0031-3998/94/3605-0601$03.00/0
PEDIATRIC RESEARCH

Vol. 36, No. 5, 1994
Printed in U.S.A.

Simultaneous Measurements of Cerebral Circulation with Electromagnetic Flowmetry and Doppler Ultrasound Velocity in the Newborn Pig

KIRSTI HAALAND, BENTE KARLSSON, EVA SKOVLUND, AND MARIANNE THORESEN

Department of Pediatrics [K.H., M.T.] and Institute for Experimental Research, Ullevål University Hospital, Oslo [B.K.]; Department of Mathematics, University of Oslo, Oslo [E.S.]; and Pediatric Research Institute, University of Oslo, The National Hospital, 0027 Oslo, Norway [M.T.]

ABSTRACT

Cerebral blood flow measurement has been an important investigative tool in newborns at risk for perinatal brain damage. The validity of Doppler cerebral blood flow velocity measurements depends on a constant vessel diameter. We have validated Doppler against the electromagnetic flowmeter (EM) using a modified common carotid artery model in the 1-d-old piglet. Two sets of continuous and simultaneous recordings were performed: *1*) the Doppler and EM probe on the same common carotid artery (extracerebral branches were ligated), and *2*) the EM probe on the common carotid artery and the Doppler probe recording from an intracerebral artery through an artificial fontanel. Arterial partial pressure of carbon dioxide ($Paco_2$) was manipulated (2.8–7.4 kPa), as was arterial blood pressure (3.7–9.3 kPa). Simultaneous EM flow and estimated Doppler flow were compared. Ninety-three recordings were obtained with both transducers on the modified carotid artery, and 49 were obtained with the Doppler insonicating an intracerebral artery. A multiple regression model was used for statistical analysis. The correlation between EM and both sets of Doppler measurements for individual animals was >0.95 and was unaffected by changes in arterial blood pressure or $Paco_2$. Thus, the common carotid and the intracerebral artery investigated did not change their diameter significantly in response to $Paco_2$ or arterial blood pressure. The relationships between EM and Doppler in the individual animal were all linear but revealed great variability in the slopes due to the unknown vessel diameter and angle of insonication. We conclude that relative changes of cerebral blood flow velocity in the modified common carotid artery and intracerebral arteries show the same changes as common carotid artery blood flow (determined by an EM) in the healthy 1-d-old piglet. (***Pediatr Res* 36: 601–606, 1994**)

Abbreviations

CBF, cerebral blood flow
CBFV, cerebral blood flow velocity
EM, electromagnetic flowmeter
$Paco_2$, arterial partial pressure of carbon dioxide
MABP, mean arterial blood pressure

There is evidence that ischemia is an important cause of cerebral damage in the newborn infant (1). It is therefore important to be able to study processes controling CBF in newborn infants and animal models (2). Doppler ultrasound is the only noninvasive method that can be easily used bedside on a sick infant clinically (3, 4) as well as in research (5, 6). The important and well-known limitation of the method is that only CBFV and not volume flow is measured (7). The object of this study was to perform continuous and simultaneous recordings on cerebral arteries in the newborn piglet with Doppler ultrasound and the EM during wide variations in flow induced by changing $Paco_2$ or MABP. Due to the size of the transducers compared with the length of the internal carotid artery, it was impossible to record from the internal carotid artery itself. We therefore converted the common carotid artery into a precerebral vessel by ligation of extracerebral branches. Simultaneous measurements were undertaken with the instruments set up in two different combinations: *1*) with both devices next to each other on the modified common carotid artery, and *2*) with the EM probe still on the common carotid artery while the Doppler probe insonicated an intracerebral artery. Using this model, we found good correlation

Received December 23, 1993; accepted June 2, 1994.
Correspondence and reprint requests: Marianne Thoresen, M.D., Ph.D., Pediatric Research Institute, University of Oslo, The National Hospital, 0027 Oslo, Norway.
Supported by grants from the Laerdal Foundation for Acute Medicine and the Norwegian Research Council (K.H. and B.K. were research fellows).

between the two methods of measurement in individual animals over a wide range of flow.

METHODS

Nine White Landrace piglets, median age 1 d (range 4 h to 4 d) with median weight 1.9 kg (range 1.4 to 2.5 kg) were studied. They were obtained from a local farm and kept with the sow until 3 h before the experiment started. Venous access was secured during brief ether inhalation, and initial doses of chloralose 50 mg/kg and urethane 250 mg/kg were given. These were followed by maintenance fluid (5% dextrose) 7.5 mL/kg/h containing 12.5 mg/kg/h chloralose and 62 mg/kg/h urethane. The piglets were either intubated or tracheostomied, paralyzed with pancuronium 0.1 mg/kg/h, and mechanically ventilated with 25–30% O_2. End-expiratory (alveolar) P_{CO_2} (Beckman L_2 CO_2 analyzer, Beckman Inst. GmbH, Munich, Germany) was continuously monitored 2 cm from the tip of the tracheal tube, and ventilator settings were adjusted to obtain end-expiratory P_{CO_2} values between 4.0 and 5.0 kPa during instrumentation. The umbilical artery and vein were catheterized for blood sampling, continuous blood pressure recording, and infusion of fluid and drugs. Rectal temperature was continuously measured and kept normal for newborn pigs (8) between 38.5 and 39.5°C by means of a radiant heater and a heating pad.

We intended to position an EM probe and a Doppler transducer next to each other on the internal carotid artery. The extensive dissection necessary to do this would be mutulating to the superior cervical ganglion and nerve fibers in the area. We therefore converted the common carotid artery into a precerebral artery by ligating the external carotid and the small occipital artery arising from the internal carotid. This was validated by dye injection showing that the modified common carotid supplied intracranial tissue only. The surgical wound was filled with saline solution at 39°C and kept open to allow for positioning of the transducers and clamping of the modified common carotid for zero flow calibration of the EM during the experiment.

Doppler ultrasound. To measure intracerebral velocities with Doppler ultrasound, an artificial fontanel 1 cm in diameter with intact dura was made. It was positioned lateral and rostral to the midline where the sutures meet on the same side as the exposed common carotid artery.

A 10-MHz flat-surface single element transducer with an aperture diameter of 3 mm was positioned in a stereotactic holder and used for both intracerebral and common carotid velocity recordings. The mean depth of the sampling volume was 10 mm for both recording sites. A bidirectional ultrasound Doppler velocitymeter (SD 100, Vingmed Sound, Horten, Norway) was interphased to a microcomputer (Apricot XI ACT, Apricot UK Ltd., Halesowen, England) running a dedicated data collection and analysis program (9). The Doppler instrument includes an intensity-averaged mean velocity estimator that calculates the average velocity of the whole cross-sectional area. This instantaneous mean velocity was fed into the computer and integrated for each R-R interval. If the cross-sectional area of the vessel does not change during the recording, the time-averaged mean velocity per heartbeat is proportional to the average volume flow during each cardiac cycle (7). The time-averaged mean of the average cross-sectional velocity signal is found to be the best single estimate of changes in flow (10). To reduce the noise from the pulsating arterial wall, a high pass filter of 116 Hz that removed velocities less than 1.05 $cm \cdot s^{-1}$ was used.

The calculated velocities from the Doppler-shifted frequencies vary with the cosine of the angle between the vessel and the direction of insonication and diameter. Because the angle of insonication and the vessel diameter are often unknown, absolute flow values cannot be obtained. Relative changes in flow can be estimated for a constant angle of insonication if the average vessel diameter over the cardiac cycles studied does not change.

For the common carotid artery Doppler flow calculations, we estimated the inner diameter to be 1.5 mm for all animals. The Doppler probe was fixed in a stereotactic holder with an angle of insonication of 30°. From the internal cerebral artery, satisfactory signals were obtained by adjusting the depth of the sampling volume and the direction of the sound beam while observing the spectrum on an oscilloscope and listening to the audio signal on the loudspeaker. The angle of insonication as well as the diameter was unknown. We chose a 1.5-mm diameter and a 30° angle as constants for these calculations as well.

Flow calculations from the electromagnetic signal. We used a 2.0-mm EM probe (Nycotron flowmeter 372, Nycotron A/S, Drammen, Norway) that fit closely around the common carotid artery of all piglets. An EM probe induces a magnetic field through the vessel, and the voltage generated when blood as a conductor cuts through the magnetic field is proportional to the volume flow (11). Theoretically, when the magnet drive is removed, the EM flow signal is zero and the output of the device should coincide with zero flow as obtained by mechanical occlusion of the vessel. In practice, this does not occur because of variable quantities of transformer voltage being detected in the demodulation circuit. This added signal results in a DC component in the output that can be measured and is superimposed on the flow signal (12). Zero flow calibration was performed three to five times during each experiment by complete occlusion of the carotid artery distal to the flow cuff. Carotid Doppler recordings showed zero velocities. These mechanically occlusive zeros were compared with electrical zeros and adjustments made. *In vivo* calibration of the EM probe *in situ* was performed for each experiment before the animal was killed by rapid injection of KCl. The carotid artery was cannulated distally to the site of the transducer, and measured volumes of blood were withdrawn and later reinjected. A calibration factor was obtained and used when calculating volume flow from the traces. The mean

Table 1. *MABP (kPa) and $Paco_2$ (kPa) values before and after hemorrhage and transfusion and before and during hyperventilation and CO_2 ventilation**

		Hemorrhage			Transfusion			Hyperventilation			5% CO_2 ventilation		
		n	Before	After	*n*	Before	After	*n*	Before	During	*n*	Before	During
Precerebral Doppler	MABP	9	7.7 ± 0.5	3.6 ± 0.5	9	6.8 ± 0.3	9.3 ± 0.5	9	6.3 ± 0.1	5.1 ± 0.4	9	6.1 ± 0.3	6.4 ± 0.5
and precerebral EM	$Paco_2$	9	5.4 ± 0.3	5.7 ± 0.2	9	5.4 ± 1.6	6.1 ± 0.2	9	5.1 ± 0.2	2.8 ± 0.4	9	5 ± 0.1	7.4 ± 0.2
Intracerebral Doppler	MABP	5	6.1 ± 0.3	3.7 ± 0.3	3	5.5 ± 0.4	9.1 ± 1.1	4	6.3 ± 0.8	5.7 ± 0.8	4	5.6 ± 0.8	6.7 ± 0.8
and precerebral EM	$Paco_2$	5	5.6 ± 0.2	5.2 ± 0.1	3	5.5 ± 0.1	5.7 ± 0.3	4	5.2 ± 0.3	3.6 ± 0.6	4	5.1 ± 0.3	7.5 ± 0.2

* Values are mean ± SEM. To convert kPa MABP to mm Hg MABP, multiply by 7.5.

calibration factor for the transducer obtained from nine experiments was 60.5 (95% confidence interval = 55.9–65.2).

Experimental protocol. A recovery period of at least 20 min was allowed after instrumentation. Arterial blood gases were analyzed by an AVL 945 (Biomedical Instruments, Schaffenhausen, Switzerland) and were corrected for actual Hb and temperature.

Each animal was subjected to CO_2 inhalation, hyperventilation, hemorrhage, and blood transfusion. The interventions were randomly performed to avoid time-dependent results. In five animals, Doppler recordings were obtained from both the common carotid artery and an intracerebral artery and the interventions were repeated.

Blood pressure changes. If hemorrhage was the first intervention, hypotension was induced after a baseline period of 10 min by drawing blood (1–2 mL/kg/min) from the umbilical vein until the MABP was reduced by 40%. In individual animals, 20 mL/kg (median; range 12–33 mL/kg) was removed. When the MABP had stabilized at the low value for at least 10 min, the blood was retransfused. To increase the blood pressure by 50% from baseline, 31 mL/kg (median; range 22–97 mL/kg) cross-matched pig donor blood was transfused. Blood samples for blood gas analysis were taken before and 1 min after hemorrhage and transfusion.

CO_2 changes. After a baseline period of 10 min, either a period of hypercapnia was induced by adding 5% CO_2 to the inhalation gases for at least 15 min or hypocapnia was induced by increasing the ventilator frequency from 20/min (inspiratory time 0.3 s, expiratory time 2.7 s) to 100/min (0.3 s/0.3 s). Blood gases were analyzed before and during the last minute of hypercapnia or hypocapnia.

Statistical analysis. $Paco_2$ and MABP not only regulate CBF independently but also interact with one another (13). To estimate the separate influences of MABP and CO_2 variations, exclude biologic variation between piglets, and control for a varying number of measurements from each animal, the results were analyzed by multiple linear regression methods (BMPD 1R) (14) and general mixed model analysis of variance (BMPD 3V) (14). In the last model, EM flow and Doppler estimated flow were dependent variables, the piglet was a random variable,

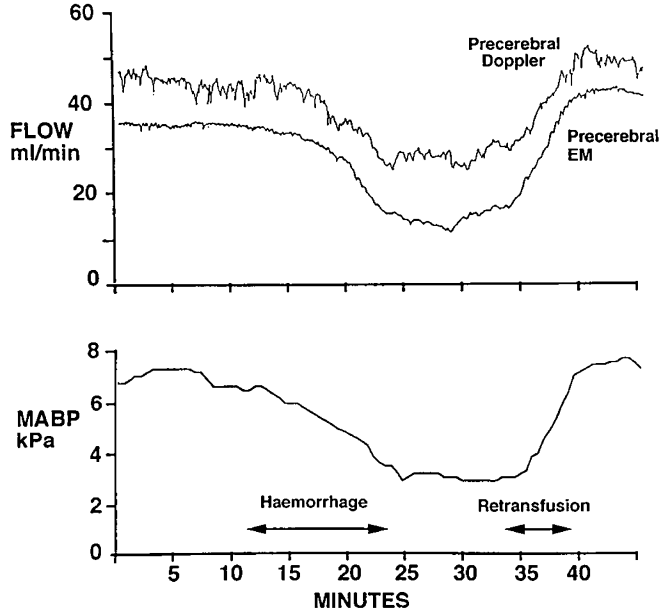

Figure 1. The CBF (electromagnetic flowmetry) and CBFV (Doppler) recorded from the modified common carotid artery (*upper panel*) and MABP (*lower panel*) in response to hemorrhage and subsequent retransfusion.

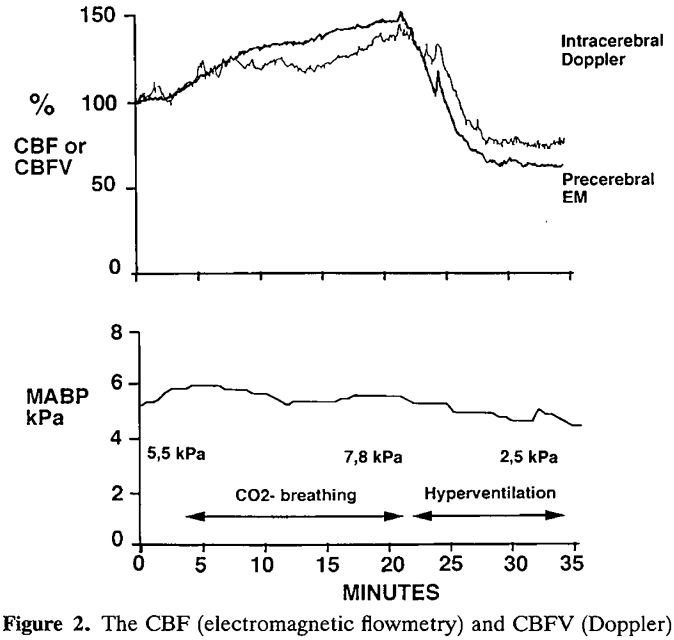

Figure 2. The CBF (electromagnetic flowmetry) and CBFV (Doppler) in response to 5% CO_2 inhalation followed by hyperventilation. Baseline normocapneic values were normalized to 100% for both CBF and CBFV. The CBF was recorded from the modified common carotid artery and CBFV recorded from an intracerebral artery. The MABP is shown in the *lower panel*. The $Paco_2$ values during normocapnia, hypercapnia, and hypocapnia are written on the lower panel.

Table 2. *Estimated effect of MABP (kPa) and $Paco_2$ (kPa) changes on relationship EM flow/Doppler flow when recordings were performed either on modified common carotid artery (precerebral) or intracerebral arteries*

	Precerebral EM and precerebral Doppler		Precerebral EM and intracerebral Doppler	
Flow change by	MABP	$Paco_2$	MABP	$Paco_2$
Estimate ± SEM	0.015 ± 0.008	−0.005 ± 0.013	0.023 ± 0.023	−0.025 ± 0.023
Two-tail probability	0.18	0.69	0.25	0.27
Variance of residuals	0.023		0.029	

and MABP and CO_2 were the independent variables in the analysis. The following model was used: $y_i = \beta_{mabp}$ $MABP_i + \beta_{co2}$ $CO_{2i} + a_i + e_i$. y_i is the flow value (either Doppler or EM), β_{mabp} and β_{co2} are the factors flow changes with per unit change in MABP and CO_2, a_i is the constant controlling the variability between piglets, and e_i (the residual) is the random error based on the difference between the observed and the predicted flow.

The calculated mean values of a representative 1-min period in 142 different CO_2- and MABP-induced flow situations were compared for EM flow and estimated Doppler flow. Ninty-three of these recordings from all nine piglets were obtained with both transducers on the modified common carotid artery. In five of the piglets, 49 recordings were obtained with the EM transducer unchanged on the modified common carotid artery (precerebral) and with the Doppler transducer recording from an intracerebral artery (most likely the middle cerebral).

The study was approved by the Norwegian Animal Research Committee.

RESULTS

One hundred forty-two simultaneous recordings with Doppler ultrasound and EM in different flow situations were obtained, with the average MABP changing from 3.7 to 9.3 kPa (*i.e.* 28 to 70 mm Hg) and the average $Paco_2$ varying from 3.0 to 7.4 kPa. Mean values with SEM for MABP and $Paco_2$ are given in Table 1. Individual examples of two continuous 40-min recordings are shown in Figures 1 and 2. Changes in EM and estimated Doppler flow when MABP is varied between 2.7 and 7.6 kPa follow each other closely (Fig. 1). The changes in CBFV from an intracerebral artery (Fig. 2) also closely follow the precerebral EM flow (upper panel) in response to CO_2 breathing and hyperventilation. The $Paco_2$ values during normo-, hyper-, and hypocapnia are shown in the lower panel. When the regression model is applied to the results from the two sets of recordings, the residuals (*i.e.* the differences between the observed values and the fitted values obtained from the model) are randomly distributed in relation to MABP and $Paco_2$ values (Table 2). Hence, the correlation EM/Doppler with either both transducers on the modified common carotid artery or with the Doppler probe on an intracerebral artery was unaffected by changes in MABP or $Paco_2$. The estimated coefficients for the effects of MABP and $Paco_2$ on the relationship EM/Doppler were not significantly different from zero (Table 2).

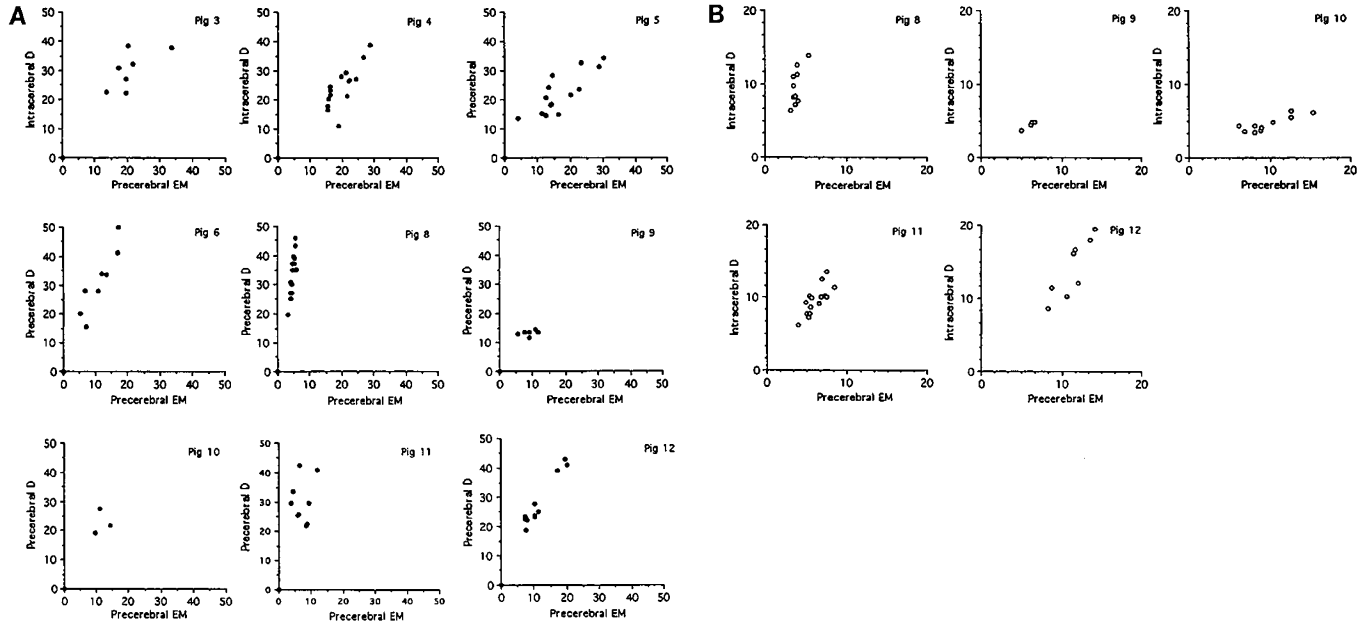

Figure 3. *A*, The relationship between electromagnetic flow and estimated Doppler flow values for each of the nine animals recorded from the same modified (extracerebral branches ligated) common carotid artery. *B*, The relationship between electromagnetic flow recorded from the common carotid artery and estimated Doppler flow values recorded from an intracerebral artery in five of the nine animals.

Table 3. *Multiple R^2 correlation for relationship between EM flow and Doppler estimated flow in modified common carotid artery (precerebral) in nine animals and correlation between precerebral EM and intracerebral Doppler in recordings from five animals**

Animal number	Precerebral EM and precerebral Doppler				Precerebral EM and intracerebral Doppler			
	Number of observations	Slope	SEM	R^2	Number of observations	Slope	SEM	R^2
3	7	1.392	0.119	0.958				
4	15	1.224	0.055	0.972				
5	14	1.234	0.078	0.951				
6	9	2.882	0.187	0.968				
8	18	7.193	0.180	0.989	10	2.490	0.146	0.970
9	6	1.420	0.131	0.959	4	0.743	0.012	0.999
10	3	1.902	0.298	0.953	10	0.463	0.021	0.982
11	9	3.624	0.376	0.921	15	1.559	0.055	0.983
12	12	2.337	0.092	0.983	8	1.254	0.067	0.980

* The values are displayed in Figure 3. For the precerebral comparison, the angle of insonication was measured to be 30° and the diameter of the common carotid estimated to be 1.5 mm. The same constants were used when calculating intracerebral Doppler flow; however, both angle and diameter were unknown.

There was a linear relationship between common carotid EM flow and estimated Doppler flow (either common carotid or intracerebral) for the two sets of recordings (Fig. 3). The substantial difference in the slope of the lines (Table 3) revealed that the diameter of the common carotid artery was not constant between animals as assumed in the calculations. In Figure 3*A*, the diameter range was calculated to be from 0.56 to 1.33 mm to fit individual slopes to the line of identity.

DISCUSSION

Previous investigations comparing Doppler ultrasound with other methods for CBF measurements have given important information and have generally shown good agreement. The information has been limited because most studies compared Doppler ultrasound with noncontinuous methods, *i.e.* radioactive tracers or microspheres (15–20). The rapid flow changes shown with continuous methods like electromagnetic flowmetry and Doppler ultrasound in response to MABP or $Paco_2$ (Figs. 1 and 2) could not be detected by noncontinuous measurement methods. The essential question when validating CBFV measurements obtained with a constant angle of insonication is whether the diameter of the vessel investigated changes during the study. Simultaneous recordings were performed with Doppler ultrasound and electromagnetic flowmetry because electromagnetic flowmetry is an established continuous method in blood flow measurements (11). The main disadvantages are that the method needs dissection and a surgically exposed vessel and that drift of zero flow voltage requires repeated cross-clamping of the artery for adjustments.

In most earlier comparative studies, the flow changes have been induced by one method only, namely CO_2 changes (15). Knowing that the CO_2 reactivity is low in young animals (18–21) and that cerebral autoregulation is often impaired after hypoxia (22), we studied CBF in response to both blood pressure and $Paco_2$ changes. We chose the newborn piglet, which is a suitable model in cerebral neonatal research due to the similarity in body size, brain maturation (23, 24), cerebrovascular structure (25), and function.

There is disagreement as to whether large arteries change their diameter during blood pressure changes (26–28). There is less disagreement that the resistance regulation during CO_2 changes takes place distally in small vessels (29, 30). Our results show the same correlation between changes in Doppler estimated flow and EM flow during blood pressure– and CO_2-induced changes. From this we state that in our model neither the precerebral common carotid nor the intracerebral artery investigated changes its diameter significantly in the MABP range from 3.7 to 9.3 kPa or $Paco_2$ range from 3.0 to 7.4 kPa. The relationships between EM and Doppler flow in the individual animals were all linear (Fig. 3, Table 3) but revealed great variability of the slopes. During recordings when both transducers were on the common carotid artery, the angle of insonication was known. Thus, the great variability of the slopes must be due to individual differences in vessel diameter. However, the vessel diameter must have been constant throughout the experiment for each animal, because the relationship between the two methods was linear. From the slope of the line for each animal, a common carotid internal diameter was calculated. All diameters were between 0.56 and 1.33 mm. Normal variability of carotid artery diameter in the 1-d-old piglet is not known. Vessel tone might have been altered in response to nerve damage during dissection. Anesthesia may also affect vessel diameter. Chloralose/urethane is not shown to influence cardiovascular regulatory responses (31, 32). When the Doppler recordings were obtained "blindly" from an intracerebral artery, both the diameter and angle of insonication were given arbitrary values for estimation of Doppler-derived flow changes. The relationship between the two methods in each animal was linear and the slopes were different. An estimation of the diameter could not be made because the angle of insonication was unknown.

We conclude that relative changes of Doppler-estimated flow in both the modified common carotid

artery and intracerebral arteries for each individual showed the same relative variations as volume flow obtained by the EM. The poor agreement between the slopes of the lines was mainly caused by the unknown vessel diameter and did not affect the ability of Doppler ultrasound to predict relative changes in CBF in individual subjects. These results were obtained on anesthetized, healthy 1-d-old piglets within a defined blood pressure and $Paco_2$ range.

Acknowledgments. The authors thank Lars Walløe and Severin Leraan for expert advice on the computerized Doppler system and the electromagnetic flowmeter, respectively.

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