

# Cardiac Output Measurement in Ventilated Lambs with a Significant Left-to-Right Shunt Using the Modified Carbon Dioxide Fick Method

Willem P. de Boode<sup>a</sup> Jeroen C.W. Hopman<sup>b</sup> Marc H.W.A. Wijnen<sup>c</sup>  
Ronald B. Tanke<sup>d</sup> Hans G. van der Hoeven<sup>e</sup> K. Djien Liem<sup>a</sup>

Departments of <sup>a</sup>Neonatology, <sup>b</sup>Pediatrics, <sup>c</sup>Pediatric Surgery, <sup>d</sup>Pediatric Cardiology and <sup>e</sup>Intensive Care Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

## Key Words

Cardiovascular function, neonatal · Cardiac output · Hemodynamics · Carbon dioxide Fick method, modified · Systemic blood flow · Shunt · Patent ductus arteriosus · Neonatal lambs

## Abstract

**Background:** It remains a great challenge to measure systemic blood flow in critically ill newborns. In a former study we validated the modified carbon dioxide Fick (mCO<sub>2</sub>F) method for measurement of cardiac output in a newborn lamb model. In this new study we studied the influence of a left-to-right shunt on the accuracy of the mCO<sub>2</sub>F method. **Objective:** To analyze the influence of a left-to-right shunt on the agreement between cardiac output measurement with the mCO<sub>2</sub>F method and ultrasonic transit time pulmonary blood flow in a lamb model. **Methods:** The study was approved by the Ethical Committee on Animal Research of the Radboud University Nijmegen and performed in 8 random-bred lambs. A Gore-Tex<sup>®</sup> shunt was placed between the left pulmonary artery and the descending aorta. This aortopulmonary shunt was intermittently opened and closed, while cardiac output was manipulated by creating hemorrhagic hypotension. Cardiac output measurement with the mCO<sub>2</sub>F method (Q<sup>mCO<sub>2</sub>F</sup>) was compared with pulmonary blood flow obtained by a transit time ultrasonic flow

probe positioned around the common pulmonary artery (Q<sup>APC</sup>). **Results:** Bias, defined as Q<sup>mCO<sub>2</sub>F</sup> – Q<sup>APC</sup>, was calculated for each measurement. With an open shunt there was a significant left-to-right shunt (mean Q<sub>p</sub>/Q<sub>s</sub> ratio 2.26; range 1.56–3.69). Mean bias (SD) was –12.3 (50.4) ml·kg<sup>-1</sup>·min<sup>-1</sup> and –12.3 (42.7) ml·kg<sup>-1</sup>·min<sup>-1</sup> for measurements with a closed and open shunt, respectively (no statistical significant difference). **Conclusions:** Cardiac output measurement with the mCO<sub>2</sub>F method is reliable and easily applicable in ventilated newborn lambs, also in the presence of a significant left-to-right shunt.

Copyright © 2009 S. Karger AG, Basel

## Introduction

In neonates, cardiac output is usually estimated from indirect parameters of systemic blood flow, like blood pressure, urine output, blood gas analysis and capillary refill time, but these clinical variables are unreliable [1]. Objective cardiac output measurement remains very complicated in newborns. This is related to the specific cardiovascular changes that occur in the transition from fetus to newborn. The presence of intra- and/or extracardiac shunts potentially reduces the reliability of most methods of cardiac output measurement in infants and adults. Moreover, several technologies of cardiac output

monitoring cannot be applied to critically ill newborns due to size restraints and the use of potentially toxic indicators. Functional echocardiography is increasingly used on neonatal intensive care units for the assessment of cardiac output (left ventricular output and right ventricular output) and cardiac input (superior vena cava flow). It also provides the clinician with information about myocardial function, intra- and extracardiac shunts, organ blood flow, and tissue perfusion [2, 3]. However, not every neonatologist is skilled in functional echocardiography.

In search of a reliable, easily applicable, (semi)continuous method of objective cardiac output measurement in critically ill newborns, we previously validated the modified carbon dioxide Fick (mCO<sub>2</sub>F) method [4]. In general, the direct oxygen Fick method is regarded as the gold standard in cardiac output measurement. We preferred the mCO<sub>2</sub>F method because it does not require any specific additional equipment, such as a metabolic monitor. We concluded that measurement of cardiac output with the mCO<sub>2</sub>F method is reliable in newborn lambs without a ductal shunt and that it can be used for trend monitoring. It was shown that venous blood sampling from the right atrium, superior vena cava or inferior vena cava could all be used, although sampling the right atrium for measurement of the venous carbon dioxide concentration resulted in the most accurate calculated cardiac output. In that study, the ductus arteriosus was ligated to exclude any influence of a potential shunt on the cardiac output measurement. We stated that theoretically the mCO<sub>2</sub>F method is not influenced by any intracardiac and/or intrapulmonary shunt, as long as the measurement is done in a phase of steady state.

In the current study, we analyzed the influence of a left-to-right shunt on the accuracy of the mCO<sub>2</sub>F method in a lamb model.

## Materials and Methods

We compared mCO<sub>2</sub>F-derived cardiac output (Q<sup>mCO<sub>2</sub>F</sup>) with pulmonary blood flow measured with a perivascular ultrasonic flow probe (Q<sup>APC</sup>) positioned around the common pulmonary artery.

### Modified Carbon Dioxide Fick Method

According to the Fick principle, carbon dioxide production in tissue equals pulmonary carbon dioxide exchange ( $\dot{V}CO_2$ ) in a steady state.

In a ventilated patient, pulmonary  $\dot{V}CO_2$  can be measured using a computer-aided analysis of expiratory airflow (Q<sub>exp</sub>) and carbon dioxide fraction in expiratory air (FeCO<sub>2</sub>).

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

$\dot{V}CO_2$  = carbon dioxide exchange (liters/min); Q<sub>exp</sub> = expiratory airflow (liters/min); FeCO<sub>2</sub> = carbon dioxide fraction in expiratory air (gradient); T = time (min).

Carbon dioxide production (CO<sub>2</sub>P) is the product of cardiac output (Q) and the venoarterial difference in carbon dioxide concentration (C<sub>(v-a)</sub>CO<sub>2</sub>).

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

CO<sub>2</sub>P = carbon dioxide production (ml/min); Q = cardiac output (liters/min); C<sub>v</sub>CO<sub>2</sub> = venous carbon dioxide concentration (ml/l); C<sub>a</sub>CO<sub>2</sub> = arterial carbon dioxide concentration (ml/l).

Carbon dioxide concentration in blood (c<sub>b</sub>CO<sub>2</sub>) can be measured using different methods, depending on the calculation method of carbon dioxide concentration in the erythrocyte [5–8]. In this study we used the Douglas equation [8]:

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

c<sub>p</sub>CO<sub>2</sub> = total carbon dioxide concentration in plasma (ml/100 ml); c<sub>b</sub>CO<sub>2</sub> = total carbon dioxide concentration in blood (ml/100 ml); Hb = hemoglobin concentration (g/dl); sO<sub>2</sub> = oxygen saturation (gradient).

Total carbon dioxide concentration in plasma (c<sub>p</sub>CO<sub>2</sub>) is calculated using the Henderson-Hasselbalch equation:

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

c<sub>p</sub>CO<sub>2</sub> = total carbon dioxide concentration in plasma (ml/100 ml); 2.226 = conversion factor mEq to ml/100 ml; s = solubility coefficient of carbon dioxide in plasma (mEq/mm Hg); pK' = apparent pK; pCO<sub>2</sub> = partial carbon dioxide pressure (mm Hg).

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

s = solubility coefficient of carbon dioxide in plasma (mEq/mm Hg); T = temperature (°C).

$$pK' = 6.086 + [0.042 \cdot (7.4 - pH)] + \{(38 - T) \cdot [0.00472 + 0.00139(7.4 - pH)]\} \quad (6)$$

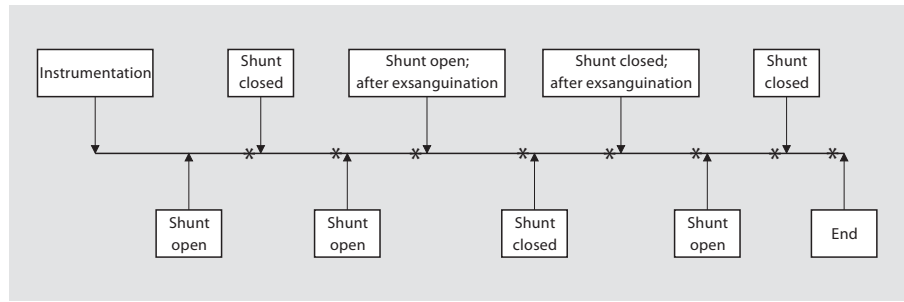
For use in calculations CO<sub>2</sub>P and  $\dot{V}CO_2$  need to be converted into 'standard temperature pressure, dry' (STPD) conditions.

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

CO<sub>2</sub>P<sup>STPD</sup> = carbon dioxide production under STPD conditions; CO<sub>2</sub>P<sup>BTPS</sup> = carbon dioxide production under body temperature pressure, saturated (BTPS) conditions; T<sub>0</sub> = standard temperature (273 K); T<sup>BTPS</sup> = temperature under BTPS (K); P<sup>BTPS</sup> = pressure under BTPS conditions (kPa); pH<sub>2</sub>O = partial pressure of water vapor at T<sup>BTPS</sup> (kPa); P<sub>0</sub> = standard pressure (101.4 kPa).

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

$\dot{V}CO_2^{STPD}$  = pulmonary carbon dioxide exchange under STPD conditions;  $\dot{V}CO_2^{ATPS}$  = pulmonary carbon dioxide exchange under ambient temperature pressure, saturated (ATPS) conditions;



**Fig. 1.** Study protocol. Crosses indicate the timing of measurements.

$T_0$  = standard temperature (273 K);  $T^{\text{ATPS}}$  = ambient temperature (K);  $P^{\text{ATPS}}$  = pressure under ATPS conditions (kPa);  $p_{\text{H}_2\text{O}}$  = partial pressure of water vapor at  $T^{\text{ATPS}}$  (kPa);  $P_0$  = standard pressure (101.4 kPa).

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

$$Q = \frac{(\dot{V}\text{CO}_2)^{\text{STPD}}}{(C_{(v-a)}\text{CO}_2)^{\text{STPD}}} \quad (9)$$

$Q$  = cardiac output (liters/min);  $(\dot{V}\text{CO}_2)^{\text{STPD}}$  = pulmonary carbon dioxide exchange under STPD conditions (ml/min);  $(C_{(v-a)}\text{CO}_2)^{\text{STPD}}$  = 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 (RU-DEC No. 2005-034) and performed in 8 random-bred lambs (4.7–12.5 kg) in accordance with the Dutch national legislation concerning the guidelines for the care and use of laboratory animals. After intramuscular administration of midazolam ( $2 \text{ mg}\cdot\text{kg}^{-1}$ ), pentobarbital ( $15\text{--}20 \text{ mg}\cdot\text{kg}^{-1}$ ) and ketamine ( $10\text{--}15 \text{ mg}\cdot\text{kg}^{-1}$ ) the lambs were orotracheally intubated with a cuffed endotracheal tube (ID 5–6 mm; Kruse, Marslev, Denmark). The lambs were mechanically ventilated in a pressure-control mode with a Babylog 8000 Plus ventilator (Dräger Medizintechnik, Lübeck, Germany). Anesthesia was maintained using the continuous intravenous administration of sufentanil ( $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), midazolam ( $0.2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ), ketamine ( $0.16 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and pancuronium (loading dose  $0.05 \text{ mg}\cdot\text{kg}^{-1}$ ; maintenance dose  $0.02 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ). The ventilator settings were adjusted in order to aim at normoxemia ( $\text{paO}_2$  75–113 torr (10–15 kPa)) and normocapnia ( $\text{paCO}_2$  30–41 torr (4.0–5.5 kPa)). A servo-controlled heating mattress was used to maintain rectal temperature between 38 and 40°C. Intravascular catheters were surgically inserted. The arterial catheter was inserted via the femoral artery with the tip positioned in the abdominal aorta. The venous catheter was inserted via the femoral vein with the tip in the right atrium. The position of the tip of the venous catheter was estimated using a pressure curve during insertion. The final position of the venous line was evaluated postmortem. A left-sided thoracotomy was performed and after preparation of the common pulmonary artery, the left pulmonary artery and the descending aorta, the native ductus arteriosus was ligated. A non-stretch, thin-walled vascular graft (ID 6 mm,

Gore-Tex®, W.L. Gore & Associates Inc., Flagstaff, Ariz., USA) was inserted between the left pulmonary artery and the descending aorta. Adequately sized perivascular ultrasonic flow probes (PAX series, Transonic® Systems Inc, Ithaca, N.Y., USA) were placed around the common pulmonary artery ( $Q^{\text{APC}}$ ) and proximal ( $Q^{\text{AOpri}}$ ) and distal ( $Q^{\text{AOpst}}$ ) to the aortopulmonary shunt on the descending aorta.

#### Experimental Protocol

After a stabilization period of 30 min the study protocol was started (fig. 1). Intermittently the aortopulmonary shunt was fully opened and closed during the experiment. Next to this, cardiac output was manipulated by creating hemorrhagic hypotension by stepwise withdrawal of blood from the venous catheter to obtain a decrease in mean arterial blood pressure (MABP) of 10 mm Hg. After each intervention (shunt opening or closure, blood withdrawal), a 30-min period of stabilization was used in order to ensure a steady state. Steady state was assumed when pulmonary  $\dot{V}\text{CO}_2$  was stable for at least 6 min. After stabilization blood samples were taken from the right atrium and abdominal aorta. Blood gas analysis was performed immediately after sampling using a GEM Premier 3000™ analyzer combined with co-oximetry with the GEM OPL™ (Instrumentation Laboratory, Barcelona, Spain).

$\dot{V}\text{CO}_2$  was measured continuously with the  $\text{CO}_2\text{SMO}$  Plus Respiratory Profile Monitor (Model 8100, Respironics, Pittsburgh, Pa., USA). According to the manufacturer, the bias of carbon dioxide measurement is  $-0.8\%$  with an accuracy of  $\pm 3.6\%$  [9]. We used biomedical data acquisition software (Poly, Inspektor Research Systems BV, Amsterdam, The Netherlands) to store the following data during the experiment with a 200-Hz sampling rate: pulmonary blood flow ( $Q^{\text{APC}}$ ), aortic blood flow proximal ( $Q^{\text{AOpri}}$ ) and distal ( $Q^{\text{AOpst}}$ ) to aortopulmonary shunt, systolic arterial blood pressure (SABP), mean arterial blood pressure (MABP), diastolic arterial blood pressure (DABP), rectal temperature ( $T_{\text{rectal}}$ ) and PEEP level. The shunt flow was calculated as the difference between  $Q^{\text{AOpst}}$  and  $Q^{\text{AOpri}}$ . The  $Q_p/Q_s$  ratio was calculated using the following equation:

$$Q_p/Q_s = \frac{Q^{\text{APC}} + Q^{\text{AOpri}} - Q^{\text{AOpst}}}{Q^{\text{APC}}} \quad (10)$$

The lamb was sacrificed at the end of the experiment after which the position of the venous catheter was verified by autopsy. Likewise the flow probes were checked for zero flow value directly postmortem.

**Table 1.** Hemodynamic data for each lamb during the experiment

Lamb	Measurements n	MABP, mm Hg		ScvO <sub>2</sub> , %		Qp/Qs ratio	Total hemorrhage ml·kg <sup>-1</sup>
		max	min	max	min		
1	8	56	28	62	42	2.16	13.2
2	8	53	35	70	48	1.56	5.1
3	5	78	29	60	18	1.65	3.2
4	8	64	38	61	40	1.93	7.4
5	8	76	40	63	32	3.10	15.8
6	8	68	44	59	43	1.95	9.5
7	8	62	43	66	49	3.69	7.5
8	8	54	36	57	41	2.03	18.4

MABP = Mean arterial blood pressure; ScvO<sub>2</sub> = central venous oxygen saturation (right atrium); Qp = pulmonary blood flow; Qs = systemic blood flow.

### Statistical Analysis

After each intervention mCO<sub>2</sub>F-derived cardiac output (Q<sup>mCO<sub>2</sub>F</sup>) was measured and compared with pulmonary blood flow (Q<sup>APC</sup>). The method described by Bland and Altman [10] was used to assess the agreement between the two methods of cardiac output measurement (Q<sup>mCO<sub>2</sub>F</sup> and Q<sup>APC</sup>). Mean bias, defined as Q<sup>mCO<sub>2</sub>F</sup> - Q<sup>APC</sup>, with standard deviation (SD) was calculated for the measurements with an open aortopulmonary shunt versus the measurements with a closed shunt. Limits of agreement are defined as mean bias ± 1.96 SD. The differences in mean bias between measurements with a closed and an open aortopulmonary shunt were statistically analyzed using the Mann-Whitney test. A p value of <0.05 is considered statistically significant. Data management was performed using Excel for Windows® (Office 2003, Microsoft, Seattle, Wash., USA) and SPSS 14.0.2 for Windows® (SPSS Inc., Chicago, Ill., USA) was used for statistical analysis.

### Results

Hemodynamic data for each lamb are shown in table 1. With an open shunt the mean Qp/Qs ratio was 2.26 (range 1.56–3.69). With the aortopulmonary shunt opened the mean aortic blood flow proximal to the shunt (Q<sup>AOp<sub>pre</sub></sup>) was 1,395 (range 830–1,950) ml/min and distal to the shunt (Q<sup>AOp<sub>post</sub></sup>) the mean aortic blood flow was 511 (range 310–952) ml/min. At autopsy a correct position of the venous line with the tip in the right atrium was observed in all the lambs.

The difference between cardiac output obtained by the mCO<sub>2</sub>F method and pulmonary blood flow is listed in table 2. Mean bias (SD) was -12.3 (42.7) and -12.3 (50.4) ml·kg<sup>-1</sup>·min<sup>-1</sup> for measurements with an open and closed aortopulmonary shunt. There was no significant difference between cardiac output measurements during an

**Table 2.** Difference between cardiac output measurement obtained by the modified carbon dioxide Fick method (Q<sup>mCO<sub>2</sub>F</sup>) and pulmonary blood flow (Q<sup>APC</sup>) with or without aortopulmonary left-to-right shunt

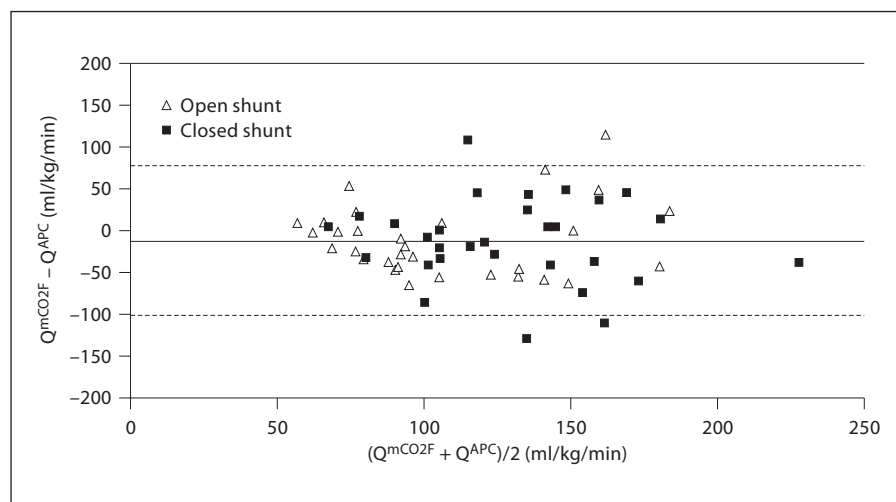
Q <sup>mCO<sub>2</sub>F</sup> - Q <sup>APC</sup> ml·kg <sup>-1</sup> ·min <sup>-1</sup>	Left-to-right shunt		p value <sup>a</sup>
	present	absent	
Mean	-12.3	-12.3	0.629
(95% CI)	(-27.9 to 3.39)	(-31.2 to 6.49)	
SD	42.7	50.4	
LOA	-96.0 to 71.4	-111.1 to 85.5	

SD = Standard deviation; LOA = limits of agreement.

<sup>a</sup> Mann-Whitney test.

open or a closed shunt. The mean bias was not statistically significantly different from zero. We excluded one measurement from the 5th experiment because there was a non-physiological negative venoarterial carbon dioxide concentration difference in a phase with a closed aortopulmonary shunt. This was probably due to a pre-analytical error in the measurement of the venoarterial carbon dioxide concentration difference. The Bland-Altman plot is shown in figure 2 for the combined measurement with an open and closed aortopulmonary shunt. Mean bias was -12.3 ml·kg<sup>-1</sup>·min<sup>-1</sup> with a precision (1.96 SD) of ±90.5 ml·kg<sup>-1</sup>·min<sup>-1</sup>. The limits of agreement are -102.8 and 78.2 ml·kg<sup>-1</sup>·min<sup>-1</sup>, respectively.

**Fig. 2.** Bland-Altman plot for comparison of the modified carbon dioxide Fick-derived cardiac output ( $Q^{mCO_2F}$ ) and pulmonary blood flow ( $Q^{APC}$ ). The solid line represents mean bias and the dotted lines represent limits of agreement for all data (open and closed shunt).



## Discussion

Treatment of critically ill and hemodynamically unstable newborns remains a major challenge. It is very difficult to estimate cardiac output from clinical variables like blood pressure, heart rate, urine production, blood gas analysis, etc. [11–13]. Knowledge of the actual cardiac output likely improves the indication and choice of subsequent treatment and the response to the intervention can be monitored and evaluated. This could prevent iatrogenic damage due to both under- and overtreatment. For example, recent studies show that a too vigorous fluid therapy is associated with increased morbidity and mortality in adults [14–16]. It still has to be proven that goal-directed therapy using cardiac output measurement will eventually lead to a better outcome in the short and long term. Cardiac output measurement is available in children using several techniques [17–21], but remains complicated in the newborn.

In a former study, we validated the  $mCO_2F$  method for measurement of cardiac output in newborn lambs [4]. In that study, the ductus arteriosus was ligated on purpose to exclude any influence of a ductal shunt on the measurements. However, on a neonatal intensive care unit the incidence of a patent ductus arteriosus varies between 20 and 60% depending on the diagnostic criteria and the population studied [22]. Theoretically, as long as measurements are performed in a steady state, the  $mCO_2F$  method should not be influenced by any intracardiac and/or intrapulmonary shunt. Carbon dioxide production is calculated as the difference between carbon dioxide concentration in venous and arterial blood. This car-

bon dioxide is produced in the peripheral tissues. Although the venous and/or carbon dioxide concentration can be influenced by any shunt (left-to-right or right-to-left), in case of a steady state there cannot be a misbalance between systemic carbon dioxide production and pulmonary  $\dot{V}CO_2$ .  $mCO_2F$ -derived cardiac output can represent systemic blood flow and/or pulmonary blood flow, which depends on the site of blood sampling in relation to the position of a possible shunt. Shunting of blood will influence the venoarterial carbon dioxide concentration difference. One should be aware whether the systemic or the pulmonary venoarterial carbon dioxide concentration difference is measured. Regardless of the method of cardiac output measurement used, it is of the utmost importance to be informed about potential intra- and extracardiac shunts in order to correctly interpret the assessed cardiac output. This emphasizes the importance of functional echocardiography in critically ill newborns [2, 3]. In case of a left-to-right shunt distal to the right atrium, for example a patent ductus arteriosus,  $Q^{mCO_2F}$  will represent systemic blood flow ( $Q_s$ ), because the venous carbon dioxide concentration is not influenced by the left-to-right shunt. A significant left-to-right shunt through a patent ductus arteriosus will lead to an increased left ventricular output and a decreased right ventricular output. Measurement of cardiac output with the  $mCO_2F$  method in patients with a patent ductus arteriosus will inform the clinician about the systemic blood flow, i.e. the right ventricular output.  $Q^{mCO_2F}$  in a patient with a left-to-right shunt proximal to or at the right atrium, for example an open foramen ovale, will represent pulmonary blood flow ( $Q_p$ ). This is explained by the fact that the venous

**Table 3.** Interpretation of mCO<sub>2</sub>F-derived cardiac output (Q<sup>mCO<sub>2</sub>F</sup>) in the presence of shunts

<i>No shunt</i>	$Q^{mCO_2F} = Q_s = Q_p$
<i>Left-to-right shunt</i>	
Venous sampling site	
Proximal to shunt	$Q^{mCO_2F} = Q_s$
Distal to/at level of shunt	$Q^{mCO_2F} = Q_p$
<i>Right-to-left shunt</i>	
Arterial sampling site	
Proximal to shunt	$Q^{mCO_2F} = Q_p$
Distal to/at level of shunt	$Q^{mCO_2F} = Q_s$
Q <sub>s</sub> = Systemic blood flow; Q <sub>p</sub> = pulmonary blood flow.	

carbon dioxide concentration is decreased by mixing of central venous blood with pulmonary venous blood through the foramen ovale. In fact, by sampling venous blood in the right atrium one measures the pulmonary carbon dioxide concentration difference instead of the systemic carbon dioxide concentration difference. The interpretation of Q<sup>mCO<sub>2</sub>F</sup> in the presence of a shunt is summarized in table 3. In this study, we verified the assumption that a persistent left-to-right shunt does not have any influence on cardiac output measurement using the mCO<sub>2</sub>F method. In order to verify this hypothesis, we conducted this study after construction of an aortopulmonary shunt (artificial ductus arteriosus) and measurements were done intermittently with an open and closed left-to-right shunt. As is shown in table 2, the mCO<sub>2</sub>F method is not influenced by the shunt, which suggests that this method is applicable for cardiac output measurement in critically ill newborns.

The bias and precision found in this study during a closed aortopulmonary shunt are consistent with the result of our former study [4], when sampling venous blood from the right atrium. This implies a good reproducibility of cardiac output measurements with the mCO<sub>2</sub>F method.

Systemic blood flow was underestimated by the mCO<sub>2</sub>F method (mean  $-12.3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) with or without a left-to-right shunt, but this bias was not significantly different from zero. For clinical purposes one is interested in categorizing the level of systemic blood flow (high, high-to-normal, normal, normal-to-low or low) and being able to monitor fluctuations in response to different interventions. This implies that small biases are clinically irrelevant.

A prerequisite for the Fick principle is that measurements are done in a steady state. Despite the fact that the lambs were hemodynamically very instable with a Q<sub>p</sub>/Q<sub>s</sub> ratio up to 3.5, systemic blood flow was measured reliably when defining steady state as steady pulmonary  $\dot{V}CO_2$  for at least 6 min.

Cardiac output measurements in this study were done using a cuffed endotracheal tube. Newborns are generally intubated with an uncuffed endotracheal tube. Because endotracheal tube leakage will result in a falsely decreased pulmonary  $\dot{V}CO_2$  and therefore an underestimation of systemic blood flow, one should be cautious measuring cardiac output with the mCO<sub>2</sub>F method in the presence of a large expiratory endotracheal tube leakage. Tube leakage is usually defined as the difference between inspiratory tidal volume (VT<sub>ins</sub>) and expiratory tidal volume (VT<sub>exp</sub>) [23, 24]. The leak size is expressed in percentage, calculated by the following equation:

$$\text{Tube leakage} = \frac{VT_{\text{exp}} - VT_{\text{ins}}}{VT_{\text{ins}}} \times 100\% \quad (11)$$

Kondo et al. [25] demonstrated that endotracheal tube leakage was predominantly observed during the inspiratory phase, especially at end inspiration. In this model study they showed that with a volume leak of 22% the error in expiratory volume measured at the airway opening was only 3%. In a worst-case scenario the 3% missed expiratory volume solely consists of carbon dioxide, which would mean a falsely decreased pulmonary  $\dot{V}CO_2$  of 3%. According to the equation to calculate the mCO<sub>2</sub>F-derived cardiac output ( $\dot{V}CO_2 \div (C_{(v-a)}CO_2)$ ), this means that an endotracheal tube leakage of 22% can lead to an underestimation of cardiac output with 3% at most.

Acute changes in pulmonary gas exchange (for example pneumothorax or atelectasis) will influence pulmonary  $\dot{V}CO_2$  for a specific period. In this acute phase the mCO<sub>2</sub>F method cannot be used to measure cardiac output because a steady state is a prerequisite. But as soon as a new homeostasis has been established with a stable pulmonary  $\dot{V}CO_2$  (in general within minutes), one can measure systemic blood flow with the mCO<sub>2</sub>F method.

The accuracy of the mCO<sub>2</sub>F method is highly dependent on accurate measurement of both pulmonary  $\dot{V}CO_2$  and carbon dioxide concentration measurements in arterial and venous blood. We chose the equation of Douglas et al. [8] to calculate the carbon dioxide concentration in blood, although it is not known whether this equation can be used for fetal and neonatal blood as well. In this study, we used routine blood gas analysis and pulmonary  $\dot{V}CO_2$  measurement with satisfactory results.

Most methods of cardiac output measurements, especially indicator dilution techniques, are not applicable in patients with shunts. This excludes several categories of patients that could potentially benefit from measurements of systemic blood flow, such as premature neonates with a patent ductus arteriosus and patients with cardiac defects. In these patients cardiac output can be measured with the  $m\text{CO}_2\text{F}$  method despite their shunts.

The  $m\text{CO}_2\text{F}$  method can be applied without any additional equipment, because it only requires gas analysis of arterial and central venous (right atrial) blood, as well as of expiratory air by in-line capnography and simultaneous measurement of expiratory airflow. This is usually feasible in critically ill patients on an intensive care.

Our study has several limitations. It was not possible to directly measure blood flow in the aortopulmonary shunt, because of the limited length of the shunt and the material used (Gore-Tex®). Ultrasound does not pass the Gore-Tex® material, which implies that we could not use the ultrasound transit time flow probe to measure the blood flow in the aortopulmonary shunt. Although the registered flow patterns in the descending aorta distal to the shunt ( $Q^{\text{AOPost}}$ ) were not consistent with a partly right-to-left shunt, we cannot rule out that there was some right-to-left shunting in early systole.

An interatrial shunt is frequently seen in preterm infants with a patent ductus arteriosus with a left-to right shunt. In preterm infants <1,500 g with a 'wide-open' ductus Evans and Iyer found a left-to-right and bidirectional interatrial shunt in 44.5 and 55.5% of the selected population [26]. As no echocardiographic studies could be performed during the experiment, we have no information about a possible interatrial shunt in the phases

with an open aortopulmonary shunt. In the presence of a left-to-right shunt at both the ductal and interatrial level, the venoarterial carbon dioxide concentration difference will be decreased because of the interatrial shunting of blood. This will lead to a decreased venoarterial carbon dioxide concentration difference and therefore an overestimation of systemic blood flow ( $Q_s$ ). Because the site of venous blood sampling is proximal to the ductal shunt the  $m\text{CO}_2\text{F}$ -derived cardiac output will underestimate the pulmonary blood flow ( $Q_p$ ). In conclusion, in case of a left-to-right shunt both at the interatrial and ductal level, the  $m\text{CO}_2\text{F}$  method will represent a level in between  $Q_p$  and  $Q_s$ . The greater the ductal shunt in relation to the interatrial shunt, the more  $Q^{\text{mCO}_2\text{F}}$  will approach  $Q_s$ .

## Conclusion

We conclude that cardiac output (systemic blood flow) can be measured reliably in newborn lambs using the  $m\text{CO}_2\text{F}$  method, even in the presence of a significant left-to-right shunt. This makes the  $m\text{CO}_2\text{F}$  method a promising technique for cardiac output measurement in critically ill patients with or without intra- and/or extracardiac shunts.

## Acknowledgments

We would like to thank A.E.J. Hanssen from the Animal Laboratory and S.K. Singh, pediatric cardiothoracic surgeon, for their outstanding support and advice during this study.

## References

- 1 Tibby SM, Hatherill M, Marsh MJ, Murdoch IA: Clinicians' abilities to estimate cardiac index in ventilated children and infants. *Arch Dis Child* 1997;77:516–518.
- 2 Kluckow M, Seri I, Evans N: Functional echocardiography: an emerging clinical tool for the neonatologist. *J Pediatr* 2007;150:125–130.
- 3 Kluckow M, Seri I, Evans N: Echocardiography and the neonatologist. *Pediatr Cardiol* 2008;29:1043–1047.
- 4 de Boode WP, Hopman JC, Daniels O, van der Hoeven HG, Liem KD: Cardiac output measurement using a modified carbon dioxide Fick method: a validation study in ventilated lambs. *Pediatr Res* 2007;61:279–283.
- 5 Henderson LJ, Bock AV, Field HJ, Stoddard JL: Blood as a physicochemical system II. *J Biol Chem* 1924;59:379–431.
- 6 Kelman GR: Digital computer procedure for the conversion of  $\text{PCO}_2$  into blood  $\text{CO}_2$  content. *Respir Physiol* 1967;3:111–115.
- 7 Godfrey S: Manipulation of the indirect Fick principle by a digital computer program for the calculation of exercise physiology results. *Respiration* 1970;27:513–532.
- 8 Douglas AR, Jones NL, Reed JW: Calculation of whole blood  $\text{CO}_2$  content. *J Appl Physiol* 1988;65:473–477.
- 9 Jaffe MB: Dead Space and Carbon Dioxide Production – Technical Issues. Wallingford, Novamatrix Medical Systems, 1998, pp 1–7.
- 10 Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; i:307–310.
- 11 Tibby SM, Hatherill M, Marsh MJ, Morrison G, Anderson D, Murdoch IA: Clinical validation of cardiac output measurements using femoral artery thermodilution with direct Fick in ventilated children and infants. *Intensive Care Med* 1997;23:987–991.
- 12 Bayliss J, Norell M, Ryan A, Thurston M, Sutton GC: Bedside haemodynamic monitoring: experience in a general hospital. *Br Med J Clin Res Ed* 1983;287:187–190.

- 13 Egan JR, Festa M, Cole AD, Nunn GR, Gillis J, Winlaw DS: Clinical assessment of cardiac performance in infants and children following cardiac surgery. *Intensive Care Med* 2005;31:568–573.
- 14 Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575.
- 15 Klein MB, Hayden D, Elson C, et al: The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg* 2007;245:622–628.
- 16 Arlati S, Storti E, Pradella V, Bucci L, Vitolo A, Pulici M: Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. *Resuscitation* 2007;72:371–378.
- 17 Fanconi S, Burger R: Measurement of cardiac output in children. *Intensive Care World* 1992;9:8–12.
- 18 Tibby SM, Murdoch IA: Measurement of cardiac output and tissue perfusion. *Curr Opin Pediatr* 2002;14:303–309.
- 19 Tibby SM, Murdoch IA: Monitoring cardiac function in intensive care. *Arch Dis Child* 2003;88:46–52.
- 20 Skowno JJ, Broadhead M: Cardiac output measurement in pediatric anesthesia. *Paediatr Anaesth* 2008;18:1019–1028.
- 21 Lemson J, de Boode WP, Hopman JC, Singh SK, van der Hoeven JG: Validation of transpulmonary thermodilution cardiac output measurement in a pediatric animal model. *Pediatr Crit Care Med* 2008;9:313–319.
- 22 Wyllie J: Treatment of patent ductus arteriosus. *Semin Neonatol* 2003;8:425–432.
- 23 Kuo CY, Gerhardt T, Bolivar J, Claire N, Bancalari E: Effect of leak around the endotracheal tube on measurements of pulmonary compliance and resistance during mechanical ventilation: a lung model study. *Pediatr Pulmonol* 1996;22:35–43.
- 24 Nikischin W, Lange M: Correction of compliance and resistance altered by endotracheal tube leaks. *Pediatr Crit Care Med* 2003;4:344–352.
- 25 Kondo T, Matsumoto I, Lanteri CJ, Sly PD: Respiratory mechanics during mechanical ventilation: a model study on the effects of leak around a tracheal tube. *Pediatr Pulmonol* 1997;24:423–428.
- 26 Evans N, Iyer P: Assessment of ductus arteriosus shunt in preterm infants supported by mechanical ventilation: effect of interatrial shunting. *J Pediatr* 1994;125:778–785.