III.2

Contrast Ultrasound in Cerebrovascular Disease and Stroke Management

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Introduction

Over the past decade there has been a rapid evolution in the development of contrast agents to increase the back-scattered ultrasound signal. The effect of ultrasound contrast agents is based on the presence of microscopic particles that enhance and augment ultrasound information. A variety of fluids have been used as conventional contrast agents, from the hand-agitated saline used initially, to the suspension of microair, or microgasbubbles with a diameter of less than 10 micrometers that is used today.

The most substantial advance in the use of contrast agents was the development of stabilized contrast agents capable of crossing the pulmonary vasculature, a specific region of interest (ROI) to be examined - e.g., myocardium, liver, kidney, extra- and intracranial cerebral vessels - following intravenous administration [1-3]. The stability of the bubbles was increased by the introduction of an encapsulating shell to prevent gas loss, and the optimizing of surface tension and viscosity of the agent. Currently available transpulmonary products comprise stabilized microbubbles filled either by air (first-generation contrast agents) or by an inert gas (second-generation contrast agents) [4, 5].

In neurosonology, ultrasound contrast agents can be used to improve the insonation conditions (e.g., in the case of an insufficient temporal bone window in transcranial imaging) and/or to enhance the backscattered signal from the blood vessels in the case of reduced blood flow velocities in pathological situations (e.g., in an occlusive disease of an artery supplying the brain).

The purpose of this chapter is to describe indicative situations in which the application of contrast agents would provide an additional diagnostic benefit for patients with cerebrovascular disease and to illustrate these with typical contrast-enhanced ultrasonographic findings of the extra- and intracranial brain-supplying arteries. The findings were selected with a view to their relevance for routine diagnostics in stroke prevention and in stroke management. The last part of this chapter describes findings in the evaluation of cerebral perfusion deficit in stroke patients using the contrast agent SonoVue.

SonoVue is a novel second-generation ultrasound contrast medium, consisting of microbubbles stabilized by a highly elastic phospholipid shell. It consists of sulfur hexafluoride (SF_6), an innocuous, poorly soluble gas, which is eliminated through the lungs. In the previous chapter of this book, Droste describes the properties of SonoVue and practical considerations regarding its injection. The safety issues involving this substance were also covered. In our experience, SonoVue is well tolerated in all patients and there have been no side effects observed in association with its use.

Contrast-Enhanced Evaluation of the Extracranial Brain-Supplying Arteries

In the contrast-enhanced sonographic evaluation of the extracranial brain-supplying arteries, it is possible to obtain more detailed information about the anatomical course of the cerebral vessels and about the pathological conditions, especially if the native scanning is insufficient. If a low-velocity flow is detected, the technical parameters of the sonographic system should first be adjusted to optimize the examination, as follows:

- Pulse repetition frequency (PRF) should be set to the lowest value.
- The color box should be as small as possible.
- The frame rate and the wall filter have to be adjusted.
- The global gain and intensity threshold need to be optimized.

If a proper assessment of the structures of diagnostic interest is not possible after the system settings have been adjusted, the use of contrast agents should be considered [8].

The origin of the internal carotid artery is the most frequent site of atherosclerosis in cerebrovascular disease. Therefore, in the extracranial sonographic examination, a reliable assessment of the proximal segments of the internal carotid artery is crucial in the management of patients with stroke risk. Ultrasound contrast agents have proven useful in the quantification of high-grade stenoses of the internal carotid artery, which can only be suboptimally imaged - if at all - by means of native sonographic examination [9] (Fig. 1). Additionally, ultrasound agents provide a clear diagnosis, if the distinction between preocclusive stenosis and occlusion is difficult (Fig. 2).

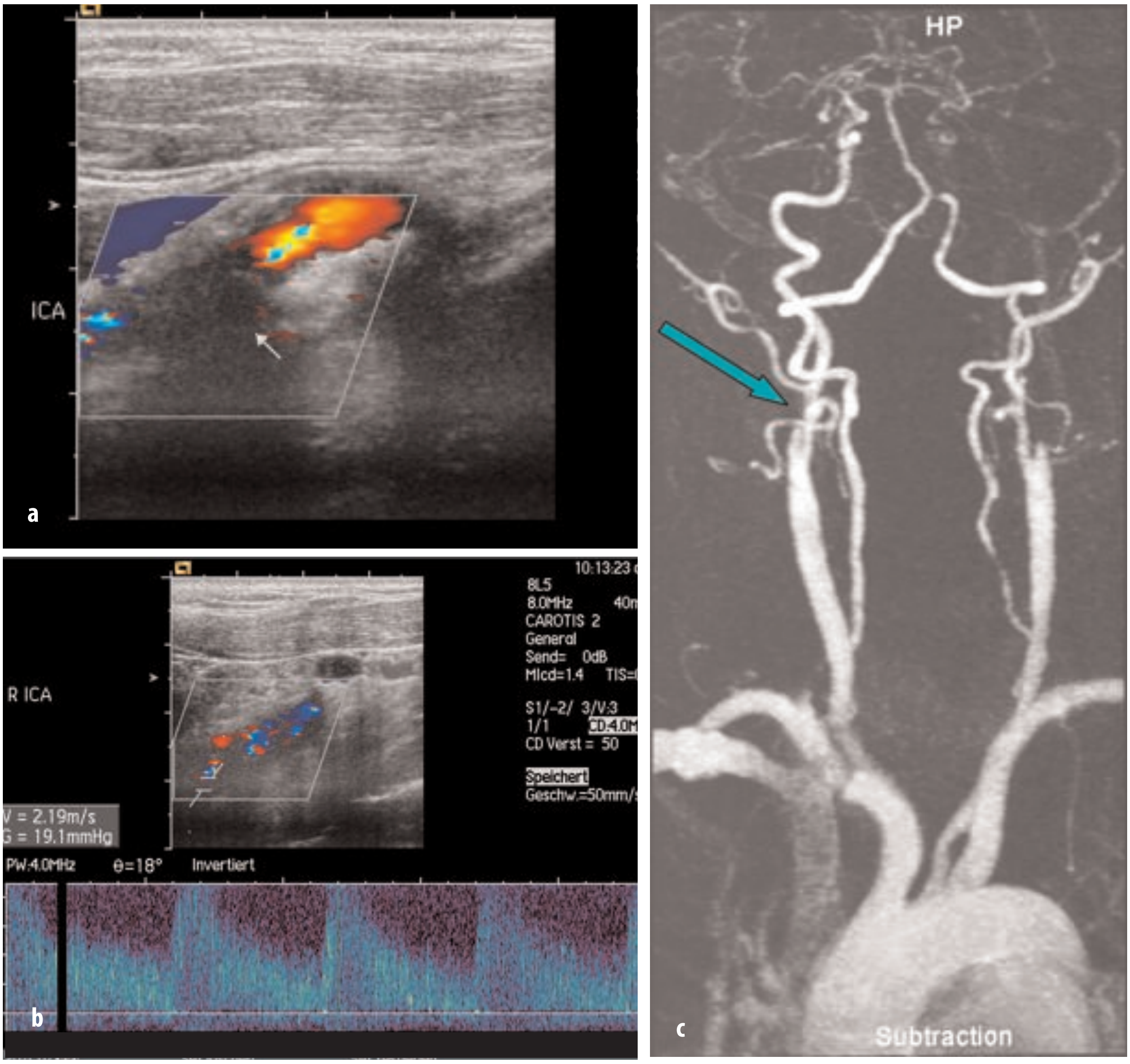
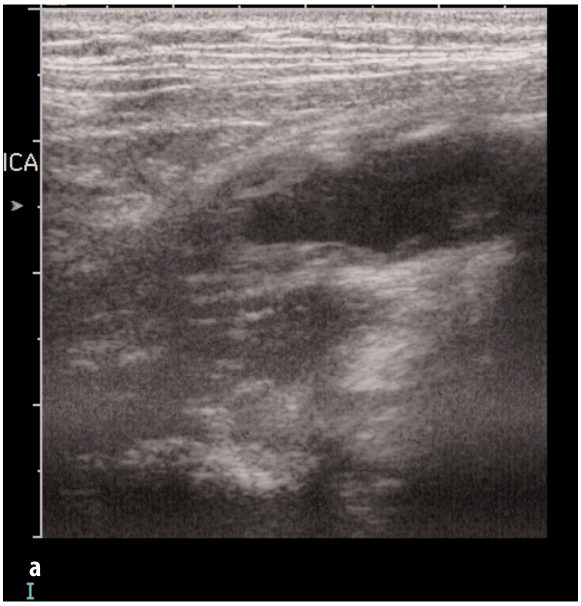
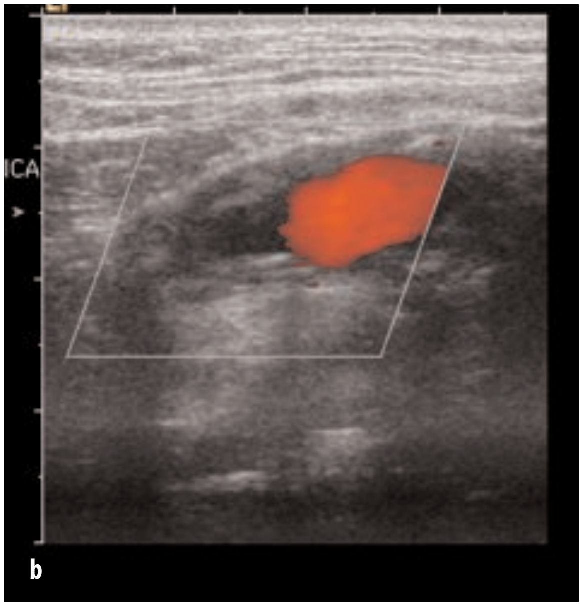
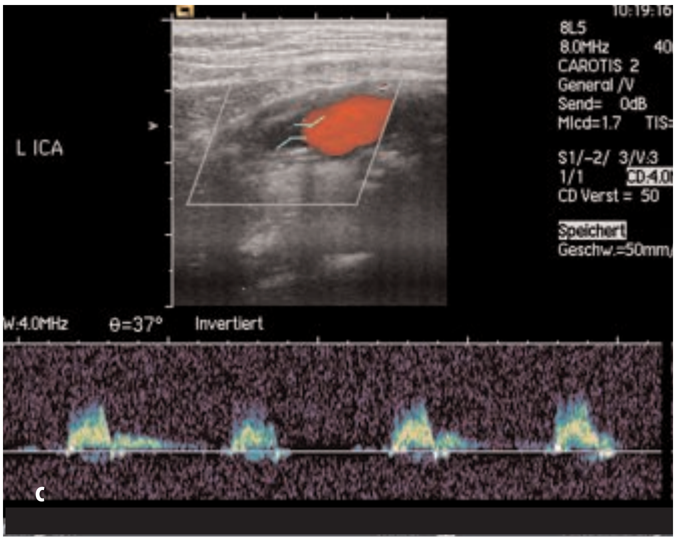


Fig. 1a-d. Stenosis of the right internal carotid artery in a 60 year old patient with an acute ischemia in the right middle cerebral artery territory. **a** View of the origin of the right internal carotid artery. Due to acoustic shadowing, an adequate assessment of the area of stenosis (*arrow*) is not possible. **b** After application of SonoVue, color coded flow signal with an aliasing phenomenon can be registered. In this region, Doppler spectrum shows an increase in angle-corrected maximum systolic flow velocity to 219 cm/s, indicating a moderate stenosis (the white signals in the Doppler spectrum represent the bubbles of the contrast agent SonoVue). **c** MR-angiography shows a stenosis of the right internal carotid artery (arrow)







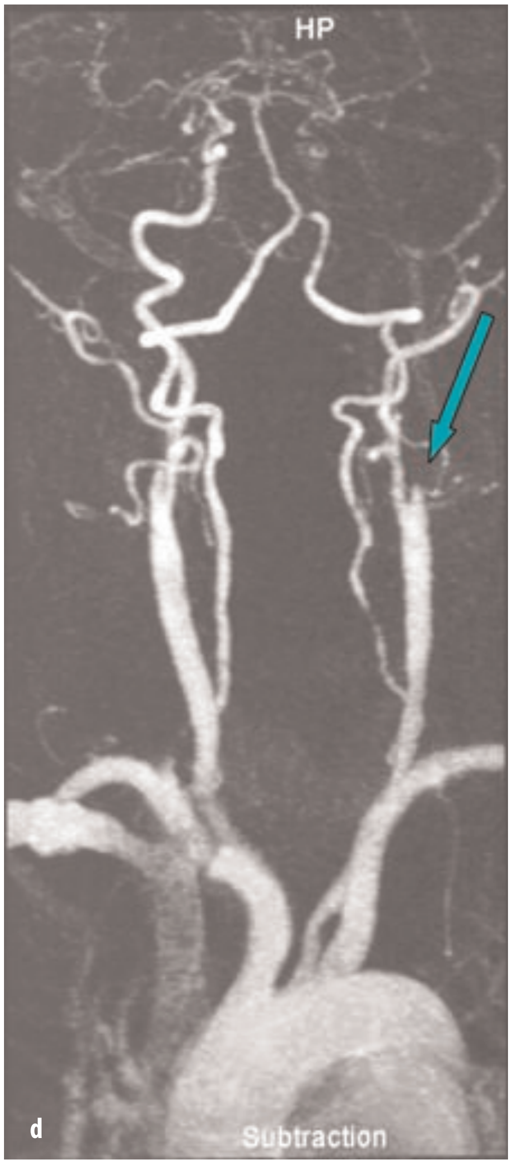
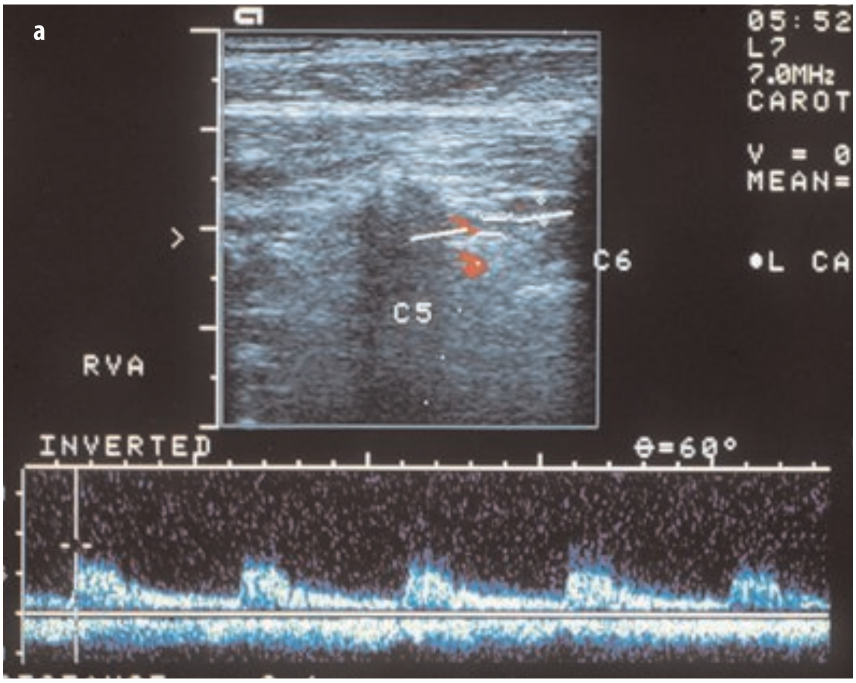


Fig. 2a-d. Stenosis of the left internal carotid artery in the same patient demonstrated in Figure 1. **a** Insufficient view (B-mode) of the origin of the left internal carotid artery because of difficult insonation conditions. **b** After application of SonoVue, no color-coded flow signal in the internal carotid artery can be registered. In this region, the Doppler spectrum is pathological due to an occlusion (the Doppler curve has no diastolic component) (**c**). **d** MR-angiography shows an occlusion of the left internal carotid artery (arrow)

Detection of low blood flow velocities in cases of dissection is easier using echo contrast agents in ultrasonography of the extracranial vertebral arteries [10, 11]. Under difficult examination conditions, it is possible to differentiate better between a hypoplastic vertebral artery and an occlusion at the origin (Fig. 3).

Contrast-Enhanced Evaluation of the Intracranial Arteries Supplying the Brain

With the aid of an echo contrast agent, examination with transcranial Doppler sonography as well as color-coded duplex ultrasonography is possible even in patients with an unfavorable acoustic bone window [1, 12]. Following intravenous injection of the first generation contrast agent Levovist, the backscattered signal can be enhanced up to 25 dB because of a transient increase in echogenicity of the blood [13]. Figure 4 illustrates a contrast-enhanced study of the posterior circulation, which offers more detailed information about the anatomical course of the basal cerebral arteries. After application of SonoVue, a longer stretch of the basilar artery is visible. Furthermore, the posterior inferior cerebellar artery (PICA), the anterior inferior cerebellar artery (AICA), and the superior cerebellar artery can be displayed. Better visualization of the intracranial arteries facilitates the diagnostic assessment of pathological conditions.



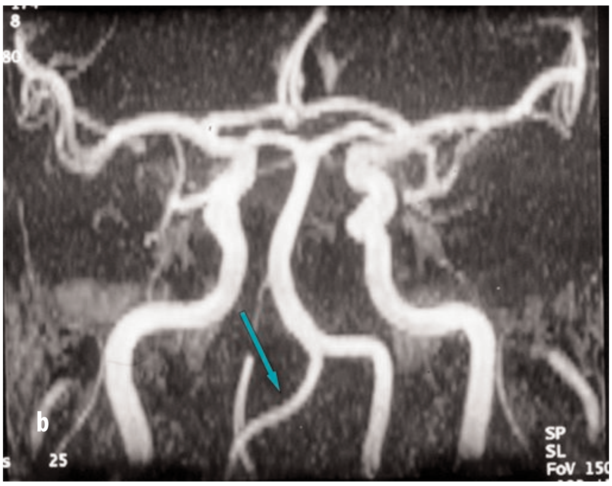


Fig. 3a, b. Hypoplasia of the right extracranial vertebral artery in a 62 year old patient. **a** Insufficient B-mode image of the midcervical course of the right extracranial vertebral artery. After application of SonoVue a weak color-coded signal in the vessel lumen can be detected. Under difficult examination conditions, using echo contrast it is possible to better differentiate between a hypoplastic vertebral artery and an occlusion at the origin. The diameter of the artery is 2.1 mm. **b** MR-angiography shows a hypoplasia of the right vertebral artery. RVA = right vertebral artery, C5 = 5th vertebra, C6=6th vertebra

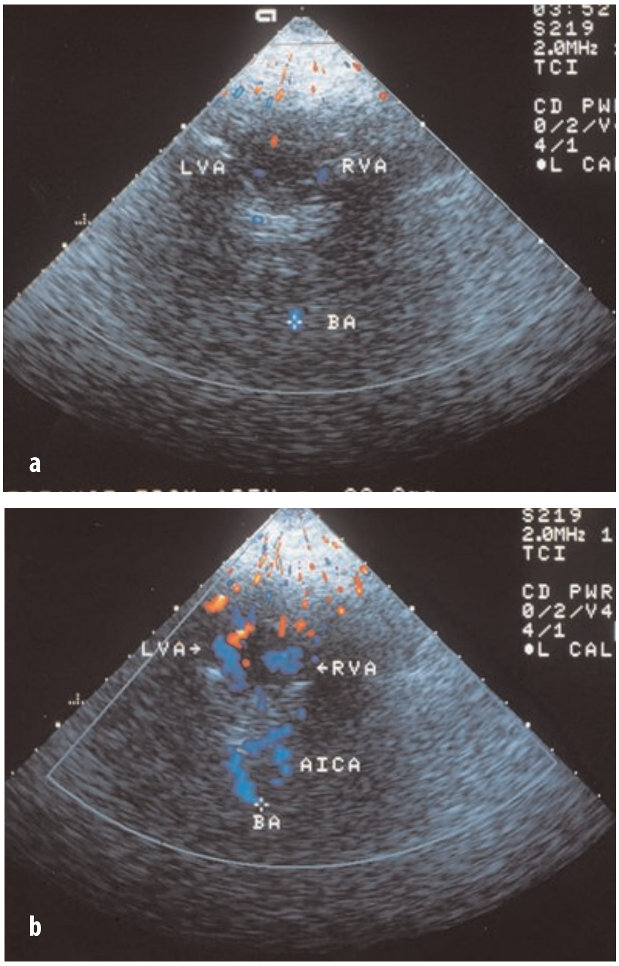


Fig. 4a, b. Patient with an insufficient occipital insonation window before (**a**) and after (**b**) application of SonoVue. Color mode, normal finding. After application of SonoVue, more detailed information about the anatomical course of the basal cerebral arteries can be obtained. BA = basilar artery, RVA = right vertebral artery, LVA = left vertebral artery, AICA = anterior inferior cerebellar artery

The results obtained from a multicenter, open-label, randomized cross-over study investigating the diagnostic potential of SonoVue using transcranial color-coded duplex sonography (TCCS) confirm this clinical observation [14]. In a group of forty patients, echo enhancement contributed to converting a non-diagnostic study into a diagnostic one in more than half of the indications (in 66%), and increased the confidence of diagnosis in 74 %. In a non-trial situation, this would have allowed the diagnosis to be reached more quickly.

In patients with acute stroke, cerebral ischemia is most often due to thromboembolic occlusion of an artery supplying the brain. Using transcranial color-coded duplex sonography as a complementary mobile procedure, the intracranial occlusion can be examined non-invasively at the bedside. The aim of therapeutic intervention is to restore or improve the blood supply. To make good treatment decisions, early, reliable information about the condition of the arteries of the Circle of Willis is necessary [15].

Especially in those patients whose baseline scans are not of good quality, contrast enhancement is of great value to improve the diagnostic results (Fig. 5). For further diagnostic steps and for therapy in cases of an occlusion in a middle cerebral artery, it is important to know whether failure to visualize a cerebral vessel is due to methodological problems or to a pathological condition. The absence of a color-coded signal for the middle cerebral artery is indicative of an occlusion, if a good contrast-enhanced signal for the ipsilateral posterior cerebral artery can be displayed (Fig. 6). In a posterior circulation, contrast enhancement is needed in many cases for an unequivocal diagnosis of high-grade stenosis of the intracranial vertebral or basilar arteries, although no data from systematic large series are available [12, 16] (Fig. 7). A further advantage of TCCS lies in the monitoring of stroke patients during and after therapy.

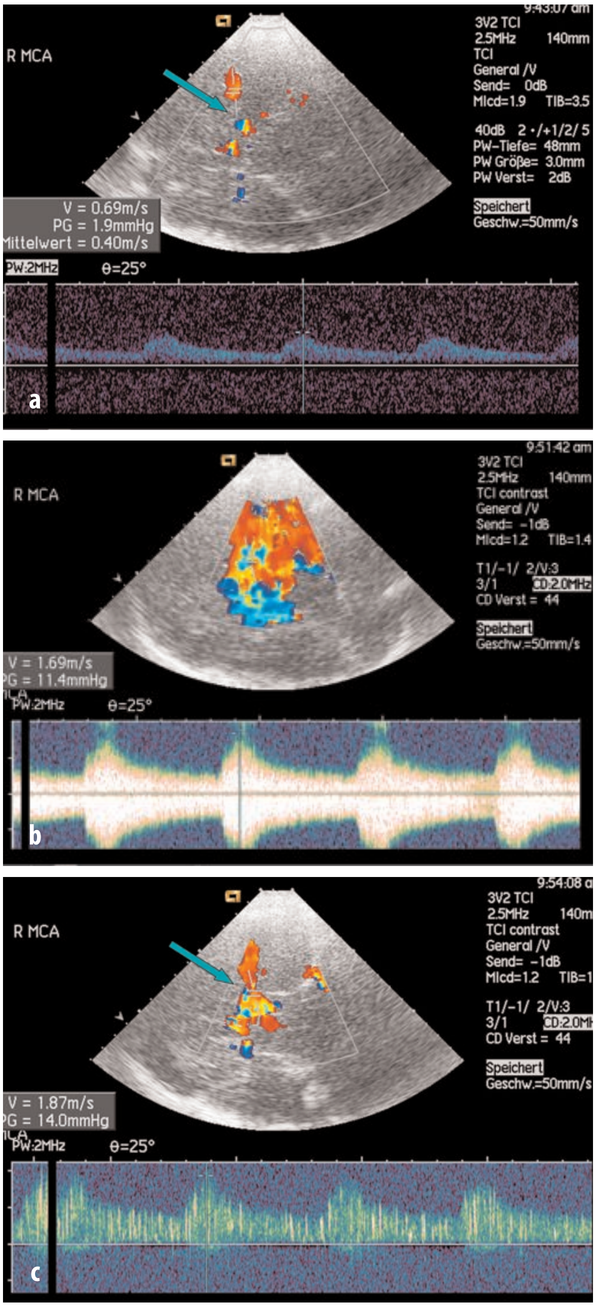
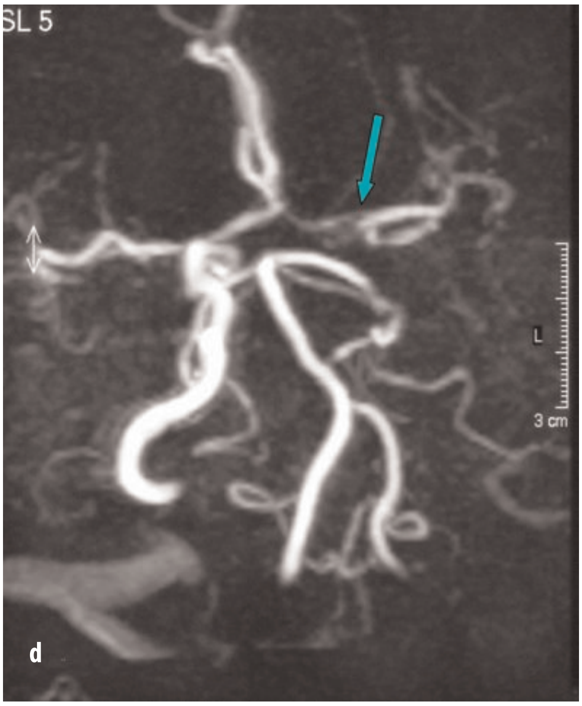


Fig. 5a-d. Stenosis of the right middle cerebral artery in a 60 year old patient with acute ischemia in the right middle cerebral artery territory. Extracranial ultrasonographic findings are shown in Figure 1 and 2. **a** Native transcranial color-coded image using a right transtemporal approach. The area of the stenosis of the right middle cerebral artery (MCA) cannot be visualized clearly (*arrow*). **b** Blooming effect after the injection of the contrast agent. **c** The stenotic region can be better displayed after application of the contrast agent SonoVue. The Doppler spectrum at the site of the stenosis shows an increase in angle-corrected maximum systolic flow velocity to 187 cm/s, indicating a moderate stenosis (the white signals in the Doppler spectrum represent the bubbles of the contrast agent SonoVue). **d** Magnetic resonance angiogram of a stenosis of the right MCA. The left MCA is filled by a hypoplastic left anterior cerebral artery (arrow) and shows a weak signal due to an extracranial occlusion of the left internal carotid artery at the origin. R MCA = right middle cerebral artery

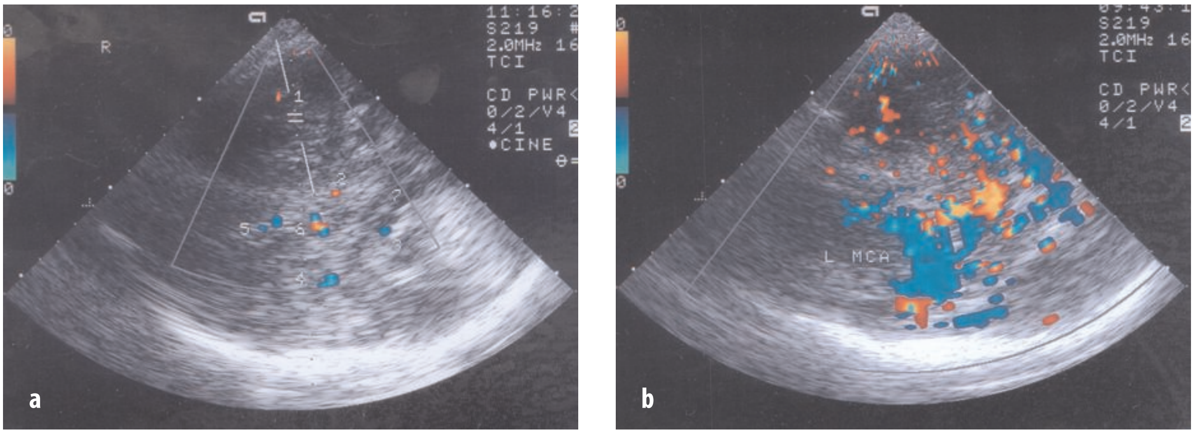


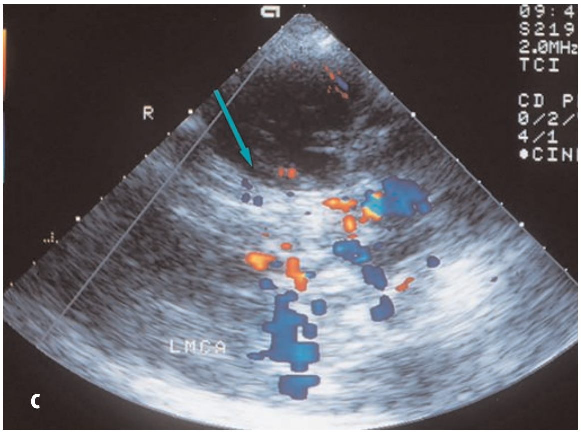
Evaluation of Cerebral Perfusion Deficit in Stroke Patients

The use of echo contrast agents in the color-coded examination of the extra- and intracranial brain-supplying arteries has already become part of the clinical routine for the diagnosis of cerebrovascular disease. At present, further clinical research is focused on the imaging of blood flow in the capillaries of the brain parenchyma and on the evaluation of cerebral perfusion with the aim of imaging the cerebral perfusion deficit in stroke patients. Based on experience from myocardial perfusion imaging, several reports have recently been published on the imaging of cerebral perfusion [17, 18].

The catalyst for further progress in contrast ultrasound was the advent of harmonic imaging technology during the second half of the 1990s [19-21]. When exposed to the ultrasound beam, microbubble contrast agents oscillate. These oscillations have a strong tendency to produce resonance, and the resonant frequency of microbubbles happens to be within the range of diagnostic ultrasound. With increasing transmission power, the bubbles show an increasingly nonlinear response (i.e., the backscattered signal contains frequencies that differ from the insonating frequency and the returned signal is thus distorted). The nonlinear signals contain overtones or harmonic and subharmonic signals at multiples and fractions of the insonating frequency. The second harmonic signal, which occurs at twice the incidence frequency, is used in a new ultrasound technique known as second harmonic imaging [22-25]. When the energy of the insonating beam is further increased to mechanical indexes (MI) greater than approximately 0.3, there is a corresponding rise in the destruction of the microbubbles. This destructive process is very fast, taking place during a single or a few ultrasound pulses during which a strong and highly nonlinear signal is returned from the bubble. It is called 'stimulated acoustic emission (SAE)' or 'loss of correlation (LOC) -imaging' and is a specific *high MI imaging modality*.

In the applications where the microbubbles need to be preserved (e.g., in imaging of very low blood flow velocities in the capillaries of the brain parenchyma), the *low MI imaging modality* is a preferred approach. Different techniques such as pulse inversion harmonic imaging,





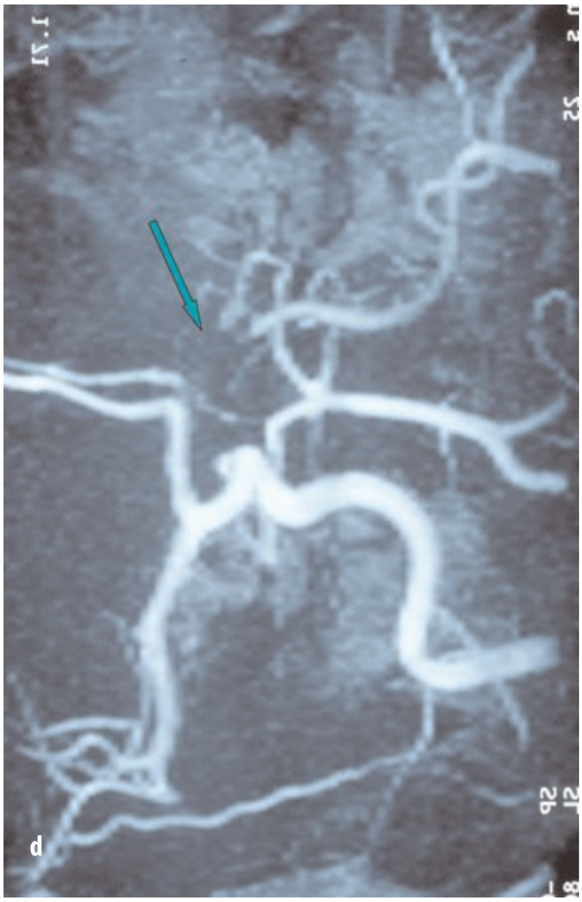


Fig. 6a-d. Occlusion of the right MCA in 26 year old patient with a dissection of the right internal carotid artery. **a** Native transcranial color-coded image using a right transtemporal approach with an unfavorable temporal bone window. The visualization of the basal cerebral arteries is of insufficient quality, only fragments of the arteries are visible. (1) No detectable signal of the right middle cerebral artery (MCA); (2) signal of the right posterior communicating artery; (3) left posterior cerebral artery (PCA); (4) left MCA; (5) A2 segment of the left anterior cerebral artery (ACA). **b** Blooming effect after the injection of the contrast agent. **c** After application of an echo contrast agent, good visualization of the contralateral (*left*) MCA, PCA and ACA and ipsilateral (*right*) PCA. There is no signal registered for the right MCA (*arrow*). MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery. **d** Magnetic resonance angiogram of an occlusion of the right MCA (*arrow*). The intracranial segment of the right internal carotid artery shows a weak signal due to a dissection at the origin (*two arrows*)

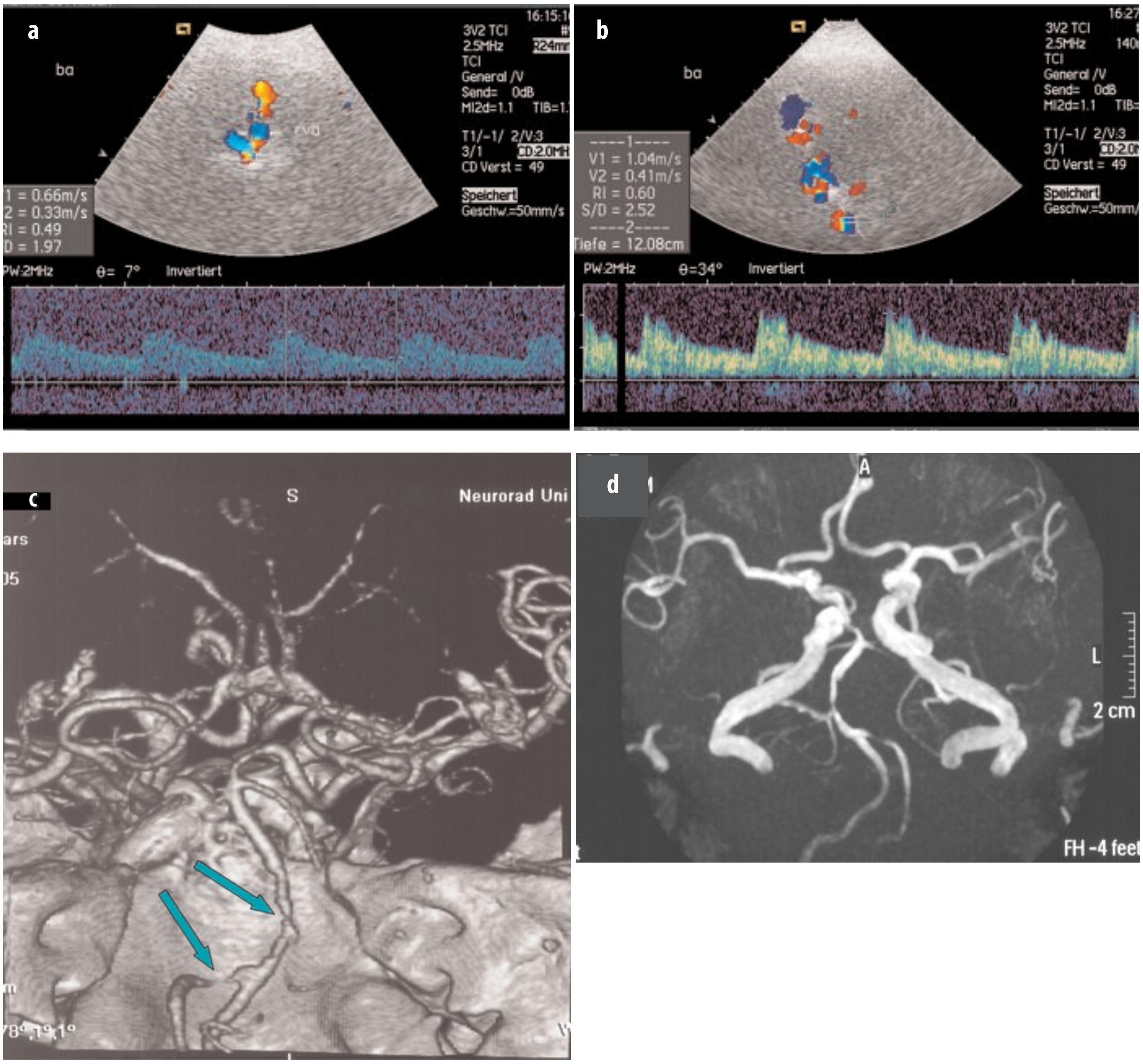


Fig. 7a-d. Findings in a 72 year old patient with vertebrobasilar TIA. Clinical symptoms: double vision, vertigo, dizziness. The native extracranial sonography revealed nonstenotic heterogeneous plaques at the bifurcation and a difference in the sides regarding flow of the extracranial vertebral artery (*right>left*). No signs of a distal flow obstruction were found. The transcranial examination showed no pathological findings. The findings of the basilar artery revealed normal signal up to a depth of 90 mm. In response to the pathological MRA findings, which revealed a high-grade, short-length stenosis of the basilar artery and the intracranial left vertebral artery, for further therapeutic decision making, targeted sonographic examination with the contrast agent Sonovue was performed. Using a suboccipital insonation, we recorded a high frequency Doppler signal at the depth of 120 mm and found an aliasing phenomenon as an indication of a middle-grade stenosis. As a result of the contrast-enhanced intracranial examination, a better assessment of the stenosis was possible, providing a better basis for the consequent therapeutic decision. The patient was treated with antithrombotic agent and his condition has improved. **a** Suboccipital insonation - native image. Visualization of the vessels is insufficient. The signal of the basilar artery can be recorded only to a depth of 80 mm. The Doppler spectrum at this depth is normal, maximum systolic blood flow velocity is 66 cm/s, and there are no signs of a distal flow obstruction. **b** Suboccipital insonation – contrast enhanced image. Visualization of the vessels is better, and possible to a greater depth. The signal of the basilar artery can be recorded to a depth of 120.1 mm. The Doppler spectrum shows a low-to-moderate grade stenosis. Maximum systolic blood flow velocity is slightly increased (104 cm/s), and there are no signs of a distal flow obstruction. **c** MR angiography and (**d**) CT angiography show a stenosis of the basilar artery and hypoplasia and stenosis in the intracranial V4 segment of the left vertebral artery

power modulation, harmonic power Doppler imaging, and contrast pulse sequencing are described to evaluate perfusion in microcirculation [26]. For quantification of brain tissue perfusion, bolus injection kinetics, refill injection kinetics or diminution kinetics are currently being explored. After a bolus injection of the contrast agent, time intensity curves with wash-in and wash-out phases can be analyzed. Postert and Seidel were able to measure time-intensity curves through the intact skull with transcranial sonography using the bubble response from the contrast agents Levovist and Optison, respectively [27-30]. 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 [31, 32].

In the therapy of acute stroke, an early assessment of the hypoperfused area and the quickest possible treatment and reperfusion of the ischemic deficit is necessary for an optimum clinical outcome. The size of the ischemic area plays an important role in prognosis. With cranial computed tomography, the early ischemic signs may only be visible several hours after the onset of the acute symptoms. For this reason, imaging of the hypoperfused region is preferably performed by magnetic resonance imaging (MRI) techniques. Using perfusion- and diffusion-weighted MRI (PWI, DWI), the permanently damaged tissue as shown in DWI can be distinguished from the potentially salvageable tissue (following the so-called “mismatch theory”) within minutes to hours after onset of the first symptoms [33]. However, MRI examination is still not widely accessible in the early management of stroke. Therefore, ultrasound techniques could be considered as a possible diagnostic alternative for the early visualization of the ischemic area. The main advantage in comparison to the MRI techniques is the bedside application and the real-time results of the sonographic examination.

However, at the present time, imaging of cerebral perfusion is limited because of methodological problems, especially if the temporal bone window is not suitable for the insonation [34, 35]. The higher MI needed to penetrate the temporal bone window is one of the key restraints in transcranial sonography. To learn more about cerebral perfusion sonography (and to avoid the temporal bone problem), our group performed a study on the contrast imaging of cerebral perfusion deficits in acute stroke patients following decompressive craniectomy [36] (Figs. 8-10). This study, in which a lower MI was used, demonstrated the capability of the contrast agent SonoVue to image cerebral perfusion and the less perfused areas of the brain.

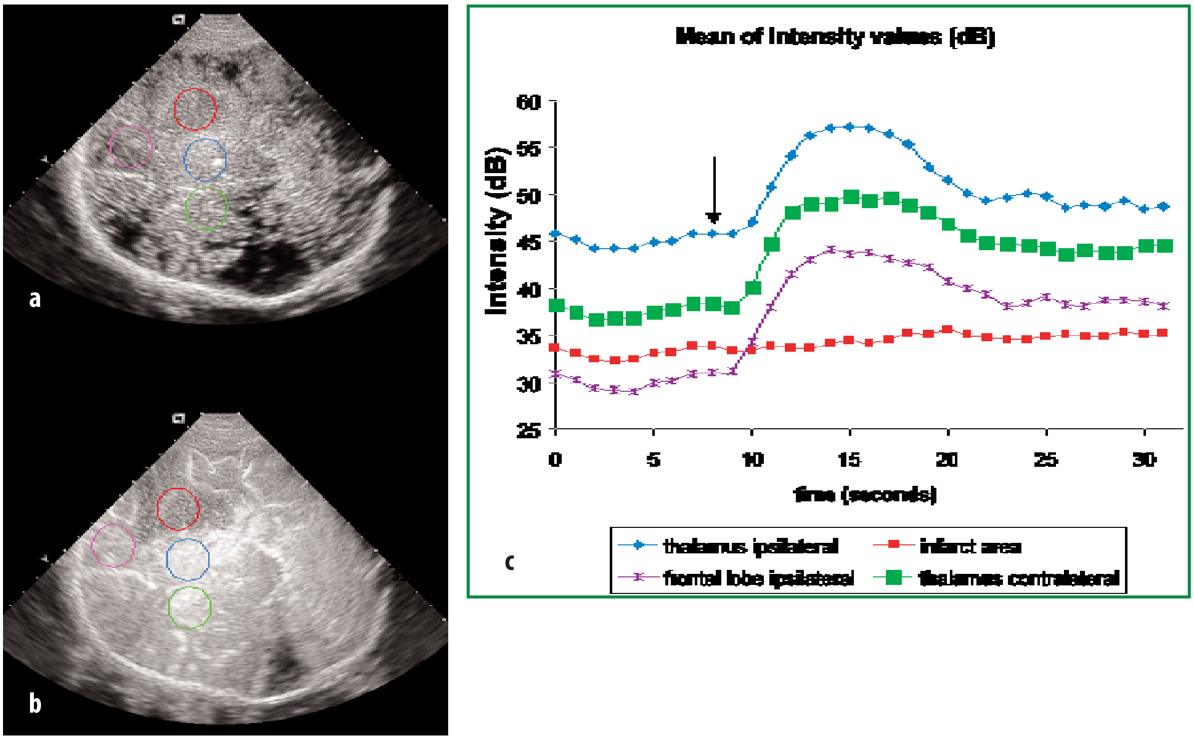


Fig. 8a-c. Transcranial B-mode sonography in the axial diencephalic plane in a 49 year old female patient with malignant MCA infarction following decompressive craniectomy before (**a**) and after (**b**) application of the contrast agent. The region of the perfusion deficit is hypoechoic on both images 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** Time intensity curves showing the mean intensity values in the infarct area, thalamus ipsi- and contralaterally and in the frontal lobe ipsilaterally. No increase of intensity in the infarct area (red line), whereas in the ipsilateral thalamus and midline area (blue line) hyperperfusion with a clear increase of intensity can be observed. After the bolus effect of approximately 9 seconds, a steady-state plateau with higher intensities than the baseline intensities can be observed. *Arrow:* injection of the contrast agent. *With permission: Bartels E, Bittermann H-J (2004) Transcranial contrast imaging of cerebral perfusion in stroke patients following decompressive craniectomy. Ultraschall in Med 25:206-213, Georg Thieme Verlag*

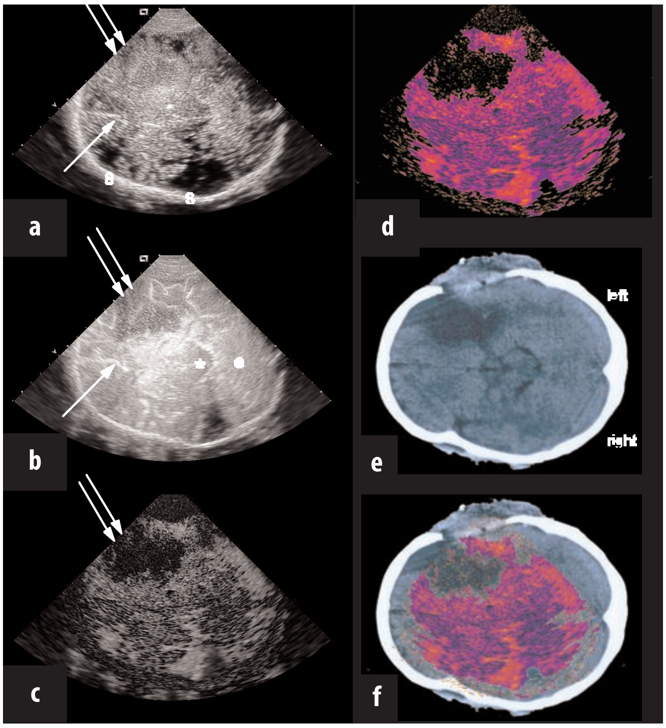


Fig. 9a-f. Calculation of image parameters demonstrated in the same patient in Figure 8. **a** View of a background image (before application of the contrast agent) established by averaging six non-enhanced images. *Arrow:* midline shift, *two arrows:* hypoperfusion in the infarction area. **b** Contrast 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** View of a difference-image created by subtracting the intensity of the background image from the contrast enhanced image. **d** View of the difference-image transferred in color. **e** CT scan showing status following decompressive craniectomy and the area of the malignant space-occupying infarction in the left MCA territory. **f** Superimposition of (d) and (e) demonstrating the good correspondance of the CT and ultrasound findings. *With permission: Bartels E, Bittermann H-J (2004) Transcranial contrast imaging of cerebral perfusion in stroke patients following decompressive craniectomy. Ultraschall in Med 25:206-213, Georg Thieme Verlag*

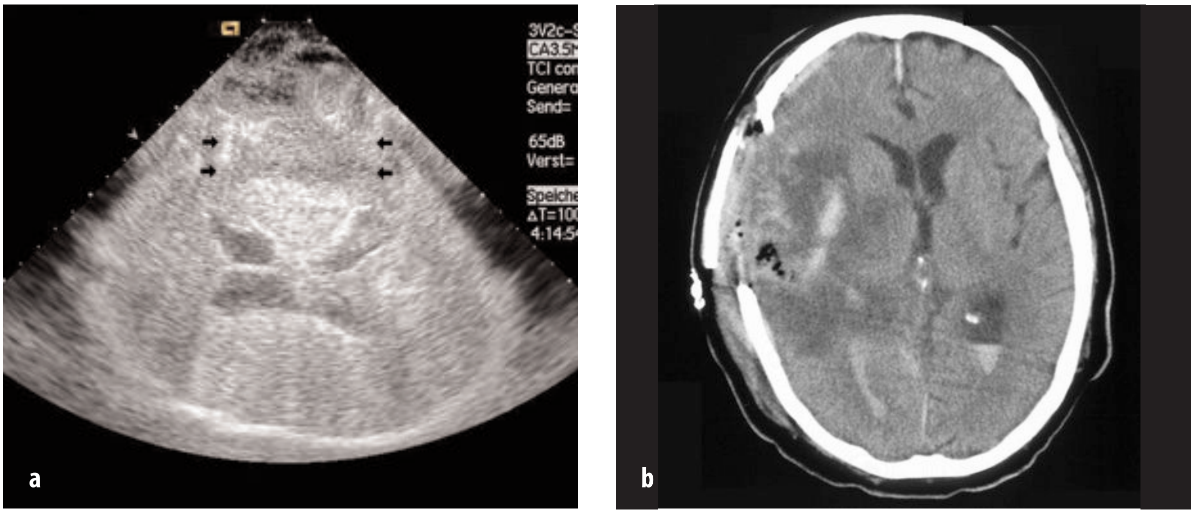


Fig. 10a, b. Transcranial B-mode sonography in a 69 year old man with malignant MCA infarction and a secondary hemorrhage in the ischemic area, following decompressive craniectomy. **a** After application of the contrast agent SonoVue, the hypoechoic area of perfusion deficit can be recognized (black arrows) in the modified diencephalic insonation plane. **b** CT scan of status following decompressive craniectomy due to malignant MCA infarction showing a secondary hemorrhage in the infarction area

Building on our experience from this report, in our most recent preliminary study we evaluated the feasibility of analyzing cerebral perfusion deficits using a new contrast imaging technology, namely Cadence contrast pulse sequencing technology (CPS), in addition to the contrast agent SonoVue. In this study, continuous and triggered registrations with pulsing intervals of 1000 ms were performed. The MI was set at 1.1 for the triggered registration and at 0.28 for the continuous registration [37].

Using CPS imaging technology in young, healthy volunteers with a good insonation temporal bone window, the distribution of the contrast agent was easier to detect than in previous studies. The contrast-enhanced signal could also be well recognized in the contralateral hemisphere right up to the skull crown, because the depth-dependent attenuation of the backscattered ultrasound waves was less pronounced (Fig.11).

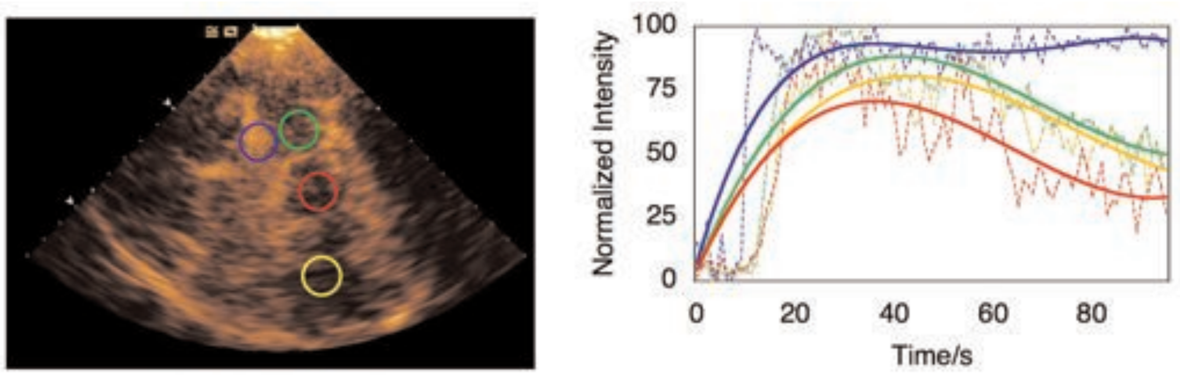


Fig. 11. Contrast-enhanced transcranial B-mode sonography in the axial diencephalic plane in a 23 year old healthy volunteer after intravenous application of the contrast agent SonoVue (left), and the time intensity curves in the ipsi- and contralateral MCA territories (right), showing the mean intensity values and a good distribution of the contrast agent after 15 seconds - not only ipsilaterally, but also on the contralateral side. Triggered registration with a pulsing interval of 1000 ms (MI = 1.1). Raw data is shown in dotted lines. The trend lines more clearly depict the perfusion dynamics (the region of interest marked with a blue circle and a blue line shows higher intensity values than those measured in the neighbouring regions, as it was placed in the area of the left middle cerebral artery). *With permission: Bartels E, Henning S, Wellmer A et al (2005) Evaluation of cerebral perfusion deficit in stroke patients using new transcranial contrast imaging CPS^{TM} technology. Preliminary results. Ultraschall in Med 26:478-486, Georg Thieme Verlag*

In the group of older stroke patients with poorer insonation conditions, the distribution of the contrast agent and the detection of the less perfused areas were possible not only ipsilaterally, but also contralaterally in about one third of the patients (Fig.12).

Pitfalls in the assessment of intensities in ischemic regions occur if the ROI selected is over a vessel (e.g., the branch of a middle cerebral artery). Moreover, in evaluating the intensities of smaller lesions, mistakes can occur due to a limited spatial resolution, if the ROI also covers parts of a non-affected brain region.

Furthermore, careful adjustment of the position of the transducer during the insonation is critical and errors here render the evaluation problematic since slight shifts in transducer placement can make exact calculations of perfusion values and time-intensity curves impossible.

Future Aspects

In clinical practice, recently developed sonographic techniques, such as harmonic power Doppler imaging, or CPS technology, offer new perspectives for the imaging of organ perfusion.

Much effort has been invested in the development of targeted ultrasound contrast agents using ligands (e.g., specific drugs) with the aim of transporting them to a specific site.

Under certain conditions, microbubbles could be used as a therapeutic agent. At present, different research groups are investigating the combination of tissue plasminogen activator (tPa) therapy with application of microbubbles in stroke patients. It has been demonstrated that thrombolysis is potentiated by concomitant ultrasound treatment [38, 39].

In cerebral ischemic disease, another possible therapeutic application of microbubbles is the delivery of genes mediating neuroprotection, nerve regrowth, and revascularization.

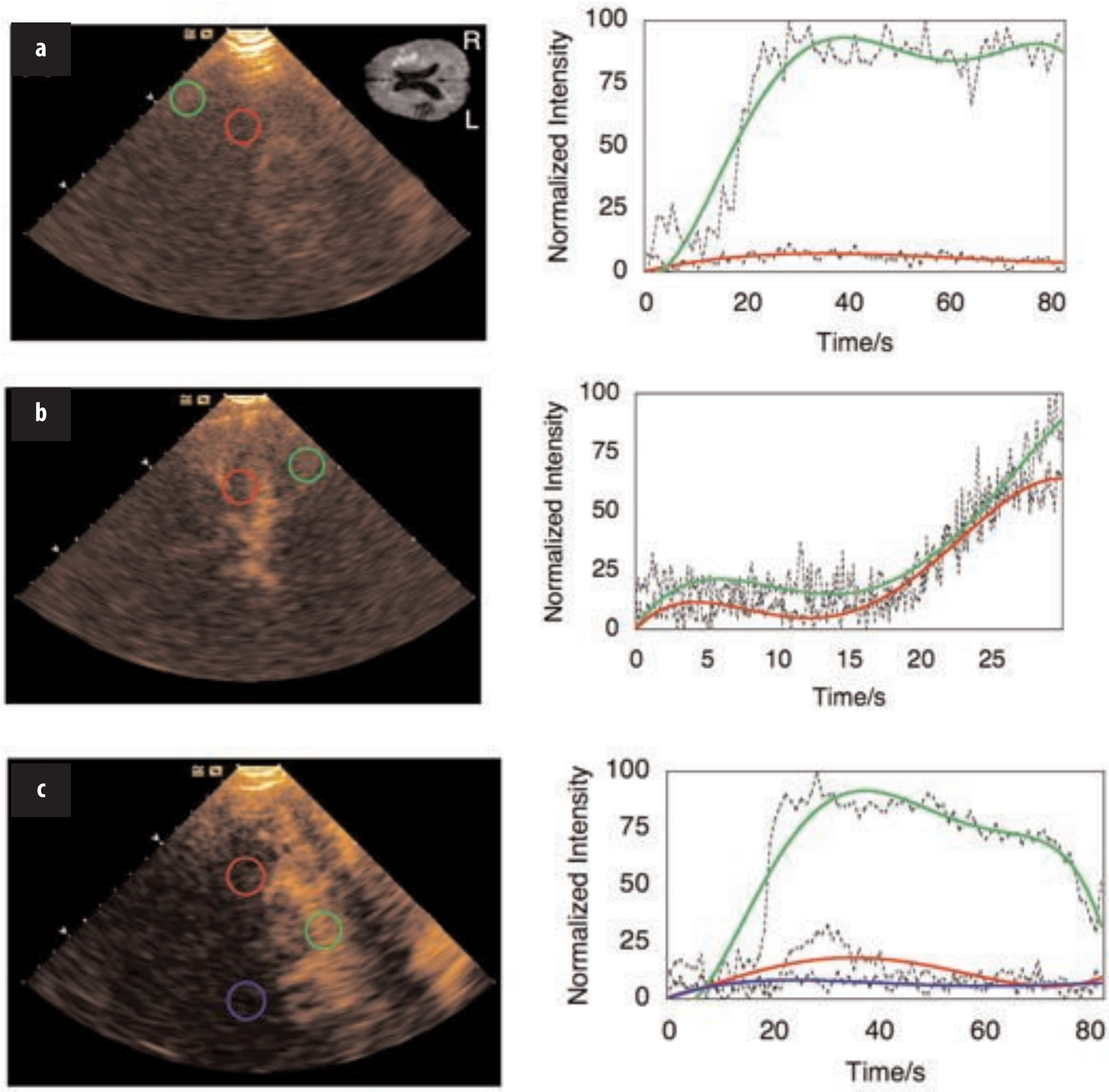
Key points

- In neurosonology, ultrasound contrast agents improve the insonation conditions - e.g., in the case of an insufficient temporal bone window in transcranial imaging. They enhance the backscattered signal from the blood vessels in cases of reduced blood flow velocities in pathological extra- and/or intracranial conditions.

- In extracranial examination, echo contrast agents allow a clear diagnosis, if the distinction between preocclusive stenosis and occlusion is difficult.

- An easier visualization of the intracranial arteries facilitates the diagnostic assessment of the obstruction in the middle cerebral artery and /or basilar artery flow of patients with acute stroke.

- Ultrasonographic imaging of cerebral perfusion is possible using echo contrast agents. Further improvement in sonographic technology is necessary to increase the diagnostic reliability of contrast-enhanced imaging of cerebral perfusion deficit in stroke patients.



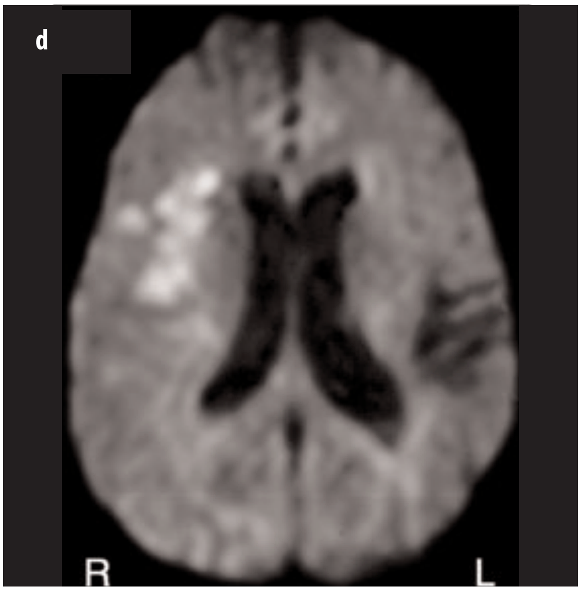


Fig. 12a-d. Contrast-enhanced transcranial B-mode sonography images in the axial diencephalic plane and time-intensity curves in a 62 year old man with a recent infarction in the right MCA territory and an old infarction in the left MCA territory. **a** Right temporal insonation showing a perfusion deficit in the right MCA area, using a triggered registration with a pulsing interval of 1000 ms (MI=1.1). **b** above, using a continuous registration (MI=0.28). CE1 **c** Left temporal insonation showing a perfusion deficit in the old left MCA infarct area (red line), and the recent perfusion deficit on the contralateral side (blue line). Triggered registration with a pulsing interval of 1000 ms (MI=1.1). **d** MR imaging shows old left temporal infarction and recent right temporal infarction (FLAIR sequence). Raw data is shown in dotted lines. The trend lines more clearly depict the perfusion dynamics. The region of the ipsilateral perfusion deficit is hypoechoic on all three images and is marked by a red circle. Note the acoustic shadowing behind the old infarct zone that can lead to misinterpretation (**c**). *With permission: Bartels E, Henning S, Wellmer A et al (2005) Evaluation of cerebral perfusion deficit in stroke patients using new transcranial contrast imaging CPS™ technology. Preliminary results. Ultraschall in Med 26:478-486, Georg Thieme Verlag*

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