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

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Zusammenfassung


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

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Bibliography

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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-
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 \( \times 10^6 \) 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.
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-

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**Fig. 1** Time intensity curve in the ipsilateral thalamus region in a healthy volunteer. Arrow: injection of the contrast agent. *: motion artifact.


**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)

<table>
<thead>
<tr>
<th>parameter</th>
<th>perfusion deficit area (s)</th>
<th>non-affected region (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) time between the application of the contrast agent and its first appearance in the tissue (s)</td>
<td>5.4</td>
<td>2.6</td>
</tr>
<tr>
<td>2) time to peak intensity (s)</td>
<td>11.6</td>
<td>6.8</td>
</tr>
<tr>
<td>3) duration of the bolus effect (s)</td>
<td>6.2</td>
<td>10.0</td>
</tr>
<tr>
<td>4) mean intensity of the grey scale image before the application of the contrast agent (dB)</td>
<td>47.3</td>
<td>41.7</td>
</tr>
<tr>
<td>5) mean intensity during the bolus effect (dB)</td>
<td>52.3</td>
<td>58.9</td>
</tr>
<tr>
<td>6) mean bolus perfusion quotient (bolus peak intensity divided by basal intensity) (%)</td>
<td>110.5</td>
<td>141.2</td>
</tr>
<tr>
<td>7) mean intensity during the steady state plateau (dB)</td>
<td>49.0</td>
<td>53.1</td>
</tr>
<tr>
<td>8) steady state perfusion quotient (%)</td>
<td>103.6</td>
<td>127.3</td>
</tr>
</tbody>
</table>
The perfusion deficit could be detected ipsilaterally according 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. 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.

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. 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.

The presence 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.

References