cuffed endotracheal tube. The cuff was inflated to a standard pressure. It was verified by auscultation that there was no air leak around the cuffed tube. Animals were artificially ventilated with a Babylog 8000 Plus ventilator (Dräger Medizintechnik, Lübeck, Germany) using pressure control. Anesthesia was maintained with fentanyl (loading dose, 0.2 mg·kg⁻¹; maintenance dose, 0.2 mg·kg⁻¹·h⁻¹) and midazolam (0.3 mg·kg⁻¹·h⁻¹), and muscle paralysis was performed using pancuronium (loading dose, 0.1 mg·kg⁻¹; maintenance dose, 0.02 mg·kg⁻¹·h⁻¹). Ventilator settings were adjusted to maintain normoxaemia (Pao₂ 12–15 kPa; Sao₂ 90%–95%) and normocapnia (Paco₂ 4.0–5.5 kPa). A servocontrolled heating mattress was used to maintain the rectal temperature between 38° and 40°C. In clinical practice, it is difficult to position the tip of a central venous

catheter exactly in the RA. To be able to evaluate the effect of different venous sample sites on the accuracy of the mCO₂F method, we surgically inserted intravascular lines with the tip positioned in the RA, the IVC, and SVC, respectively. The position of the tip of the catheters was estimated using the registered pressure waves during insertion. The final position of the catheters was verified by postmortem evaluation. An intra-arterial catheter was inserted in the abdominal aorta through the femoral artery. A left-sided thoracotomy was performed, and after cautious preparation and identification of major structures, the ductus arteriosus was ligated. This was done to exclude any possible influence of a ductal shunt (left to right and/or right to left) on the measurement. An adequately sized ultrasonic flow probe (Transonic Systems Inc., Ithaca, NY) was placed around the pulmonary trunk.

Experimental protocol. Measurement of the pulmonary blood flow (Q^{up}) was considered the gold standard because it is equal to systemic flow, when any shunts are excluded. Measurement of aortic flow will underestimate the systemic flow because the coronary flow will be missed.

After a 30-min period of stabilization, cardiac output was reduced by creating hemorrhagic hypotension. Blood was withdrawn in a stepwise manner to obtain a decrease of mean arterial blood pressure (MABP) of 10 mm Hg. After each reduction in blood pressure, a 15-min stabilization period ensured steady state. Steady state was assumed when carbon dioxide exchange was stable for at least 6 min. The mCO₂F method-derived cardiac output was measured before manipulating cardiac output and after each stabilization period. Blood samples were taken from the different sampling sites for blood gas analysis, *i.e.* arterial blood from the abdominal aorta and venous blood from the RA, SVC, and IVC. Gas analysis of the blood samples was done immediately after sampling using a Synthesis 25 analyzer (Instrumentation Laboratory, Barcelona, Spain). The stated 90% confidence interval is ± 2 mm Hg for Pco₂, ± 10 mPpH for pH, ± 0.25 mmol/L for Hb concentration and $\pm 1.5\%$ for oxygen saturation. Carbon dioxide exchange was measured using the CO₂SMO Plus Respiratory Profile Monitor (Model 8100, Novamatrix Medical Systems Inc., Wallingford, CT). According to the manufacturer, the bias of carbon dioxide measurement is -0.8% with a precision of $\pm 3.6\%$ (11). At the time of measurement, the following data were recorded: atmospheric pressure (P_{atm}), positive end-expiratory pressure level, systolic arterial blood pressure (SABP), MABP, diastolic arterial blood pressure (DABP), rectal temperature (T_{rectal}), and pulmonary blood flow via the Transonic flow probe (Q^{up}).

At the end of the experiment, the lamb was killed and the positions of the intravascular catheters were verified by autopsy.

Statistical analysis. The Q^{mCO₂F} was calculated using the results of blood gas analysis from the three different venous sample sites, respectively, RA, SVC, and IVC.

To evaluate the applicability of the mCO₂F method in monitoring the trend of cardiac output, correlation coefficients were assessed between Q^{mCO₂F} and Q^{up}. Bias, defined as Q^{mCO₂F} – Q^{up}, was calculated for each measurement. For every venous sampling site, the mean bias with standard deviation (SD) was calculated. A *t* test was used to determine whether the bias was significantly different from zero. Bland-Altman plots were used to assess the agreement between cardiac output measurement using the mCO₂F method versus the Q^{up} (12).

RESULTS

Table 1 shows the major hemodynamic data for each lamb at the start and the end of the experiment. Also the number of

Table 1. Hemodynamic data for each lamb during the experiment

Lamb no.	No. of measurements	Change in cardiac output during experiment (mL/min)		Change in MABP during experiment (mm Hg)		Change in SvO ₂ during experiment(%)		Total hemorrhage (mL/kg)
		Start	End	Start	End	Start	End	
1	5	1050	460	71	39	78	40	41.0
2	4	700	480	31	17	72	59	31.0
3	5	740	230	57	19	66	14	37.1
4	4	1470	720	50	29	48	15	29.9
5	4	710	280	70	29	75	37	31.7
6	6	1150	250	64	21	62	13	48.9
7	2	1120	1010	83	60	63	55	21.9

SvO₂, central venous oxygen saturation (RA).

Table 2. Agreement and correlation of Q^{mCO_2F} and Q^{ufp} for the three different venous sample sites

Venous sample site	Mean bias* (L·min ⁻¹)	SD (L·min ⁻¹)	Limits of agreement (L·min ⁻¹)	Correlation coefficient
RA	-0.082	0.123	-0.328 to 0.164	0.93†
SVC	-0.085	0.125	-0.335 to 0.165	0.92†
IVC	-0.183	0.116	-0.415 to 0.049	0.93†

* $Q^{mCO_2F} - Q^{ufp}$.

† $p < 0.01$ (t test for correlation).

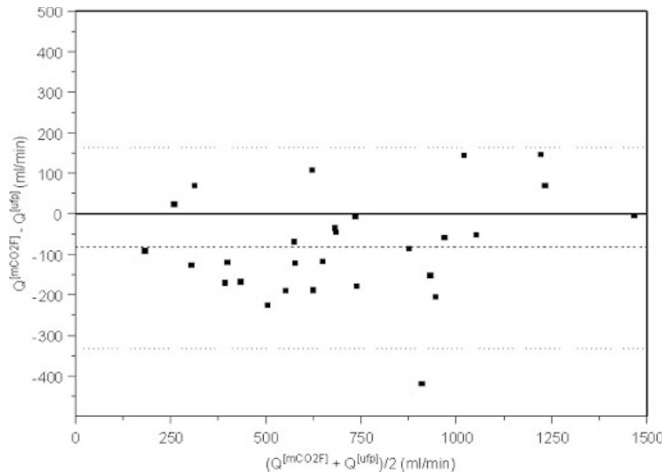


Figure 1. Bland-Altman plot for the cardiac output bias ($Q^{mCO_2F} - Q^{ufp}$) sampling the RA. Dashed line represents mean bias. Dotted lines represent limits of agreement.

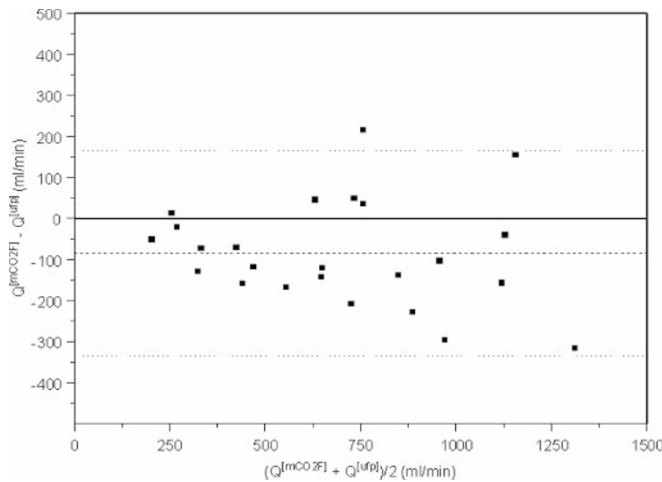


Figure 2. Bland-Altman plot for the cardiac output bias ($Q^{mCO_2F} - Q^{ufp}$) sampling the SVC. Dashed line represents mean bias. Dotted lines represent limits of agreement.

measurements per lamb and the total amount of blood withdrawn during the experiment are shown.

In all the lambs, a correct position of the intravascular catheters was observed during autopsy at the end of the experiment.

Agreement and correlation of cardiac output measurement obtained by the mCO₂F method and Q^{ufp} for the three different venous sample sites are listed in Table 2. The mean bias was lowest with venous blood from the RA or SVC. The biases were statistically significant different from zero ($p < 0.01$). Bland-Altman plots for the three different venous sample sites

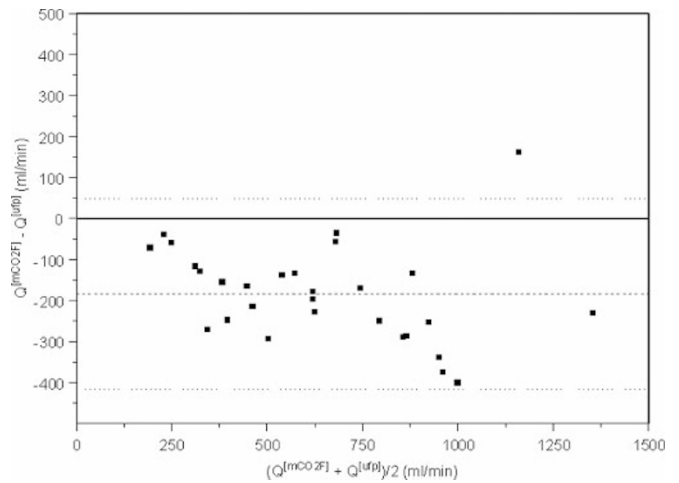


Figure 3. Bland-Altman plot for the cardiac output bias ($Q^{mCO_2F} - Q^{ufp}$) sampling the IVC. Dashed line represents mean bias. Dotted lines represent limits of agreement.

are shown in Figures 1 to 3. There was no significant relationship between the bias and cardiac output.

DISCUSSION

This study shows that cardiac output can be measured reliably in ventilated newborn lambs using the mCO₂F method.

Monitoring cardiac function in neonates is difficult as there are no clinical parameters (solitary or in combination) that reliably predict cardiac output (4). This illustrates the need for an accurate method of cardiac output monitoring. Objective data reflecting the hemodynamic status of a critically ill newborn may lead to a more rational treatment.

In 1870, Adolph Fick (13) described a method for cardiac output measurement using the principle of preservation of oxygen. Cardiac output can be calculated using oxygen consumption and arteriovenous oxygen concentration difference. This principle can be modified by using carbon dioxide exchange and venoarterial carbon dioxide concentration difference. In several methods of noninvasive cardiac output monitoring, the Fick principle is used. In the majority of these Fick-derived noninvasive methods, oxygen consumption is estimated by measuring carbon dioxide exchange and calculating oxygen consumption from an assumed respiratory quotient (RQ). In general the direct oxygen Fick method is regarded as the gold standard in cardiac output monitoring. We preferred a modified carbon dioxide Fick method, because this does not require any specific additional equipment, like a metabolic monitor. Rebreathing techniques are not safely applicable in newborns, because of its potential effect on cerebral blood flow by a fluctuating partial carbon dioxide pressure in blood (14). Several studies show that modified carbon dioxide methods are at least as accurate as the oxygen Fick method (15–17).

From all published methods for calculating total carbon dioxide concentration in blood, we selected the Douglas equation (10). Unfortunately, it is not known whether this algorithm is also applicable to fetal and/or neonatal blood.

In this study, the ductus arteriosus was ligated to exclude any influence of a ductal shunt on the measurement of pul-

monary blood flow. Theoretically, the carbon dioxide Fick equation for calculating systemic blood flow should not be influenced by any intracardiac and/or intrapulmonary shunt, as long as the measurement is performed in steady state. Steady state is a prerequisite for the Fick principle, as only under these circumstances does carbon dioxide exchange equal carbon dioxide production. As with every method of cardiac output measurement, the obtained value of cardiac output should be interpreted with knowledge of the actual hemodynamic circuit with the potential existence of shunts. Possible limitations of the $m\text{CO}_2\text{F}$ method are the potential calculation errors due to a too small venoarterial carbon dioxide concentration difference.

In this study, the lambs were ventilated *via* a cuffed endotracheal tube. However, newborns are always intubated with an uncuffed tube. One should be cautious in interpreting cardiac output values in the presence of an endotracheal tube leakage. A large leakage of the endotracheal tube leads to an underestimation of $\dot{V}\text{CO}_2$ and will result in a falsely lower cardiac output.

The $m\text{CO}_2\text{F}$ method of measuring cardiac output requires a steady state. The most interesting moments for cardiac output measurements are probably characterized by an absence of steady state. However, in our model, we were able to determine cardiac output reliably in hemodynamically unstable lambs, when defining steady state as steady carbon dioxide exchange for at least 6 min.

Sampling the RA for measuring the venous carbon dioxide concentration resulted in the most accurate calculated cardiac output. In general, in patients in a neonatal intensive care unit, the tip of a central venous catheter is positioned in the transition zone between the RA and SVC or IVC. However, this study shows that the position of the tip of the central venous catheter, in the IVC or SVC, has no significant influence on the measurement of cardiac output with the $m\text{CO}_2\text{F}$ method.

In this study, $Q^{\text{mCO}_2\text{F}}$ underestimated pulmonary blood flow. Although statistically significant, the bias is small and of no clinical relevance.

An evaluation of the $m\text{CO}_2\text{F}$ method according to the eight desirable characteristics for cardiac output monitoring described by Shephard *et al.* (18) shows that the accuracy and reproducibility are adequate and that the method is easy to apply and operator independent.

Several methods for cardiac output measurement in children are available, such as thermodilution, oxygen Fick and dye indicator techniques, bioimpedance, and Doppler echocardiography. These methods differ in applicability due to technical and size constraints and reliability (1–3). In comparison with published data concerning bias and precision of several methods of cardiac output measurement in animals (19–22), children (23–30), and adults (31–38), this study produced favorable results.

Without the use of additional equipment, one can measure cardiac output by the $m\text{CO}_2\text{F}$ method. It requires gas analysis of both arterial and central venous blood as well as of expiratory air by in-line capnography and simultaneous measurement of expiratory airflow. Usually, this is feasible in critically ill patients in a neonatal intensive care. This suggests that

the method may be cost-effective without a risk of additional morbidity or mortality. Unfortunately, the response time of this method is not very fast because steady state is a prerequisite. This also implies a semicontinuous method of cardiac output monitoring.

We conclude that measurement of $Q^{\text{mCO}_2\text{F}}$ method is reliable in newborn lambs without a ductal shunt and can be used for trend monitoring. Venous blood sampling from the RA, SVC, or IVC can be used for this measurement. The $m\text{CO}_2\text{F}$ method is a promising technique that can be used to measure cardiac output in critically ill newborns.

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