Transcranial Doppler sonography during isoflurane/N_2O anaesthesia and surgery: flow velocity, "vessel area" and "volume flow"

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Transcranial Doppler sonography (TCD) constitutes an advance in noninvasive monitoring of the cerebral circulation. However, as long as the diameter and cross-sectional area of the insonated middle cerebral artery (MCA) remain unknown, the derived flow velocities (v) are not informative. It is not known how the human MCA is influenced by anaesthetic agents. However, a TCD-modification allows noninvasive determination of "vessel area" (VA) and "volume flow" (VF) in MCA by analysing the backscattered Doppler power. This investigation evaluates the effects of isoflurane (in combination with N_2O and surgery) on v, VA and VF. In 14 patients (ASA I) scheduled for minor surgical or gynaecological operations, anaesthesia was induced with droperidol, alfentanil, thiopentone and vecuronium. After intubation ventilation with N_2O:O_2 = 3:2 was adjusted, to maintain endexpiratory carbon dioxide ($FECO_2$) constant between 4 and 5%. Baseline values of heart rate (HR), oscillometric mean arterial pressure (MAP), and TCD variables (v, VA VF) were measured before adding 2.4% isoflurane to the inspiratory mixture. Further measurements were made 3, 6, 10, and 20 min after starting isoflurane. Surgery commenced between the sixth and tenth minute after isoflurane application. The MAP, $FECO_2$, and v showed only minor alterations; HR increased after 6, 10 and 20 min. Transcranial "vessel area" and "volume flow" showed increases after isoflurane inhalation. The increase of "vessel area" supports the assumption that isoflurane greater than 1 MAC dilates large human cerebral arteries, so that if flow velocities are considered alone, alterations of cerebral blood flow may easily be underestimated.

La sonographie par Doppler transcrânien (TCD) constitue un progrès dans le monitorage non invasif de la circulation cérébrale. Cependant, tant que le diamètre et la surface de la région de l'artère cérébrale moyenne (MCA) soumise aux ultrasons restent inconnus, les vélocités (v) enregistrées restent inutilisables. On ne sait pas comment la MCA humaine est influencée par les agents anesthésiques. Néanmoins, une modification de TCD procure une détermination non invasive de la « surface du vaisseau » (VA) et du « débit » (VF) dans la MCA en analysant l'importance du retour d'écho (« backscattered Doppler-power »). Cette investigation évalue les effets de l'isoflurane (en combinaison avec N_2O et la chirurgie) sur v, VA et VF. Quatorze patients (ASA 1) programmés pour des opération mineures, générales ou gynécologiques ont eu une anesthésie au dropéridol, alfentanil, thiopentone, et vécuronium. Après l'intubation, une ventilation au N_2O/O_2 = 3:2 est ajustée pour maintenir un CO_2 respiratoire ($FECO_2$) constant entre 4 et 5%. Les valeurs de base de fréquence cardiaque (HR), pression artérielle moyenne par oscillométrie (PAM), et des variables TCD (v, VA, VF) sont mesurées avant d'ajouter 2,4% d'isoflurane aux gaz inspirés. Les mesures ultérieures sont réalisées 3, 6, 10 et 20 min après le début d'administration d'isoflurane. La chirurgie a commencé entre la sixième et la dixième minute après l'administration d'isoflu-

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rane. MAP, $FECO_2$ et v montrent que des altérations mineures; HR augmente après 6, 10 et 20 min. La « surface du vaisseau » et le « débit », s'accroissent après l'inhalation d'isoflurane. L'augmentation de la « surface du vaisseau » soutient l'affirmation qu'une administration d'isoflurane supérieure à 1 MAC dilate les grosses artères cérébrales chez l'homme, de telle sorte que si la vélocité est considérée seule, les variations du débit sanguin cérébral peuvent être facilement sous-estimées.

Transcranial Doppler sonography (TCD) is a major advance in the noninvasive monitoring of the cerebral circulation during the perioperative period.[1-6] The effects of anaesethetic agents on flow velocities in the middle cerebral artery measured by TCD have been reported by several groups. Halothane[7,8] and nitrous oxide[8,9] increase flow velocities, whereas thiopentone[8] or propofol[10] cause marked reductions. Lundar *et al.*[11] investigated the effects of 1 and 2 MAC isoflurane in 12 hydrocephalic patients. They demonstrated a reduction of cerebral perfusion pressure whereas flow velocities remained unaltered. They pointed out the central problem arising with transcranial Doppler measurements: as long as the diameters of the investigated vessels remain unknown, flow velocities are not informative for clinical or scienitific evaluation. They assumed[11] that the diameter of the middle cerebral artery would not be influenced or only slightly dilated by increasing isoflurane concentrations. Measurement of middle cerebral artery diameter in humans under the influence of different anaesthetic drugs has not been performed due to ethical and methodological restrictions.

A modification of transcranial Doppler sonography can partly solve the question of vessel diameters in humans. The TCD device TC 2000 S (EME, W-7700 Überlingen, FRG) permits the determination of the reflected Doppler power which is proportional to the cross-sectional area of the insonated vessel[12-14] ("vessel area"). By multiplying "vessel area" by mean velocity, even relative changes of "volume flow" (VF) can be analyzed.[13] Isoflurane is recommended for carotid endarterectomy,[15] which is frequently monitored with transcranial Doppler sonography. This investigation evaluated the effects of isoflurane on transcranially measured flow velocities, "vessel area" and "volume flow" in human middle cerebral arteries.

Methods

After approval of the study by the Ethics Committee of the Ruhr-Universität Bochum 14 patients (ASA I) were investigated after informed consent. They were scheduled to undergo minor surgical or gynaecological procedures. After premedication with midazolam 0.05 mg · kg^{-1} *im*, anaesthesia was induced with droperidol 0.075 mg · kg^{-1}, alfentanil 10 μg · kg^{-1} and thiopentone 4 mg · kg^{-1}. When mask ventilation with 100% oxygen was established, vecuronium bromide 0.1 mg · kg^{-1} was given to provide neuroumscular relaxation. An additional dose of thiopentone 1–3 mg · kg^{-1} was injected two minutes later prior to oral tracheal intubation. After intubation, ventilation with nitrous oxide:oxygen = 3:2 was adjusted to maintain endexpiratory carbon dioxide constant between 4 and 5%. Patients received alfentanil 10 μg · kg^{-1} and droperidol 0.075 mg · kg^{-1}. The transcranial ultrasound probe was fixed to the temporal bone in a special head frame and focused to a depth of approximately 46 mm to obtain an optimal signal from the distal part of the middle cerebral artery. After probe fixation baseline values of heart rate (HR, Sirecust 403-2, Siemens, W-8520 Eriangen, FRG) oscillometric mean arterial pressure (MAP, Siemens Sirecust 888R), and endexpiratory carbon dioxide ($FECO_2$, Datex Normocap, Hoyer, W-2800 Bremen, FRG) were measured. The following TCD variables were derived from the device TC 2000 S with the special TCANALYS module (EME, W-7700 Überlingen, FRG):

(a) Mean maximal velocity (v): v was obtained by Fast-Fourier Transformation of the envelope of the backscattered frequency spectra.

(b) The relative value for "vessel area" (VA). Based on the work of Arts and Roevros,[14] Aaslid[12,13] has pointed out, that a change in real cross-sectional vessel area is accompanied by a proportional change in the reflected power of the Doppler signal, if the sample volume is larger than the insonated vessel, probe position is constant, and insonation conditions are kept constant.[12,13] By analysing the backscattered Doppler-power TCANALYS provided a numeric value for "vessel area."

(c) The relative value for transcranial "volume flow" (VF).[13] TCANALYS calculated VF by multiplying the reflected Doppler-power with mean velocity.[13]

Isoflurane 2.4% were then added to the inspiratory mixture and further measurements (HR, MAP, $FECO_2$ and TCD) performed 3, 6, 10, and 20 min after the start of isoflurane inhalation. The resulting endexpiratory isoflurane concentrations were 0.86% after three minutes, 1.16% after six minutes, 1.37% after ten minutes and 1.61% after 20 min. Surgeons were allowed to begin the planned operation six minutes after isoflurane administration. Boluses of alfentanil were provided if anaesthetic depth was deemed insufficient.

Mean ± SD of each variable was calculated at each data-point. Statistical evaluation was performed by analysis of variance for repeated measures followed by Student's t test for paired comparisons with Bonferroni cor-

TABLE Recorded data. Mean ± SD during study

	Baseline	*3 min*	*6 min*	*10 min*	*20 min*
HR	67.9 ± 12.8	71.9 ± 12.2	80.4 ± 16.3*	86.2 ± 16.9*	89.3 ± 16.4*
MAP	81.8 ± 17.3	77.9 ± 15.5	82.8 ± 16.4	83.4 ± 17.5	79.2 ± 16.6
$FECO_2$	4.15 ± 0.26	4.09 ± 0.22	4.06 ± 0.22	4.09 ± 0.29	4.07 ± 0.32
FEI	0.00 ± 0.0	0.86 ± 0.07*	1.16 ± 0.10*	1.37 ± 0.12*	1.61 ± 0.15*
v	45.4 ± 5.92	44.9 ± 8.06	48.6 ± 9.77	50.2 ± 12.4	44.1 ± 14.9
VA	0.87 ± 0.43	1.01 ± 0.51	1.49 ± 0.67*	1.49 ± 1.06*	1.79 ± 1.16*
VF	7.99 ± 3.55	9.56 ± 4.51*	10.1 ± 4.55*	11.8 ± 6.41*	13.7 ± 7.93*

HR = heart rate (beats · min^{-1}), MAP = mean arterial pressure (mmHg), $FECO_2$ = endexpiratory carbon dioxide (%; 100% ≃ 760 mmHg ≃ 101 kPa)), FEI = endexpiratory isoflurane concentration (%), v = mean maximal velocity (cm · sec^{-1}), VA = "vessel area," and VF = "volume flow" (no dimension, see text).
* $P < 0.05$ versus "baseline."

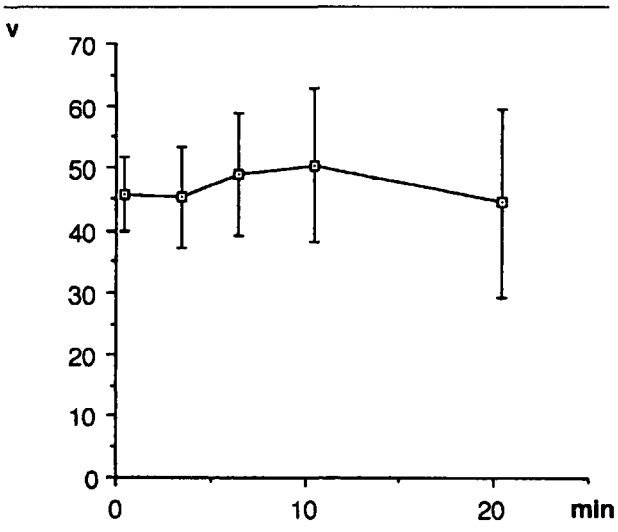

FIGURE 1 Mean maximal flow velocity v (cm · sec^{-1}; mean ± SD) showed only small, but not significant alterations. min = minutes after the start of isoflurane inhalation.

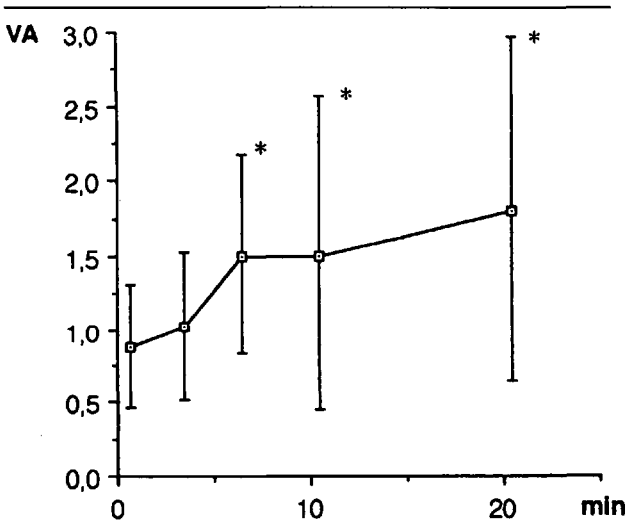

FIGURE 2 The relative value for "vessel area" (mean ± SD) nearly doubled during the first twenty minutes after isoflurane inhalation. *Significant changes versus "baseline."

rection when a significant difference was found (level of significance $P < 0.05$ = *).

Results

The results are shown in the Table. Endexpiratory carbon dioxide, mean arterial pressure, and mean maximal flow velocity v (Figure 1) showed only minor alterations. Heart rate increased during the study period. The relative value for transcranial "vessel area" increased after six minutes* and was doubled after 20 minutes* (Figure 2), the relative value for transcranial "volume flow" steadily increased from 7.99 ± 3.55 to 13.7 ± 7.92* (Figure 3).

Discussion

Although increases of heart rate after high-dose isoflurane inhalation have been reported previously,[16] the increasing heart rate observed after the sixth minute in this study is likely to have been caused by surgical stimulation. Before inhalation of isoflurane, patients received boluses of alfentanil and droperidol during probe fixation and preoperative preparations. Alfentanil causes a reduction in heart rate and decreasing plasma alfentanil concentrations may further lead to an increase of heart rate. The hypotensive effect of isoflurane[17] was not obvious in our study. Stable mean arterial pressures were achieved by the beginning of surgery after a sufficient uptake of isoflurane had taken place. This design and the type of anaesthesia before "baseline" recording and application of isoflurane are unlikely to have influenced the results: the inspired fraction of nitrous oxide, which can increase flow velocities moderately and reversibly,[8,9] was kept constant before and after isoflurane application. Alfentanil[10] and droperidol/fentanyl[7] have been shown to induce only small and temporary alterations of flow velocities. Surgery might have had an additional effect on cerebral vessels and flow velocities, but in the clinical situation

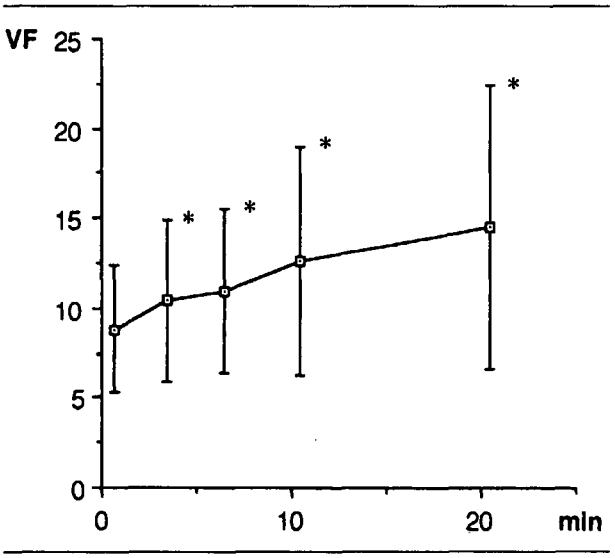

FIGURE 3 The calculated relative value for "volume flow" (mean ± SD) was enhanced significantly during the study period. *Significant changes versus "baseline."

patients who are anaesthetized and monitored are going to be operated upon. Cerebral vasodilatation due to an arousal reaction[18] as well as vasoconstrictive effects[19] can result from surgical and sympathetic stimulation. In previous studies of the same design, transcranial "vessel area" increased in patients anaesthetized with halothane, whereas this variable was not influenced in patients receiving alfentanil or propofol.[10] In this study, "vessel area" showed an increase after six minutes, before surgical stimulation occured. Thus surgery alone is unlikely to be responsible for the observed increase in "vessel area."

Since mean arterial pressure and endexpiratory carbon dioxide tension remained unaltered, autoregulatory or respiratory effects do not need to be taken into consideration when interpreting the results. It can easily be understood that more ultrasound energy is reflected from a vessel with increased cross-sectional area, if the insonated vessel remains smaller than the sample volume (approximately 4 mm) of the TCD instrument. Therefore an insonation depth of 46 millimeter was chosen to insonate the straight and smaller (approximately 2 mm) distal part of the middle cerebral artery. Our methodology allowed the determination only of relative values: it was not possible to quantify the absolute cross-sectional area of middle cerebral artery. Thus a physical unit for backscattered Doppler power ("vessel area") and "volume flow" will not be found in the text and the tables. It has to be emphasized that the results of transcranially measured "vessel area" and "volume flow" must be analyzed very cautiously and only during well-defined and short-term situations. Aaslid's second publication using this technique[12] was the subject of a critical editorial opinion.[20] Nevertheless, at the present stage of the techniuqe, analysis of "vessel area" is the only approach to the unknown real vessel cross-sectional area applicable in the clinical situation. Minimal displacement of the ultrasound probe or head rotation can induce erroneous conclusions. We used a strict experimental design in this study. All measurements were taken on anaesthetized and normocapnic patients. The ultrasound probe was fixed in a special head frame and the head and probe were not moved or touched throughout the investigation. Usually, probe displacement results in a decreased quality of the Doppler signals. Thus, it seems unlikely that the observed increase of "vessel area" was the result of inadvertent probe displacement. Standard deviation of "vessel area" and "volume flow" was high in our investigation and may be partly explainable by the wide interindividual variation of the attenuation of ultrasound in the bone or the brain.[13] Insonation conditions were kept constant meticulously throughout the whole investigation. It should be noted that the SDs of "vessel area" and "volume flow" were already high at "baseline" and increased with time. An explanation for this increase might be due to a high interindividual difference in responses to isoflurane. Furthermore, it might be speculated that isoflurane induced small alterations of intracranial insonation conditions (e.g., increases of brain volume or cerebral blood volume[21]), although extracranial fixation of the ultrasound probe was well maintained. The same phenomenon (increase of SD with time) was observed for halothane but not for propofol in previous studies using a similar design.[10]

The application of isoflurane 2.4% resulted in endexpiratory concentrations >1 MAC.[17] Thus the increased value for "volume flow" in our study is in accordance with the data reported by Eger.[17] Cerebral blood flow doubled after 1.6 MAC isoflurane, when mean arterial pressure was kept constant with phenylephrine. Unfortunately, simultaneous measurement of cerebral blood flow could not be performed during our study. Cerebral blood flow during isoflurane anaesthesia can be influenced by several variables, e.g., species, ventilation, concentration, time,[22] autoregulation and mean arterial pressure. Most studies (e.g.,[22-24]) were performed without surgical stimulation and observed decreasing or unaltered cerebral blood flow whereas mean arterial pressure decreased. The unaltered cerebral blood flow is probably the net result of a reduction in cerebral metabolic rate of oxygen[23,24] and of a counteracting direct dilating effect of isoflurane on cerebral vessels. Since isoflurane maintains CO_2 reactivity,[25] cerebral blood flow and intracranial pressure can be lowered when neurosurgical patients are hyperventilated.[26]

Our results of nearly unaltered mean maximal flow

velocities are comparable to those of Lundar *et al.*[11] and Thiel *et al.*[8] Lundar's assumption of unaltered vessel diameters[11] is not supported by our results. Isoflurane should be regarded as a potent cerebral vasodilator. Koenig *et al.*[27] used intravital microscopy and observed an increase of rat pial vessel diameters with increasing isoflurane concentrations. Recently published *in vitro* studies demonstrated a dose-dependent relaxation of rabbit basilar arteries[28] and canine middle cerebral arteries[29] exposed to halothane and isoflurane. In dogs, Werner[30] showed that increasing isoflurane concentrations increased cerebral blood flow greater than the flow velocity, which supports the assumption of isoflurane-induced dilation of large cerebral arteries. It has been mentioned already, that similar results for "vessel area" were obtained for the cerebral vasodilator halothane[10] and this is in accordance with experiments in dogs using the "vertebral-artery-wedge-pressure-technique."[31] In contrast to thiopentone and alfentanil, halothane reduced the resistance of large cerebral arteries[32] indicating a relaxing effect on large cerebral arteries and this again agrees with the results of our TCD investigations in humans. Alfentanil and propofol[10] and other *iv* anaesthetic agents such as etomidate, barbiturates and ketamine[33] did not influence "vessel area." Several authors[31,34,35] have indicated that cerebral autoregulation is at least in part located in larger extraparenchymal cerebral arteries. Interestingly, anaesthetic agents (halothane, higher concentraitons of isoflurane) which are know to disturb cerebral autoregulation,[36] were found to increase "vessel area," whereas *iv* substances do not influence autoregulation or "vessel area."

Transcranial Doppler sonography meets some of the requirements of an ideal method of cerebral blood flow monitoring: it is noninvasive, it can be performed at the bedside, it is easy to learn and allows the continuous determination of flow velocities in large basal arteries. With these advantages it is tempting to use flow velocities to draw conclusions of blood flow. However, Dahl *et al.*[37] assessed the effects of nitroglycerin on flow velocities and cerebral blood flow. They concluded that nitroglycerin causes considerable vasodilatation of the middle cerebral artery. Most studies refer to the work of Huber and Handa,[38] who demonstrated angiographically, that the diameters of large cerebral vessels remained constant under varying carbon dioxide partial pressures. Thus, transcranial Doppler sonography is a useful tool for the analysis of CO_2 reactivity. On the other hand, Magun's investigation has been neglected in the past. Using angiography he observed a diameter reduction of 15% in cerebral arteries larger than 1.5 mm, when blood pressure was pharmacologically elevated in patients without intracranial pathology.[35] If this is true for the middle cerebral artery, transcranial Doppler sonography seems not to be appropriate for the analysis of autoregulatory changes. This investigation points to another limitation: isoflurane, which was recommended for carotid endarterectomy[15] and for neurosurgical operations,[26] increased transcranial "vessel area" and "volume flow" in the middle cerebral artery. This must be kept in mind when interpreting TCD results: flow velocities alone are likely to underestimate cerebral blood flow alterations.

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