Transcranial Contrast Imaging of Cerebral Perfusion in Stroke Patients Following Decompressive Craniectomy

E. Bartels
H.-J. Bittermann

Kontrastverstärkte transkranielle sonographische Darstellung der zerebralen Perfusion bei Schlaganfallpatienten nach dekompressiver Kraniotomie

Zusammenfassung

Ziel: Mit Hilfe der kontrastverstärkten transkraniellen getriggerten B-Bild Sonographie ist es möglich, zerebrale Perfusion darzustellen. Diese Untersuchungstechnik hat jedoch methodische Probleme, insbesondere bei einem ungenügenden transtemporalen Knochenfenster. Ziel dieser Studie ist es, die Darstellbarkeit des zerebralen Perfusionsdefizits nach Applikation des Ultraschallkontrastmittels SonoVue™ bei Patienten mit einem frischen Schlaganfall nach dekompressiver Kraniotomie zu untersuchen. **Methode:** Zehn Schlaganfallpatienten (im Alter von 39 bis 59 Jahren, mittleres Alter 57 Jahre), nach einer dekompressiven Kraniotomie aufgrund einer malignen, raumfordernden zerebralen Ischämie bzw. Hämorrhagie, wurden duplexsonographisch nach Applikation des Ultraschallkontrastmittels SonoVue™ untersucht. Die transkranielle Untersuchung wurde mit dem „transient response harmonic grey scale imaging" Verfahren mit Boluskinetik, mit Hilfe von Contrast Harmonic Imaging mit „single-pulse transmission technology" – Software durchgeführt. Der mechanische Index lag bei 1.0 bis 1.1. Die Zeit-Intensitäts-Kurven aus den bestimmten Gehirnregionen wurden anhand von getriggerten Ultraschallbildern mit Pulsabständen von 1000 ms errechnet. Die sonographisch dargestellten hypoperfundierten Regionen wurden mit entsprechenden CCT und MRT Aufnahmen

Abstract

Aim: Contrast-enhanced transcranial triggered B-mode technology can be used to examine cerebral perfusion. However, this technique is still faced with methodological problems, especially the difficulty of overcoming the temporal bone window. The aim of the present study is to evaluate a deficit in cerebral perfusion after administration of the contrast agent SonoVue™ in acute stroke patients following decompressive craniectomy. **Methods:** Ten stroke patients (aged 39 to 59 years, mean age 57 years), in whom a decompressive craniectomy due to a malignant space-occupying infarction or intracerebral haemorrhage was performed, were examined with transcranial duplex sonography after application of the contrast agent SonoVue™. The transcranial examination was performed using transient response harmonic grey scale imaging with bolus kinetics based on a contrast harmonic imaging software with single-pulse transmission technology. The mechanical index was set at 1.0 to 1.1. Triggered images with pulsing intervals of 1000 ms were used for the evaluation of time intensity curves in several regions of interest. The sonographically imaged areas of hypoperfusion were compared with CT or MRI findings. **Results:** After injection of the contrast agent, the perfusion deficit could be detected ipsilaterally according to the affected vascular territory in the area of the MCA

Acknowledgments
The authors thank Dr. C. Greis (Bracco/Altana Pharma) for support and for the supply of the ultrasound contrast agent (SonoVue™), S. Williams (Siemens Medical Solution) for technical and software assistance and Mrs. C. Crozier for language editing of the manuscript.

affiliation
Department of Clinical Neurophysiology,
Department of Neurology, Georg-August-University Göttingen, Germany

correspondence
MD, PhD Eva Bartels · Department of Clinical Neurophysiology, Georg-August-University Göttingen · Robert-Koch-Straße 40 · 37075 Göttingen · Germany · Tel.: ++ 49/89/297-216 · Fax: ++ 49/89/2421-7799 · E-mail: Bartels.Eva@t-online.de

received: 1.12.2003 · **accepted:** 10.2.2004

bibliography
Ultraschall in Med 2004; 25: 206–213 © Georg Thieme Verlag KG Stuttgart · New York
DOI 10.1055/s-2004-813123
ISSN 0172-4614

verglichen. **Ergebnisse:** Nach der Applikation des Kontrastmittels konnte das Perfusionsdefizit entsprechend der betroffenen Gefäßregion ipsilateral bei 5 Patienten im Versorgungsgebiet der A. cerebri media (ACM), bei zwei Patienten im Versorgungsgebiet der ACM- und A. cerebri anterior (ACA), bei einem Patienten im Versorgungsgebiet der ACM, ACA und A.cerebri posterior (ACP) sowie bei zwei Patienten im Bereich der intrakraniellen Hämorrhagie dargestellt werden. Die Differenzbilder zeigten eine gute Übereinstimmung des sonographischen Befundes mit der Computertomographie bzw. Kernspintomigraphie bezüglich der Fläche und der Form des Perfusionsdefizits. Zusätzlich konnten wir einige interessante Kontrastmittel-induzierte Phänomene im Gehirnparenchym beobachten sowie spezifische Zeit-Intensitäts-Kurven aus verschiedenen Gehirnregionen ermitteln. **Schlussfolgerung:** Mit Hilfe der Kontrastmittel-verstärkten Duplexsonographie mit der „transient response harmonic imaging" – Technologie ist es möglich, das zerebrale Perfusionsdefizit in der Mikrozirkulation bei Patienten nach dekompressiver Kraniotomie darzustellen und neue Einblicke in die Patophysiologie der hypoperfundierten Areale zu gewinnen. Weitere Studien durch die intakte Schädelkalotte sollten bei Patienten mit akutem Schlaganfall durchgeführt werden, um diese Methode zu standardisieren und die Darstellung des zerebralen Perfusionsdefizits zu optimieren.

Schlüsselwörter
Transkranielle Duplexsonographie · Harmonic Imaging · Ultraschallkontrastmittel · Schlaganfall · dekompressive Kraniotomie

in 5 patients, in the area of ACA and MCA in 2 patients, in the area of the MCA, ACA and PCA in one patient and in the area of intracranial haemorrhage in 2 patients. The calculated average peak images corresponded precisely with the superimposed CT or MRI images in shape and size in all patients. Additionally, it was possible to observe several interesting contrast-induced phenomena in the cerebral parenchyma, as well as specific transit-time curve characteristics in the perfusion deficit area. **Conclusions:** Using contrast-enhanced transcranial duplex sonography with transient response harmonic imaging, it is possible to depict the perfusion deficit in cerebral microcirculation in patients following decompressive craniectomy and to obtain new insights into the pathophysiology of the hypoperfusion areas. Further studies should be done in stroke patients through the intact skull to standardise this method for early diagnosis of acute deficit in cerebral perfusion.

Key words
Transcranial duplex ultrasonography · native tissue harmonic imaging · contrast media · stroke · decompressive craniectomy

Introduction

Based on experience from myocardial perfusion imaging, several reports were recently published on the imaging of cerebral perfusion. A new technique – *transient response harmonic grey scale imaging* – proved useful in assessing perfusion in microcirculation. Postert and Seidel were able to measure time-intensity curves through the intact skull with transcranial sonography using the microbubble response from the contrast agents Levovist™ and Optison™ respectively [1–3]. They showed that the examination is feasible not only in young adults with a good acoustic temporal bone window. The value of this diagnostic method could also be demonstrated in pathological conditions, e. g. in patients with acute hemispheric stroke [4, 5]. With this technique, the bolus kinetics of the contrast agent are analysed during a defined time interval after microbubble destruction.

SonoVue™, a second-generation ultrasound contrast agent, is suitable for this new imaging modality, because of the specific physical properties of microbubbles, which are stabilised by a highly elastic phospholipid shell and consist of sulphur hexafluoride (SF6), an innocuous, poorly soluble gas eliminated through the lungs. This gas has a low solubility in blood (unlike air), and provides microbubbles with a higher resistance to pressure, allowing them to reach the capillary network [6]. This property, in addition to the high echogenicity of microbubbles, makes SonoVue™ suitable for marking the blood flow in capillaries of normal or pathologic tissue.

However, the imaging of cerebral perfusion is still faced with methodological problems, especially the difficulty of overcoming the temporal bone window. The aim of the present study is to evaluate cerebral perfusion deficit after administration of the contrast agent SonoVue™ in acute stroke patients following decompressive craniectomy.

Craniectomy is taken into consideration in stroke patients with space-occupying lesions if conventional brain oedema therapy does not sufficiently reduce critically elevated intracranial pressure [7, 8].

This is the first report in the literature on the use of the contrast agent SonoVue™ with single pulse transmission ultrasound technology for the evaluation of cerebral perfusion.

Subjects and Methods

Subjects

In the present study, 10 consecutive stroke patients (4 men and 6 women) aged 39 to 59 years (mean age 57 years), in whom a decompressive craniectomy due to a malignant space-occupying infarction or intracerebral haemorrhage was performed, were examined with contrast-enhanced transcranial duplex sonography in the intensive care unit.

Five patients suffered from severe intracranial hypertension due to a malignant middle cerebral artery (MCA) infarction. In one of these patients, a secondary haemorrhage in the area of the in-

farction following intravenous fibrinolysis occurred, two patients had an ischaemic stroke in the territories of the MCA and anterior cerebral artery (ACA), one patient had an infarction in the territories of the MCA, ACA and posterior cerebral artery (PCA), and the remaining two patients (one with intraventricular bleeding) had a space-occupying intracranial haemorrhage due to hypertension.

Prior to the beginning of this study, transcranial examination was performed through the intact skull in ten healthy volunteers (aged 25 to 35 years, mean age 31 years) with the aim to obtain information about the distribution of the contrast agent SonoVue™ in the regions of interest (ROIs) of the brain parenchyma, and to learn more about the specific properties of this substance using transtemporal insonation. The study complied with the Declaration of Helsinki in its revised form and with the Guidelines for Good Clinical Practice, and was approved by our local ethics committee.

Ultrasound contrast agent

The contrast agent SonoVue™ (Bracco/Altana Pharma) is commercially available and approved for cerebrovascular examination by the German authorities. This substance was administered as a slow intravenous bolus. SonoVue™ was provided as a sterile, pyrogen-free, lyophilised powder contained in a septum-sealed vial. A milky suspension of sulphur hexafluoride microbubbles was obtained by adding 5 ml of physiological saline (0.9% sodium chloride) to the powder (25 mg), using standard clinical aseptic techniques followed by shaking of the solution. After reconstitution, the bubble concentration was in the range of 1 to 5×10^8 microbubbles/ml, with 90% of microbubbles less than 8 micrometers in diameter [9]. After administration of the contrast agent, the system was flushed with 10 ml of saline.

Ultrasound system

The transcranial examination was performed with an Acuson Sequoia™ 512 US (Siemens Medical Solutions, Nürnberg, Germany), equipped with a 2 – 4 MHz phased array transducer using a contrast harmonic imaging software based on *single-pulse transmission technology*. With this technology, a single pulse packet is transmitted along the line of sight. The returning signal of this pulse packet is registered, and a single pulse of ultrasound is then transmitted along the next consecutive line of sight. The phase of this ultrasound pulse is inverted in comparison to the previous one. The overlap region between the two lines of sight is the region in which returning signals are added up so that the linear signals from tissue are cancelled out, while the nonlinear signals from microbubbles are amplified [10].

Examination technique

In the group of healthy volunteers, two axial cerebral scanning planes were visualised: first the plane through the mesencephalic brainstem, and second the diencephalic plane [11, 12]. Prior to the contrast examination, angle-corrected spectral Doppler measurements in the MCA, ACA and PCA were carried out on both sides. During the contrast examination, the mechanical index was set at 1.6 and remained constant during the session.

In the group of patients with a malignant space-occupying lesion, the examination was performed within 24 – 48 hours after the decompressive craniectomy. The decision for decompressive surgery was made on the basis of a clinical protocol for malignant middle cerebral artery infarction. The onset of stroke in these patients lay between 1 – 4 days prior to decompressive craniectomy.

The examination was performed in the intensive care unit by both examiners. The transducer was placed temporally on the skin in the area of the craniectomy, taking great care to avoid applying any pressure to the brain structures. The transducer was held by hand by one of the examiners (EB or HJB), while the other injected the contrast agent, then adjusted and optimised the parameters of the ultrasound system. Transmitting power setting and gain were optimised for each patient at the beginning of the examination and were kept constant. Imaging of the intracranial structures was performed following the same protocol as in the healthy control group. The study was carried out using *transient response harmonic grey scale imaging (TRI)* with bolus kinetics based on the studies described by Postert and by Seidel [13, 14]. For this purpose, triggered images with pulsing intervals of 1000 ms were performed by the trigger integrated in the ultrasound system. The mechanical index was set at 1.0 in seven patients and at 1.1 in three patients. It was adjusted at the beginning of the examination and remained constant during the session. The decision to use a lower mechanical index, as in the control group, was made because the sensitivity was very high with a mechanical index at 1.6, and the pathological tissue could consequently not be visualised. The duration of ultrasound exposure was about four minutes. No complications were observed during and after the insonation. The authors did not find any reports in the literature about adverse events for insonation through soft tissue after craniectomy with MI > 1.

The entire investigation was recorded in a continuous loop review memory on the hard disk and saved on the magneto-optical-disk for off-line analysis.

Calculation of the image parameters and of the flow parameters using time-intensity curves

The grey scale images of the healthy control persons and of the patient group were compared before and after the application of the contrast agent. The intensity of the grey-scale signal was analysed over time, and, in the patients' group, only an increase in intensity of maximally 15% was regarded as reduced perfusion. Calculation of the image and flow parameters were performed off-line using the following procedure:

1. The background image (before application of SonoVue™) was established by averaging at least 6 native images.
2. The original images (after injection of the contrast agent) were used to create the difference-images by subtracting the intensity (dB) of the background image from the intensity of the original (contrast enhanced) image. By repeating this procedure using images which were saved every 1000 ms (according to the triggering interval), the time intensity values were obtained.
3. The average peak image (API) was created based on averaging at least 6 difference-images.
4. Finally, the grey scale images were transferred in colour-coded images using a colour scale and superimposed onto the CT or MRI images.

Image parameters and flow parameters were calculated using the commercially available software Data Pro (Noesis S.A., France). The ultrasound images on the screen, the electronically saved background images, original images and API images were analysed independently by two investigators (EB and JHB). The third ventricle, the midline, the brain stem and the pineal gland served as anatomical landmarks. The homogeneity of the ultrasound images, of the enhancement of the contrast agent, the possible presence of artefacts and, especially, agreement with the CT- or MR images were assessed.

Results

All subjects in the control group exhibited adequate cerebral contrast enhancement under good insonation conditions. The regions of interest for the measurement of cerebral perfusion were selected in the diencephalic axial plane. We measured in the area of the thalamus and in the MCA territory on both sides and in the frontal lobe ipsilaterally. After application of the contrast agent, acoustic intensities increased in the regions of interest in all of the control persons. The most homogeneous area of perfusion was found in the region of the thalamus on both sides and in the MCA territory ipsilaterally, where the perfusion signal was weaker contralaterally due to greater insonation depth. Fig. **1** shows an example of a typical time-intensity curve in the ipsilateral thalamus region of a healthy subject. Four seconds after injection of the contrast agent, a signal enhancement could be observed in the cerebral tissue. The mean steady state perfusion quotient of 144.8 % was reached by dividing mean intensity during the steady state plateau by basal intensity. The time to peak intensity was 7 seconds followed by a steady state plateau with increased intensity values. The effect of the contrast agent could be observed in the steady state for a duration of 3 minutes.

In the group of patients with decompressive craniectomy, the insonation conditions were much more convenient because there were no problems with the acoustic temporal bone window. The anatomical structures of the brain could be clearly delineated in all patients by insonation on the affected side up to a depth in which the contralateral skull was displayed (approx. 140 mm). The typical anatomical landmarks of the B-mode brain parenchyma image, such as mesencephalic brain stem, cerebral cisterns, the gyri of the cerebellum, the third ventricle, the lateral ventricles, the pineal gland, etc. could be recognised with certainty in all patients. In patients with intracerebral haemorrhage, the echogenic formation of the intracerebral haematoma was visualised. In all patients, the midline shift due to the space-occupying lesion on the native images could be displayed. It was even possible to detect the structure of the hypoechogenic ischaemic area in some of the stroke patients. After injection of the contrast agent, a stepwise (in 1000 ms intervals) diffuse increase of the echogenicity in the cerebral parenchyma was observed. At the same time, a very impressive and exact delineation of the perfusion deficit in all patients could be seen immediately, either in the infarction or in the area of haemorrhage.

The regions of interest for calculating the image and the flow parameters in the stroke patients were not identical with those of the healthy control group. The parameters of evaluation were selected individually, based on the localisation of the ischaemic area in the CT scan or MRI image. The regions of interest were selected in the least perfused ischaemic areas of the diencephalic axial insonation plane and in the corresponding contralateral, non-affected location. Due to depth-dependent attenuation, the analyses are based not on absolute intensity values, but rather on the individual, relative changes in intensity (Table **1**). In accordance, time courses of the time intensity curves were also analysed independently of depth attenuation. The mean values of the intensity of the grey scale signals before and after the application of the contrast agent and the calculated images of a patient with a malignant space-occupying infarction in the MCA territory are shown in Fig. **2**. In the area of infarction only a small increase of signal intensity (of 10 %) appeared after the adminis-

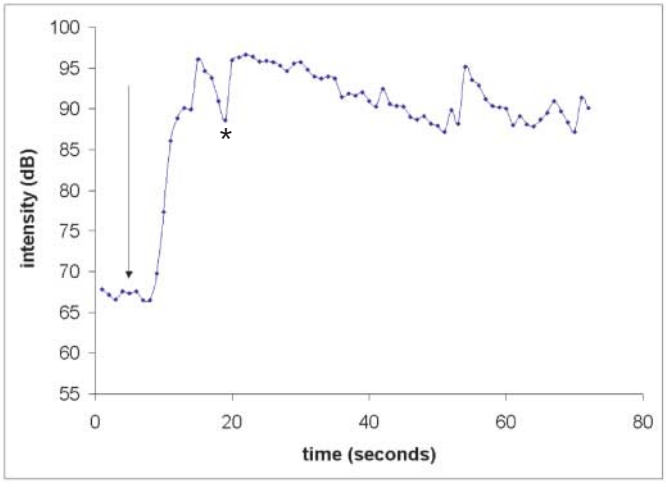

Fig. **1** Time intensity curve in the ipsilateral thalamus region in a healthy volunteer. *Arrow:* injection of the contrast agent, *: motion artifact.
Abb. **1** Zeit-Intensitäts-Kurve im ipsilateralen Thalamus bei einem gesunden Probanden. *Pfeil*: Injektion des Kontrastmittels, *: Bewegungsartefakt.

Tab. **1** Mean perfusion values in 10 stroke patients (aged 39 to 59 years, mean age 57 y) following decompressive craniectomy (comparison of the affected and non-affected areas)
Tab. **1** Mittlere Perfusionswerte bei 10 Schlaganfallpatienten (Alter 39 – 59 Jahre, mittleres Alter 57 Jahre) nach dekompressiver Kraniotomie (Vergleich der betroffenen und nicht betroffenen Areale)

		perfusion deficit area	*non-affected region*
1)	time between the application of the contrast agent and its first appearance in the tissue (s)	5.4	2.6
2)	time to peak intensity (s)	11.6	6.8
3)	duration of the bolus effect (s)	6.2	10.0
4)	mean intensity of the grey scale image before the application of the contrast agent (dB)	47.3	41.7
5)	mean intensity during the bolus effect (dB)	52.3	58.9
6)	mean bolus perfusion quotient (bolus peak intensity divided by basal intensity) (%)	110.5	141.2
7)	mean intensity during the steady state plateau (dB)	49.0	53.1
8)	steady state perfusion quotient (%)	103.6	127.3

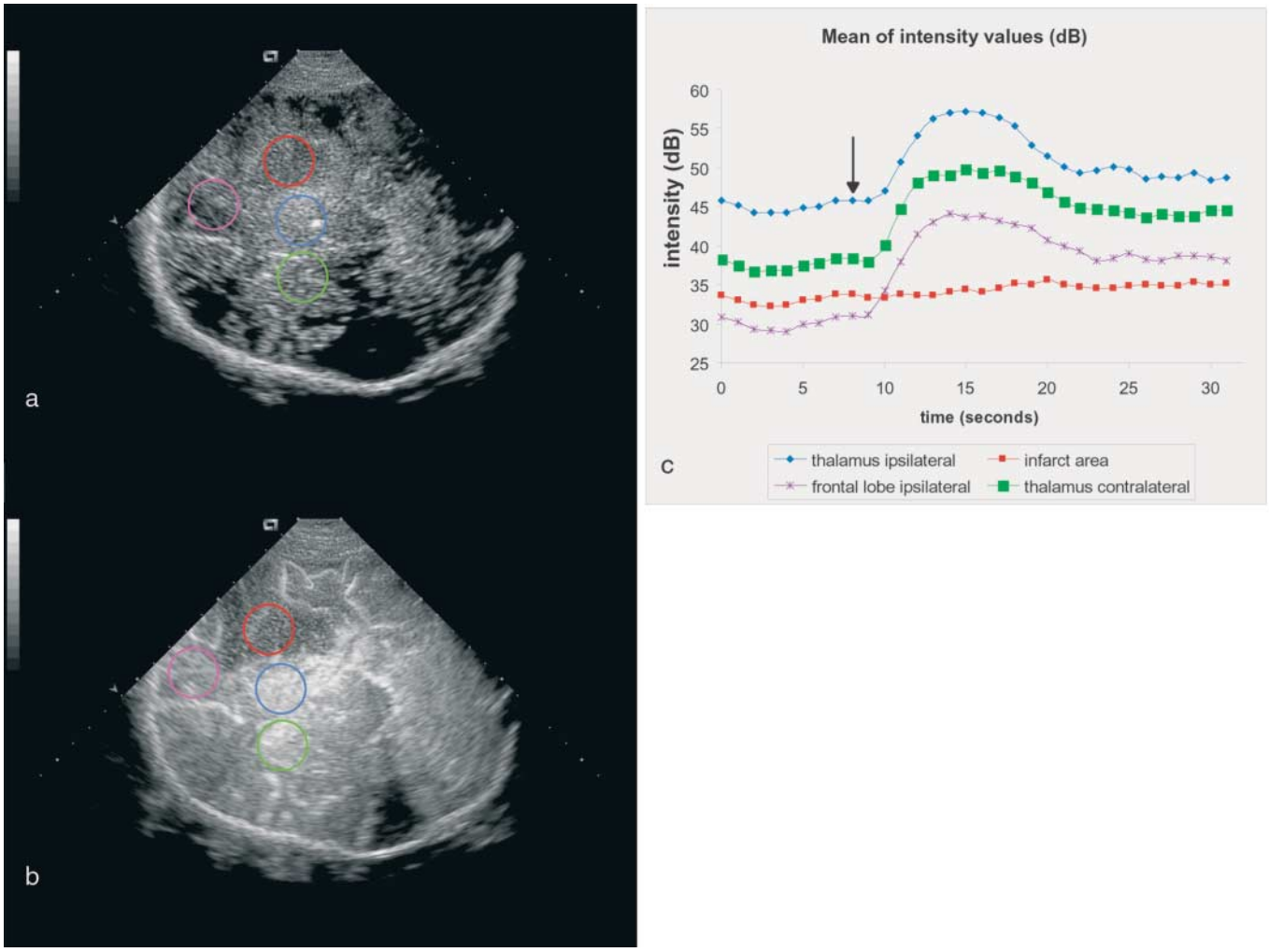

Fig. **2** Transcranial B-mode sonography in the axial diencephalic plane in a 49-year-old female patient with malignant MCA infarction following decompressive craniectomy before **a** and after **b** application of the contrast agent. The region of the perfusion deficit is hypoechoic on both images and is marked by the red circle. After application of the contrast agent, the area of hypoperfusion is clearly delineated. The ipsilateral thalamus and adjacent area of the infarct area near the midline (further from the penumbra) show hyperperfusion. **c** shows the time intensity curves showing the mean intensity values in the area of infarction, in the thalamus ipsi- and contralaterally and in the frontal lobe ipsilaterally. No increase of intensity in the area of infarction (red line) has occurred whereas in the ipsilateral thalamus and midline area (blue line) hyperperfusion with a clear increase in intensity can be observed. After the bolus effect of approx. 9 seconds a steady-state plateau with higher intensities than the baseline intensities can be observed. *Arrow:* injection of the contrast agent.

Abb. **2** Transkranielle B-Mode-Sonographie in der axialen dienzephalen Ebene bei einer 49-jährigen Patientin mit einer malignen Ischämie im Mediastromgebiet nach dekompressiver Kraniotomie vor **a** und nach **b** der Applikation eines Kontrastmittels. Auf beiden Abbildungen ist das hypoperfundierte Areal echoarm dargestellt (gekennzeichnet mit einem roten Kreis). Nach der Applikation des Kontrastmittels ist das Areal des Perfusionsdefizits deutlich erkennbar. Die Region des ipsilateralen Thalamus und die Nachbarregionen des Infarktareals in der Nähe der Mittellinie (außerhalb des vermeintlichen Penumbragebietes) sind hyperperfundiert. **c** zeigt die Zeit-Intensitäts-Kurven mit der Darstellung der mittleren Intensitätswerte im Infarktareal, im Thalamusgebiet ipsi- und kontralateral und im Frontalhirn ipsilateral. Es zeigt sich keine Zunahme der Intensität im Infarktareal (rote Linie), während in ipsilateralem Thalamusgebiet und in der Mittellininenregion (blaue Linie) eine Hyperperfusion mit einer deutlichen Zunahme der Intensität zum Vorschein kommt. Nach einem Boluseffekt von ca. 9 Sekunden Dauer erscheint ein Steady-State-Plateau mit höheren Intensitätswerten als die ursprünglichen Ausgangswerte. *Pfeil:* Zeitpunkt der Injektion des Kontrastmittels.

tration of the contrast agent. Unlike in the healthy control group, it was possible to observe a specific bolus effect in the adjacent areas with maximum contrast enhancement which lasted approximately 6 – 10 seconds and was followed by a steady-state plateau at lower intensities. (Fig. **2c**).

The perfusion deficit could be detected ipsilaterally accordingly to the affected vascular territory in all patients. In both patients with intracranial haemorrhage, the size and localisation of the perfusion deficit corresponded with the haematoma imaged on MRI. The contrast-enhanced signal was sufficient ipsilaterally, whereas the contralateral perfusion signal was weaker due to the depth-dependent attenuation of the reflected ultrasound waves.

The calculated average peak images corresponded precisely with the superimposed CT or MRI images in shape and size in all patients (Fig. **3**). During the steady-state period with a residual pre-

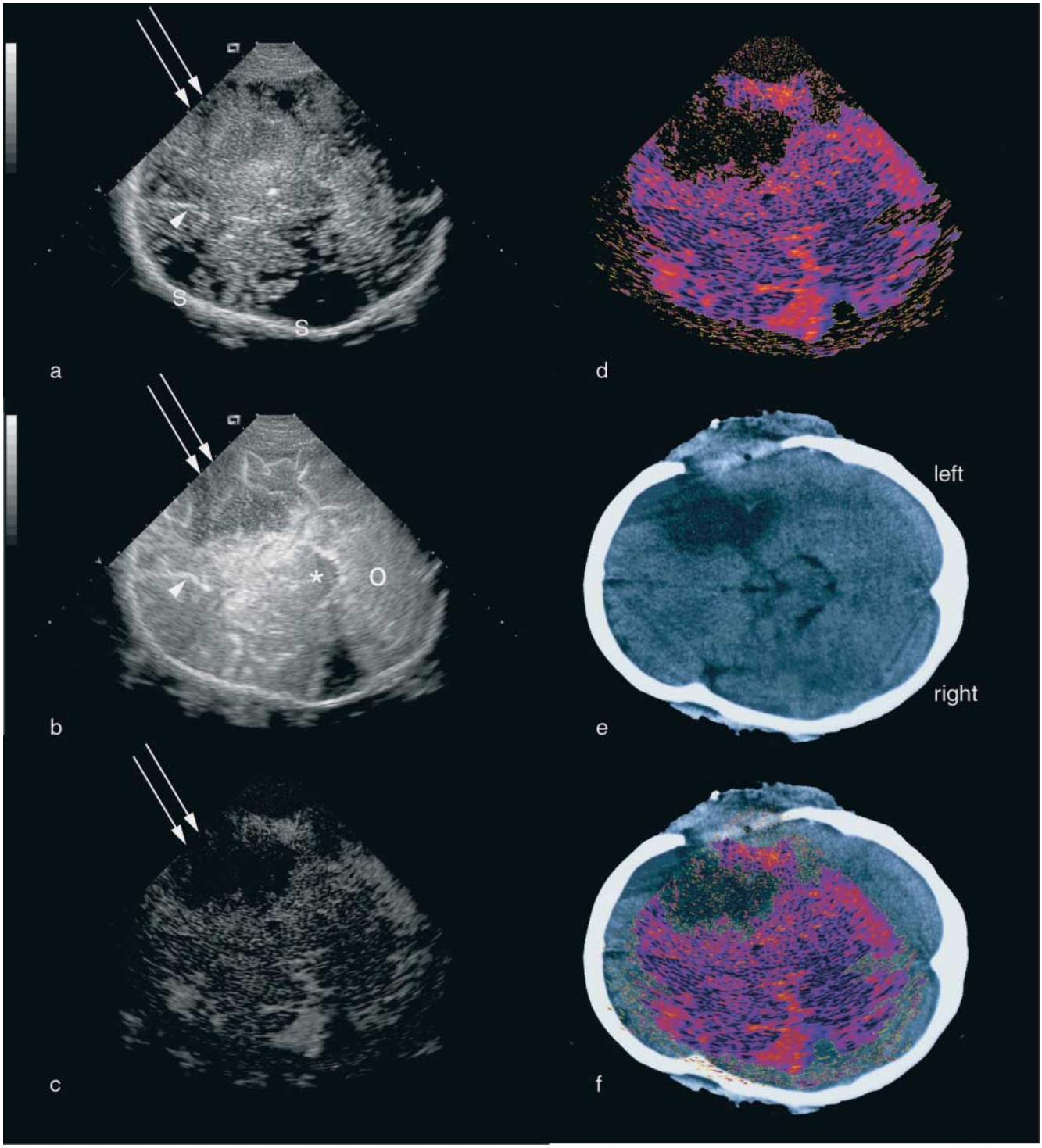

Fig. **3** Calculation of image parameters demonstrated in the patient from Fig. **2**. **a** shows the view of a background image (before application of the contrast agent) established by averaging 6 non-enhanced images. *Arrow:* midline shift, *two arrows:* hypoperfusion in the area of infarction. **b** shows the contrast enhanced B-mode image showing better delineation of the structures of the cerebral parenchyma. *Arrow:* midline shift, *two arrows:* hypoperfusion in the infarction area, *: brain stem, O: cerebellum. **c** shows the view of a difference-image created by subtracting the intensity of the background image from the contrast enhanced image (see text). **d** shows the view of the difference-image transferred in colour. **e** shows the CT scan showing the status following decompressive craniectomy and the area of the malignant space-occupying infarction in the left MCA territory. **f** shows the superimposition of **d** and **e** demonstrating the good correspondence of the CT and ultrasound findings.

Abb. **3** Darstellung der Bildparameter demonstriert bei der Patientin auf Abb. **2**. **a** zeigt die Hintergrundabbildung (vor der Applikation des Kontrastmittels) errechnet durch Mittelung von 6 Nativabbildungen. *Pfeil:* Mittellinienverschiebung, *zwei Pfeile:* Hypoperfusion im Infarktareal. **b** zeigt das kontrastverstärkte B-Bild mit einer besseren Darstellung der Strukturen des Gehirnparenchyms. *Pfeil:* Mittellinienverschiebung, *zwei Pfeile:* Hypoperfusion im Infarktareal, *: Hirnstamm, O: cerebellum. **c** zeigt die Darstellung des Differenzbildes, welches durch die Subtraktion der Intensität der Hintergrundabbildung von der Intensität des kontrastverstärkten Bildes ermittelt wurde. **d** zeigt die Darstellung des in Farbe umgewandelten Differenzbildes. **e** zeigt die computertomographische Darstellung des Zustandes nach dekompressiver Kraniotomie und des malignen raumfordenden Infarktes im Versorgungsgebiet der A. cerebri media links. **f** zeigt die Überlagerung der Abbildungen **d** und **e** und dabei eine gute Übereinstimmung des sonographischen Befundes mit der Computertomographie.

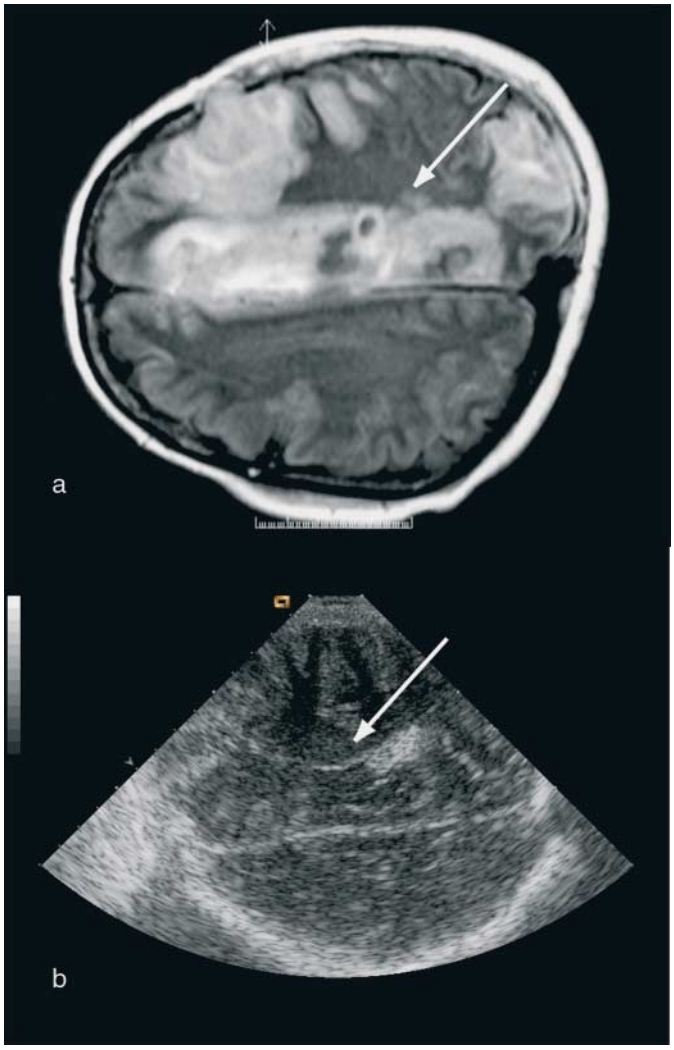

Fig. **4a** shows MRI (FLAIR image) of a malignant space-occupying MCA infarction surrounded by a massive oedema in the frontal, parietal, occipital and midline region. **b** shows contrast enhanced B-mode sonography in this patient performed in the examining plane through the cella media corresponding with the MRI plane. The arrow shows the physical boundary at the border between the oedematous region and the hypoperfusion area. Additionally, the midline shift is visible and the cerebral gyri can be recognised in the hypoperfused infarction area.

Abb. **4a** zeigt die MRT (FLAIR-Sequenz) eines malignen raumfordernden Media-Infarktes umgeben von einem massiven Ödem in der frontalen, parietalen, okzipitalen und mittelliniennahen Region. **b** zeigt die kontrastverstärkte B-Bild-Sonographie bei diesem Patienten, durchgeführt in der axialen Untersuchungsebene in Höhe der Cella media, entsprechend der MRT-Schnittebene. Der Pfeil zeigt einen Grenzzonenreflex zwischen dem ödematösen Areal und dem hypoperfundierten Gebiet. Zusätzlich sind die Mittellinienverschiebung und die Hirnfurchen im hypoperfundierten Infarktareal gut sichtbar.

sence of the contrast agent microbubbles in the cerebral tissue, it was possible to study the sonographic appearance of the cerebral anatomy in more detail in each patient for several minutes (Fig. **4**).

Transcranial colour-coded imaging with contrast agents was not performed prior to craniectomy in all patients. Additional information about contrast-enhanced, angle-corrected, blood flow velocity measurements and about a potentially increased perfusion to the brain due to hemicraniectomy are not therefore available. The transmitting power of colour-coded duplex ultrasonography is higher than in using grey scale imaging. In the group of patients with decompressive craniectomy, the authors therefore focused their examination only on grey scale imaging of the cerebral perfusion, in order not to expose the patients to higher energy colour-coded insonation.

The contrast agent SonoVue™ was well tolerated in both groups. There were no side effects observed during the injection of the agent.

Discussion

In 2000, Federlein and colleagues described the use of transient response harmonic imaging in stroke patients [4]. They used a triggering frequency of once every 2 seconds, producing an overall ultrasound sensitivity and specificity for predicting the size and localisation of infarctions by 75% and 100% respectively. In their study, a different contrast agent (Levovist™) was used, and additionally, the group of patients examined differed from the present study. In the same year Schlachetzki et al. demonstrated a perfusion deficit in 2 of 3 patients following decompressive surgery using loss of correlation imaging (LOC) and employing the contrast agent Levovist™[15]. In this study, the authors also performed 3-dimensional tissue harmonic transcranial sonography. In 2002, Stolz and colleagues described imaging of brain perfusion in two cases (in a patient with Moyamoya disease and in a patient with bilateral thalamic oedema due to thrombosis of the internal cerebral veins) using the echo-contrast agent Optison [16]. All studies published so far show that this investigative technique is possible, though it has certain methodological limitations.

The present study shows that SonoVue™ is a suitable and reliable contrast agent for the evaluation of perfusion in cerebral parenchyma under good examining conditions. In patients following decompressive craniectomy, when superimposing the appropriate plane of the CT or MRI images, the perfusion deficit corresponded exactly with the one visualised sonographically.

Additionally, several interesting, specifically contrast-induced phenomena could be observed which should be followed up in further studies:

- In the vicinity of the perfusion deficit (more distant from a suspected penumbra area), especially in the area of the basal ganglia, regions with higher echogenicity could be visualised without corresponding structural changes on CT or MRI images. The meaning of these hyperechogenic regions could be that they are either a specific physical phenomenon, or that compensatory hyperperfusion in those areas has occurred. The latter explanation could have been supported by additional blood flow velocity measurements recorded on the same day of the contrast studies. However, these measurements were not performed so as not to prolong the insonation period.
- After application of the contrast agent, an increase of echogenicity in the cerebrospinal fluid could also be seen. We suggest that not only perfusion but also diffusion phenomena can be described in this way.

– In stroke patients the course of the time intensity curves was different in comparison with the healthy group. After the application of the contrast agent, a distinct bolus effect with peak intensities followed by a steady-state plateau with lower intensities could be observed in the presumably non-affected brain regions of patients with craniectomy (Fig. **2c**). In contrast, in healthy persons no bolus effect was observed, and the steady-state plateau with maximum contrast enhancement lasted longer. Since the injection technique of the contrast agent was the same in both groups, this phenomenon can be explained by a different distribution of the contrast agent in a possibly damaged, as compared to healthy, tissue.
– The edge of the ischaemic area was very often delineated by a signal-intense hyperechogenic line that corresponded with the delineation of the region of brain oedema seen on the MRI image (Fig. **4**). The significance of this physical boundary, especially its relationship to the pathological changes in the perfusion deficit area, should be assessed in further studies to better understand the pathophysiology of sonographic findings in follow-up.

In *conclusion*, the results of our preliminary study on patients following decompressive craniectomy show the potential of contrast-enhanced imaging of cerebral perfusion deficit and the good agreement with sonographic and CT or MRI findings. Additionally, the use of contrast agents makes it possible to obtain new insights into the pathophysiology of the areas of hypoperfusion and penumbra. Further studies should be carried out in stroke patients, also through the intact skull, to increase the diagnostic confidence of this cost-effective new bedside technique and to standardise it for early sonographic diagnosis in cases of acute perfusion deficit.

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