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Bedside Assessment of Cerebral Blood Flow by Double-indicator Dilution Technique

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Background: **Currently, quantitative measurement of global cerebral blood flow (CBF) at bedside is not widely performed. The aim of the present study was to evaluate a newly developed method for bedside measurement of CBF based on thermodilution in a clinical setting.**

Methods: **The investigation was performed in 14 anesthetized patients before coronary bypass surgery. CBF was altered by hypocapnia, normocapnia, and hypercapnia. CBF was measured simultaneously by the Kety-Schmidt inert-gas technique with argon and a newly developed transcerebral double-indicator dilution technique (TCID). For TCID, bolus injections of ice-cold indocyanine green were performed *via* a central venous line, and the resulting thermo-dye dilution curves were recorded simultaneously in the aorta and the jugular bulb using combined fiberoptic thermistor catheters. CBF was calculated from the mean transit times of the indicators through the brain.**

Results: **Both methods of measurement of CBF indicate a decrease during hypocapnia and an increase during hypercapnia, whereas cerebral metabolic rate remained unchanged. Bias between CBF_{TCID} and CBF_{argon} was -7.1 ± 2.2 (SEM) $ml \cdot min^{-1} \cdot 100\ g^{-1}$; precision ($\pm 2 \cdot$ SD of differences) between methods was 26.6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$.**

Conclusions: **In the clinical setting, TCID was feasible and less time-consuming than alternative methods. The authors conclude that TCID is an alternative method to measure global CBF at bedside and offers a new opportunity to monitor cerebral perfusion of patients. (Key words: cerebrovascular; circulation; method comparison; monitoring; patient study; physiology.)**

A simple method for the bedside monitoring of cerebral blood flow (CBF) is desirable, particularly in patients in whom cerebral perfusion is endangered because of intracranial pressure. In clinical practice, transcranial Doppler sonography is commonly used to evaluate cerebral perfusion because it is noninvasive, relatively easy to learn, and inexpensive. However, transcranial Doppler sonography primarily measures blood flow velocities only and does not facilitate quantitative measurement of CBF. For instance, in patients with subarachnoid hemorrhage and vasospasm, an increase of blood flow velocities paradoxically indicates a decrease rather than an increase of CBF.[1] Methodologies for truly quantitative measurement of CBF are mostly based on diffusible tracers such as inert gases, labeled water, or others. However, these methods for quantitative measurement of CBF have mainly been applied in the context of scientific studies; they are unpractical for clinical purposes because of large and bulky equipment and/or the use of radioactive tracers.

At present, fiberoptic jugular bulb catheters are often applied for bedside monitoring of jugular bulb saturation.[2] In addition to the optical fibers, these catheters can be equipped with a thermistor probe for temperature measurement and can therefore also be used for the measurement of thermodilution curves. Because temperature (or, more specifically, heat and negative heat) behaves like a highly diffusible tracer, thermodilution curves are theoretically suited to measure CBF quantitatively in a similar paradigm as inert gases are applied in the classical Kety-Schmidt technique. In addition, fiberoptic catheters can be used to measure dye dilution curves,[3] which could provide further information on cerebral perfusion. The present study was designed to evaluate the clinical feasibility of a newly developed

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transcranial thermo/dye dilution technique for bedside measurement of CBF and to compare this technique with the established Kety-Schmidt method.

Material and Methods

Patients and Study Design

The study was approved by the local institutional review board, and written informed consent was obtained from every patient. We studied 14 anesthetized men with coronary artery disease before coronary bypass surgery. Mean age was 60 yr (range, 49–71 yr), and body weight and height were 84 ± 9 kg and 176 ± 6 cm, respectively (mean ± SD). None of the patients had a history of brain injury, and according to clinical and ultrasonic examination, none of them showed preoperative evidence of cerebrovascular disease. Preanesthetic medication was 2 mg flunitrazepam on the evening before surgery and an additional dose on the following morning.

In addition to standard hemodynamic monitoring (electrocardiogram, blood pressure, pulse oximetry), an arterial and central venous catheter (6-French, Goodale-Lubin, USCI, C.R. Bard Inc., Billerica, MA; and 8.5-French, Arrows Int., Reading, PA, respectively) were placed before induction of anesthesia. Induction of anesthesia was performed with 7 μg/kg fentanyl and 0.2 mg/kg midazolam; tracheal intubation was facilitated by administration of 0.15 mg/kg pancuronium bromide. Anesthesia was maintained with 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl and 0.15 $\mu g \cdot kg^{-1} \cdot h^{-1}$ midazolam. Two jugular bulb catheters (6-French, Goodale-Lubin; and 4-French, PV-2024, Pulsion-Medizintechnik, Munich, Germany) were inserted by retrograde puncture of both jugular veins to measure pressure, thermodilution, and dye dilution kinetics and to obtain blood samples simultaneously. The correct position of the catheter tips was verified by fluoroscopy. In addition, an arterial fiberoptic thermistor catheter (4-French, PV-2024) was placed in the thoracic aorta *via* left femoral artery (also verified by fluoroscopy) for intravascular arterial measurement of the dye and the cold indicator kinetics (fig. 1). Mechanical ventilation was performed by a volume-controlled respirator with a gas mixture of 30% O_2 and 70% nitrogen. To avoid additional pharmacologic alterations of CBF, no vasoactive drugs and no inhalational anesthetics were given.

Measurements were performed during hypocapnia (I; arterial partial pressure of carbon dioxide Pa_{CO_2} = 31 ± 3 mmHg), normocapnia (II; Pa_{CO_2} = 43 ± 3 mmHg), and hypercapnia (III; Pa_{CO_2} = 54 ± 4 mmHg) in sequence. Pa_{CO_2} was controlled by adjusting the minute ventilation.

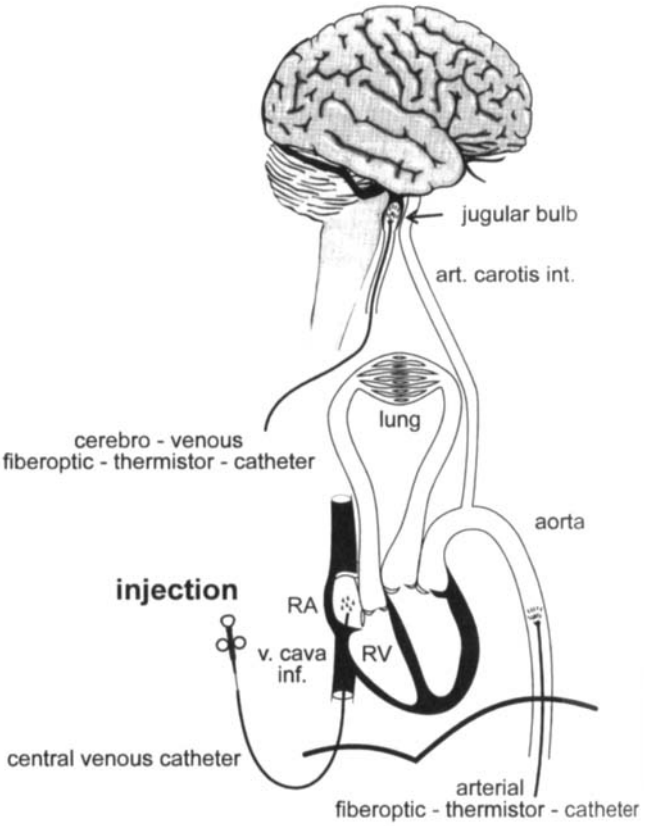

Fig. 1. Catheter placement and indicator application site for cerebral blood flow measurements using the transcerebral double-indicator dilution technique. Ice-cold indocyanine green dye bolus injections into the right atrium (RA) were performed. For intravascular detection of the indicator kinetics, two combined fiberoptic thermistor catheters were placed in the thoracic aorta and the jugular bulb. The resulting thermo-/dye-dilution curves were measured simultaneously and stored digitally with a combined thermodilution and hemoreflectometer device.

Cerebral blood flow was measured simultaneously by two methods: (1) a modified Kety-Schmidt inert-gas saturation technique[4]; and (2) the newly developed transcerebral double-indicator dilution technique (TCID).

During steady-state conditions, the measurements were performed in the following sequence: (1) blood sampling for blood gas analysis; (2) first TCID measurement; (3) Kety-Schmidt technique; (4) second blood gas analysis; and (5) second TCID measurement (fig. 2). At each measurement, electrocardiogram and arterial, cen-

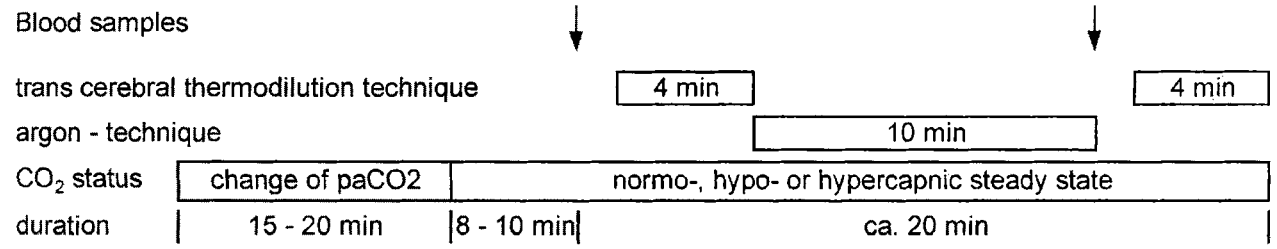

Fig. 2. Sequence of measurements performed at hypocapnia, normocapnia, and hypercapnia. During a phase of 15–20-min steady-state conditions, arterial carbon dioxide tension was adjusted to 30, 40, and 50 mmHg and verified by blood gas analysis. Over a period of 4 min, the first transcerebral double indicator dilution measurement was performed, followed by argon application *via* the lungs. Blood samples were obtained over the next 10 min to estimate the argon content and the cerebrovenous argon content difference for cerebral blood flow calculation. At the end of the argon measurement, a second blood gas analysis as well as a second TCID measurement were performed.

tral venous, and jugular bulb pressures were obtained. Thermodilution measurements of cardiac output were taken at two random times during the respiratory cycle[5] (COLD Z-021; Pulsion-Medizintechnik). Cerebral perfusion pressure was derived from mean arterial and jugular bulb pressure. Cerebral vascular resistance and cerebral metabolic rate for oxygen (CMR_{O_2}) were calculated according to standard formula.

Methods of Measurement of CBF

Kety-Schmidt Inert-gas Saturation Technique. We used the modified argon inert-gas technique developed by Tauchert *et al.*[6] In this technique, argon is used instead of nitrous oxide as indicator. Wash-in periods of 10 min were used for all measurements. A prepared gas mixture comprising 70% argon and 30% O_2 was administered to the anesthetized patient *via* the endotracheal tube by switching to a second respirator prefilled with the argon/oxygen mixture. Simultaneous blood samples from the arterial and jugular bulb catheters were withdrawn at a constant rate with glass syringes during the saturation period in duplicate using a high-precision aspiration pump (Unita I; B. Braun, Melsungen, Germany). The arterial and cerebrovenous catheters had identical dead spaces and were known to exhibit only minimal loss of inert gas by diffusion. Triple determinations of argon concentrations in each arterial and cerebrovenous blood sample were conducted after vacuum extraction by gas chromatography and ionization detection.[7] Appropriate saturation of cerebral tissue with argon was verified by comparison of arterial and cerebrovenous argon concentrations from blood sampled simultaneously at the end of each saturation period. CBF was calculated according to the following formula, whereby a brain/blood partition coefficient of 1.10 was used for argon:

$$CBF = \lambda_{argon} \cdot \frac{100 \cdot c_{cv}(t)}{\sigma \cdot \int_0^t (c_a(t) - c_{cv}(t))dt} \times [ml \cdot min^{-1} \cdot 100\ g^{-1}], \quad (1)$$

where λ_{argon} = brain/blood partition coefficient for argon (1.1),[8] $c_{cv}(t)$ = cerebrovenous argon concentration, σ = specific weight of the organ, and $\int$ = area between arterial and cerebrovenous argon saturation curve.

TCID Technique. Measurement of CBF using the TCID technique requires simultaneous assessment of thermo- and dye-dilution curves at the arterial inflow and venous outflow of the brain. For intravascular measurements of indicator kinetics, the two fiberoptic thermistor catheters (placed in the aorta and the jugular bulb, see above) were used. Bolus injections of ice-cold indocyanine green (15 mg, 40 ml, < 5°C) were performed using a 12-gauge central venous catheter. The resulting thermo-/dye-dilution curves (figs. 3A and 3B) were digitally recorded (COLD Z-021) and stored on hard disc. Further analysis of the indicator dilution curves was performed on a microcomputer (IBM, Armonk, NY; PC clone, Schlösser Computer, Göttingen, Germany). The curve analysis software was written in Pascal (Borland Pascal 7.0; Borland Inc., Munich, Germany).

Calculation of CBF. The newly developed technique for measurement of CBF by double-indicator dilution is based on the mean transit time principle, similar to the Kety-Schmidt inert-gas technique. Basically, CBF is calculated from the transcerebral mean transit time (mtt_{tc}) of a diffusible indicator and the partition coefficient λ

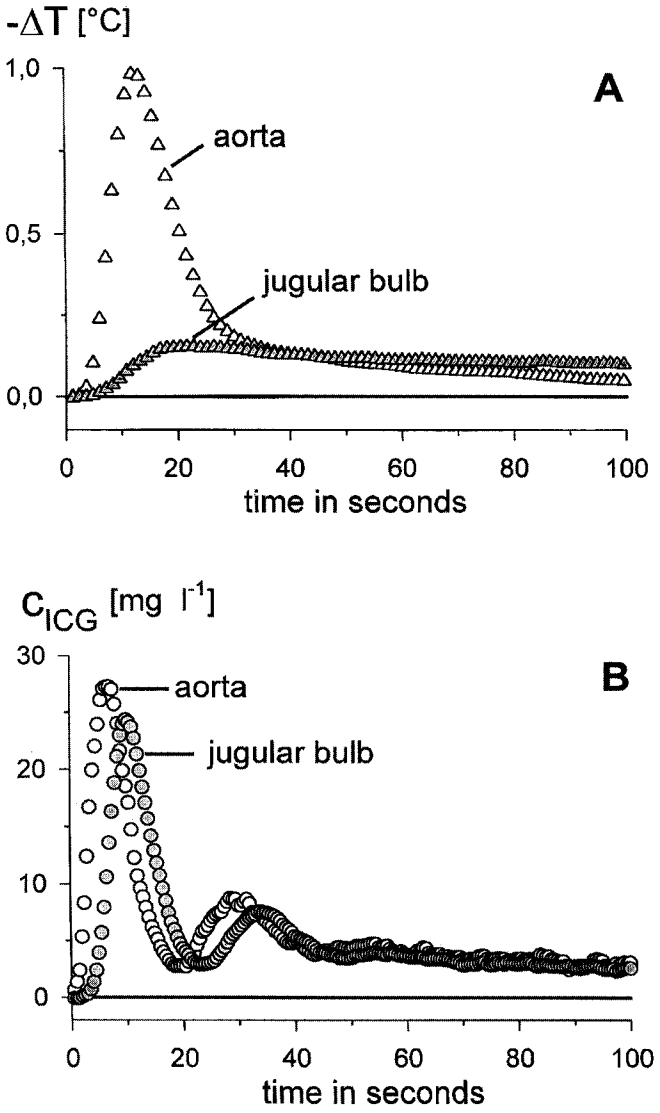

Fig. 3. (*A*) Typical thermodilution and (*B*) dye-dilution curves at the inlet of the brain (measured in the aorta) and the outlet of the brain (measured in the jugular bulb). The thermodilution curve in the jugular bulb is significantly delayed and damped because of distribution in the extravascular brain tissue, whereas the indocyanine green dye-dilution curve in the jugular bulb was only slightly delayed. The typical recirculation peak of the intravascular indicator is visible in both dye-dilution curves.

between blood and brain tissue of the respective diffusible indicator[9]:

$$CBF = \frac{\lambda}{mtt_{tc}} \quad (2)$$

In contrast to the Kety-Schmidt method, in the current methodology, negative heat (*i.e.*, ice-cold solution) is used as a highly diffusible indicator, which equilibrates nearly instantaneously with the brain tissue. With the thermodilution curves at the inflow of the brain (measured in the thoracic aorta) and the outflow of the brain (measured in the jugular bulb; fig. 3A), the mtt_{tc} can be calculated using a "black box" analysis approach of both thermodilution curves.[9]

In principle, the "black box" approach describes the passage of an indicator through an organ by a convolution integral:

$$o(t) = \int_0^t i(t-u) \cdot g(u)du \quad (3)$$

where o(t) is the indicator time course at the outflow, i(t) is the concentration time course at the inflow of the system, and u is the integration variable for the convolution procedure. The unit response function g(t) (also termed "transport function" in the context of indicator dilution theory)[10] describes the process of indicator dispersion by the organ.

In indicator dilution experiments, the "transport function" g(t) usually cannot be obtained directly; instead, the concentration time courses at the inlet [i(t)] and the outlet [o(t)] of the system are measured. Hence, the transport function must be computed by nonlinear least-square fitting based on a model assumption for g(t).[11]

The following approach was chosen to model the transport process of the negative heat through the brain. This transport process comprises two parts: (1) the intravascular transport process through the cerebral circulation [$g_{iv}(t)$]; and (2) the extravascular equilibration process with the brain tissue in the microcirculation [$g_{ev}(t)$].

In most organs, the intravascular transport process can be sufficiently modeled by a logarithmic normal density function:[3,12]

$$g_{iv}(t) = \frac{1}{\sqrt{2 \cdot \pi \cdot \sigma \cdot t}} \cdot e^{-\frac{\ln(t/mtt_{iv}) + \sigma^2/2}{2 \cdot \sigma^2}} \quad (4)$$

where g_{iv} is the intravascular transport function, t is the time since the tracer entered the system, mtt_{iv} is the mean transit time of an intravascular tracer, and σ is a measure of skewness.

Because negative heat is highly diffusible, the equilibration with the tissue can be assumed to be an almost ideal mixing process, and thus is described by an exponential function:

$$g_{ev}(t) = mtt_{ev} \cdot e^{-\frac{t}{mtt_{ev}}} \quad (5)$$

where g_{ev} is the extravascular transport function, and mtt_{ev} is the mean transit time of an extravascular tracer.

According to the principles of indicator dilution theory,[9,13] the entire transport process $[g_{tc}(t)]$ through the organ can be described by the convolution of the intravascular and extravascular transport function:

$$g_{tc}(t) = \int_0^t g_{iv}(t-u) \cdot g_{ev}(u)du \quad (6)$$

If the parameters of the characteristic intravascular and extravascular transport functions are known, the respective mean transit times (mtt_{iv}, mtt_{ev}; as parameters of the transport functions) are known as well, and the total mean transit time for the thermal indicator (mtt_{tc}) can be calculated as:

$$mtt_{tc} = mtt_{iv} + mtt_{ev} \quad (7)$$

In the current methodology, the intravascular transport function is independently determined by an intravascular indicator (indocyanine green).[14] Typical dye-dilution curves at the inlet and outlet of the brain show only a short time delay; the typical recirculation peak is also visible in the jugular bulb curve (fig. 3B). In a first step, the intravascular transport function $[g_{iv}(t)]$ is determined from the dye-dilution curves by fitting of the convolution integral of $g_{iv}(t)$ and the arterial dye curve to the dye curve at the venous outflow, whereby $g_{iv}(t)$ is modeled with a logarithmic normal density transport function (eq. 4). The results of this process are the intravascular transport parameters, mtt_{iv} and σ. Knowing these parameters, the exchange process with the extravascular brain tissue [extravascular transport function, $g_{ev}(t)$] is determined in a second step, where the thermodilution curve at the outlet of the brain [o(t)] is fitted to the convolution integral of the inlet thermodilution curve [i(t)] and the entire transcerebral transport function $[g_{tc}(t)]$:

$$o(t) = \int_0^t i(t-u) \cdot g_{tc}(u)du \quad (8)$$

In the latter fitting process, only $g_{iv}(t)$ and thus mtt_{ev} needs to be determined, because $g_{iv}(t)$ is known (see eq. 6 and 7).

Because water content of the brain is very high, the partition coefficient λ_{therm} between the brain tissue and blood was assumed to equal 1 ml/g, and CBF was calculated as:

$$CBF = \frac{1}{mtt_{tc}} [ml \cdot s^{-1} \cdot g^{-1}] \quad (9)$$

or

$$CBF = \frac{60 \cdot 100}{mtt_{tc}} [ml \cdot min^{-1} \cdot 100\ g^{-1}] \quad (10)$$

Statistics

Data are expressed as mean and SD. Comparisons between normocapnia, hypocapnia, and hypercapnia, as well as comparison between the methods of CBF measurement, were performed by Student matched pair test. Because multiple tests are necessary between the different Pa_{CO_2} states and the different methods, respectively, the levels of significance were adjusted according to Bonferroni. Results were considered statistically significant at $P < 0.01$ after correction. The three methods of CBF measurement were compared according to Altman and Bland.[15] In addition, Pa_{CO_2} response of CBF was evaluated by nonlinear regression analysis for all three methods.

Results

In total, 14 patients were included in the study. In one patient, a failure of CBF measurement by thermodilution occurred at baseline because of incorrect jugular bulb catheter position. During hypercapnia, determination of CBF by argon was not possible in two patients because the arteriojugular venous concentration differences of argon were below the detection limit.

Hemodynamic, metabolic, and blood gas data are presented in table 1. As expected, CBF decreased during hypocapnia and increased during hypercapnia with both methods. CMR_{O_2} remained unchanged at different Pa_{CO_2} levels if calculated by CBF_{argon} and CBF_{TCID} (nonsignificant; table 1).

Analysis of the relationship between CBF and Pa_{CO_2} revealed an exponential relationship for both methods of CBF measurement (fig. 4).

The comparison between the two methods of CBF

Table 1. Hemodynamic and Blood Gas Values, Cerebral Blood Flow, and Cerebral Metabolic Rate

	Hypocapnia	Normocapnia	Hypercapnia
HR (beats/min)	55 ± 8	58 ± 9	59 ± 10
MAP (mmHg)	81 ± 14	74 ± 12	75 ± 13
P_{bj} (mmHg)	10 ± 3	10 ± 4	11 ± 5
CPP (mmHg)	71 ± 15	64 ± 13	64 ± 15
CO (l/min)	4.5 ± 1.0	4.7 ± 0.8	5.9 ± 1.5*†
Hb (g/dl)	11.4 ± 1.2	11.5 ± 1.3	11.5 ± 1.2
Pa_{CO_2} (mmHg)	31 ± 3*	43 ± 3	54 ± 4*†
Pa_{O_2} (mmHg)	167 ± 39	164 ± 50	189 ± 58
CBF_{arg} (ml · min^{-1} · 100 g^{-1})	30.3 ± 7.6*	39.2 ± 9.3	68.1 ± 19.9*†
CBF_{TCID} (ml · min^{-1} · 100 g^{-1})	25.1 ± 10.1*	39.3 ± 13.9	61.5 ± 25.7*†
Sbj_{O_2} (%)	47 ± 9*	64 ± 7	80 ± 6*†
CMR_{O_2arg} (ml · min^{-1} · 100 g^{-1})	2.5 ± 0.6	2.2 ± 0.4	2.2 ± 0.6
CMR_{O_2TCID} (ml · min^{-1} 100 g^{-1})	2.0 ± 0.9	2.0 ± 0.6	1.9 ± 0.9

Hypo-, normo-, and hypercapnic states were adjusted by respirator settings. Values are mean ± SD.

* Significant differences *versus* normacapnia; $P < 0.01$, α adjusted for three tests.

† Significant differences *versus* hypocapnia; $P < 0.01$, α adjusted for three tests.

arg = argon method; CBF = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate for oxygen; CO = cardiac output; CPP = cerebral perfusion pressure; Hb = hemoglobin concentration; HR = heart rate; MAP = mean arterial pressure; P_{bj} = jugular bulb pressure; Pa_{CO_2} = arterial carbon dioxide tension; Pa_{O_2} = arterial oxygen tension; TCID = transcerebral indicator dilution method.

measurement according to the method of Altman and Bland showed a reasonable agreement between the thermodilution measurement of CBF and the argon method. The bias between both methods was −7.1 ± 2.2 (SEM) ml · min^{-1} · 100 g^{-1}; the precision (± 2 · SD) was 26.6 ml · min^{-1} · 100 g^{-1} (fig. 5).

Discussion

The aim of the present study was to compare the newly developed TCID technique with the established method for CBF measurements, the Kety-Schmidt inert-gas saturation technique. The results of the study demonstrate that with both techniques, the expected changes of CBF could be observed in response to the hypocapnic or hypercapnic challenge: CBF increased with an increase of Pa_{CO_2} and *vice versa*. Moreover, the feasibility of the TCID technique as a bedside method for measurement of CBF was proven. However, a relatively fair correlation between both methods was observed. In this study, none of the methods for measurement of CBF can be considered a "gold standard." Each methodology has clearly its limitations.

Limitations of the TCID Technique

The TCID methodology is based on the determination of mean transit times for the dye and the thermal indicator. Technically, these transit times can be assessed with a very high precision. Because only times are derived from the indicator dilution curves, an absolute calibration of the system is not required. The only prerequisite for the correct calculation of the mean transit times from the indicator dilution curves is the linearity of the systems. We therefore tested the entire measuring device (*i.e.*, fiberoptic catheter and COLD System) before the clinical study *in vitro* for linearity of the dye and temperature measurements. Linearity was verified for the dye up to a concentration of 40 mg/l (measured in blood/dye samples with increasing concentrations of indocyanine green, δc_{ICG} = 2.5 mg/l) and for the temperature measurement in the range of 27–41°C (measured in a temperature-controlled water bath with increasing temperatures, δt = 0.1°C). All clinically measured values were well within the range of linearity.

In some patients, positioning of the fiberoptic jugular bulb catheter for undistorted assessment of the dye-dilution curves was technically difficult. In contrast to the arterial catheter, where a free intravascular floating position of the catheter tip is indicated by the pulsatile nature of the reflected light intensities, pulsatility is not present at the venous outflow side of the brain. Because the currently available catheters are very difficult to visualize by radiograph, verification of correct positioning in the jugular bulb and exclusion of wall contact of the fiberoptic tip, which leads to distortion of the dye curve, is difficult. In fact, the only practical method to verify a free-floating position of the catheter tip is by visual verification of an undistorted dye-dilution curve.

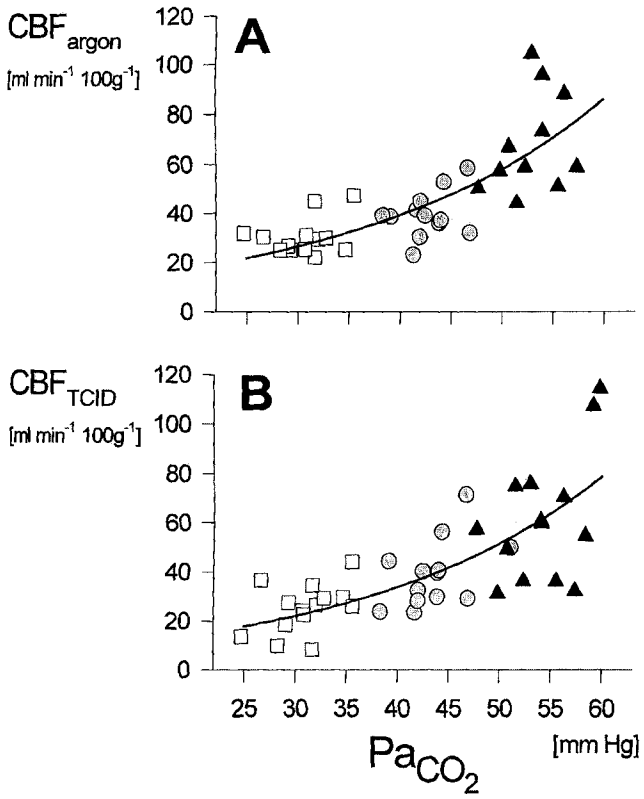

Fig. 4. Relationship between Pa_{O_2} and cerebral blood flow (CBF) at hypocapnia (square), normocapnia (circle), and hypercapnia (triangle). With both methods of CBF measurement, the relation between flow and Pa_{CO_2} can be described by an exponential function (solid line). Good correlation was found for (*A*) the Kety-Schmidt technique (CBF_{argon}; $r = 0.73$, $y = 8.2 \cdot e^{0.04 x}$) and (*B*) the transcerebral double-indicator dilution technique method (CBF_{TCID}; $r = 0.72$, $y = 6.2 \cdot e^{0.04 x}$).

Wall contact of the thermistor probe seems to be less critical because it can be considered to act like an additional coating of the probe, *i.e.*, a maximally increased response time at this measurement site of 1 s. However, this increase in response time is most likely only a minor source of error because total transcerebral mean transit times for the temperature indicator range between 50 and 600 s. The estimated error caused by a possible wall contact effect is therefore < 1%.

Temperature changes caused by a cold bolus dose may affect cerebral metabolism. Theoretically, CMR_{O_2} is decreased by 5–10% per degree Celsius of cooling. However, the maximal cooling observed in the jugular bulb (which most likely represents the cooling of the tissue) was, in general, < 0.15°C. Thus, CMR_{O_2} is not significantly affected.

The major problem of the TCID method is certainly the sensitivity to temperature drifts. The amplitude of temperature changes in the jugular bulb is very small. Although a very large amount of negative heat is applied (40 ml of ice-cold solution), only very small thermodilution curves result in the jugular bulb. The amplitude of the temperature changes in the jugular bulb ranges between 0.1°C and 0.3°C. It is therefore obvious that even very slow temperature drifts or small temperature fluctuations can cause a severe artifact in jugular bulb thermodilution curves. In particular, with very low CBF rates, the methodology becomes very sensitive to spontaneous temperature fluctuations. In our experience, the signal-to-noise ratio becomes critical at mean transit times > 400 s, which corresponds to flow rates of < 15 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. Conversely, measurement of normal and increased CBF rates results in jugular bulb thermodilution curves of excellent quality.

In this study, the partition coefficient for the temperature (or, more specifically, for the negative heat) between brain and blood tissue was assumed to equal 1. No data are available for heat partition coefficients. However, the heat partition coefficient is mainly determined by the substance with the highest heat capacity, which is water. Brain–blood partition coefficients for water (λ_{water}) have been reviewed by Herscovitch and Raichle.[16] In contrast to previous investigations, where λ_{water} was assumed in the range of 0.95–0.96 ml/g, Herscovitch and Raichle stated that the correct value for λ_{water} should be 0.90 ml/g if the density of blood is considered correctly. If it is assumed that the brain–blood partition coefficient for heat is similar to that of

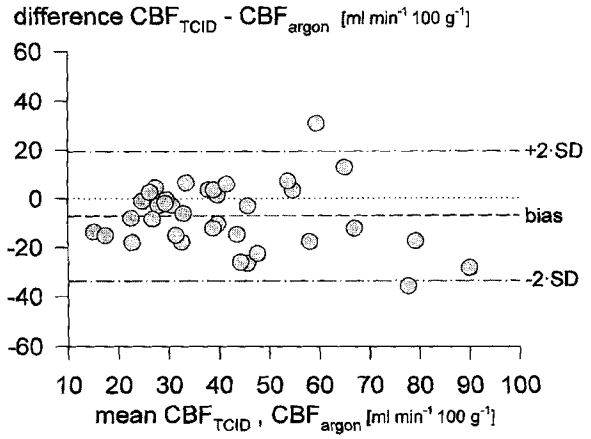

Fig. 5. Differences between the transcerebral double-indicator dilution technique (CBF_{TCID}) and the Kety-Schmidt technique (CBF_{argon}). Shown are bias (solid line) and precision (2 · SD, dashed line) according to Altman and Bland.[15] A reasonable agreement was found between CBF_{TCID} and CBF_{argon}, with a small bias and without any systematic deviation.

water, the CBF_{TCID} values must be corrected by a factor of 0.9. This would lead to a slight increase of the systematic difference between CBF_{argon} and CBF_{TCID}. However, the comparison of both methods would remain unchanged.

Limitations of the Kety-Schmidt Inert-gas Technique

Like TCID, the original Kety-Schmidt technique is also based on the determination of mean transit times, and absolute calibration of the measured inert-gas concentrations is, in principle, not required. However, in patients, only a limited number of blood samples can be drawn for CBF measurements. Therefore, a modified Kety-Schmidt technique was applied in this study, in which instead of serial arterial and venous blood samples, blood was continuously drawn with a constant speed into glass syringes by a reversed infusion pump. The advantage of this methodology is considerable blood saving. However, the disadvantage is that at states of very high CBF, the inert-gas concentration difference between the arterial and the venous sample becomes very small. Thus—in contrast to TCID, which particularly in the low range of CBF is limited—the argon technique is less accurate during high rates of CBF. As a result, the correlation coefficient between argon and TCID is 0.76, and the precision ($2 \cdot SD$) is only 26.6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$. The scatter between both methods is most likely explained by the low accuracy of the TCID method in the low-CBF range and on the other hand by the low accuracy of the argon method in the high-CBF range.

Limitations for the Comparison of Both Techniques of CBF Measurement

A limitation for the comparison of both methods could be related to the fact that jugular bulb catheters were placed on both sides. However, in most humans with normal cerebral perfusion, a fairly good mixing occurs in cerebral sinuses, and no dominant side can be observed.[17–19] However, even if differences in the perfusion of the left and right hemisphere hypothetically were present in these patients, the bias between both methods should not be affected systematically. However, part of the observed scatter between both methods might possibly be explained by intraindividual side-related differences of hemispheric perfusion.

In fact, this investigation has to be considered as a pilot study that was conducted in patients with normal cerebral perfusion. Whether this technique would succeed in patients with more severe disturbance of cerebral circulation, particularly with regional disturbances, remains to be proven.

Perspectives of the TCID Technique for Bedside Use

A bedside method for assessing CBF could be of considerable clinical value, particularly in patients with intracranial pathology. Currently available methods for direct measurement of CBF (Kety-Schmidt technique, radioactive isotopes, xenon computed tomography, single-photon emission computed tomography, *etc.*) are difficult to apply in an clinical setting and are limited with respect to the number and frequency of repeated measurements.

Another approach for CBF measurement is the continuous thermodilution technique, which is somewhat cumbersome for routine use at bedside.[20] This methodology is based on the principle of conservation of matter (Steward Hamilton or Fick principle, respectively); the measured CBF is given in absolute units (milliliters per minute). In contrast, the newly developed method for bolus thermodilution is based on the mean transit time approach; the estimated CBF is a tissue-weighted value, and values are given in milliliters per minute per 100 g (like the Kety-Schmidt approach). This is a completely different paradigm that is absolutely novel and has, to our knowledge, never been applied to thermodilution curves previously. In addition to some practical advantages (simultaneous measurement of other parameters such as cardiac output, intrathoracic blood volume, lung water, *etc.*),[3] it is important to note that useful CMR_{O2} can only be calculated based on CBF values in terms of milliliters per minute per $100\ g^{-1}$.

An advantage of the TCID method is the possibility of repeating measurements within a reasonable time frame (within 15 min) and without significant costs. Thus, even facing a limited signal-to-noise ratio, an accurate average CBF value should be assessable by repetitive TCID measurements.

Transcranial Doppler measures blood flow velocities only and is therefore only an indirect estimate of CBF. Several studies have been performed to evaluate the relation between CBF velocity in the middle cerebral artery and CBF in humans.[21,22] In fact, the relation between CBF and TCD is not always constant because of changes in cerebral artery diameter, erythrocyte velocity spectrum, and regional flow distribution.[4,23–25]

Ideally, TCID and TCD could be combined to achieve a continuous quantitative monitoring of CBF, and possibly of CMR_{O_2} as well. By calibration of TCD with TCID, a beat-by-beat measurement of CBF and metabolism

could be achieved. If deemed necessary, the calibration procedure could be repeated, *i.e.*, if significant changes of blood flow velocities are observed or if the pulsatile pattern of the TCD signal shows significant changes. An advantage of the TCID method is the repeatability at bedside. Similar to measurements of cardiac output by thermodilution, the average value of repetitive TCID measurements can be used for the calibration procedure to improve the accuracy of an combined TCID/TCD method. Moreover, cerebral venous oxygen saturation could be continuously measured with the jugular bulb catheter. Thus, on-line monitoring of CMR_{O_2} should be possible. Theoretically, the implementation of such a technology in currently available monitoring systems is possible.

We conclude that TCID is an attractive alternative for measuring global CBF at the bedside and offers a new opportunity to monitor cerebral perfusion of patients.

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