On the Ability of Ultrasound Parametric Perfusion Imaging to Predict the Area of Infarction in Acute Ischemic Stroke

Über die Möglichkeiten der transkraniellen sonographischen Perfusionsbildgebung bei Patienten mit akutem Hirninfarkt

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Key words
- contrast media
- stroke
- ultrasonography
- perfusion
- transcranial

Zusammenfassung

Ziel: Die gestörte Hirnperfusion bei Patienten mit akutem Hirninfarkt kann mit der sonographischen Perfusionsbildgebung nach Ultraschallkontrastmittelbolusinjektion dargestellt werden. Wir untersuchten die diagnostische Wertigkeit von fünf verschiedenen parametrischen Darstellungen der Hirnperfusion im Hinblick auf die Infarktentwicklung im Kontroll-CCT.
Material und Methoden: Perfusion-harmonic-imaging-Untersuchungen nach SonoVue® Bolus-Injektion wurden bei 22 Patienten mit akutem vorderen Hirninfarkt in der dienzephalen Ebene durchgeführt und mit korrespondierenden CCT-Schichten nach Infarktdemarkation verglichen. Es wurden jeweils fünf verschiedene Parameterbilder pixelweise errechnet: pixelwise peak intensity (PPI), area under the curve (AUC), positive gradient (PG), time to peak (TTP) und ein Dreifaktorbild mithilfe der Software factor analysis of medical image sequences (FAMIS).
Ergebnisse: Die Sensitivitäten und positiven prädiktiven Werte (PPV) der sonographischen Perfusionsbildgebung waren wie folgt: PPI (100 %/95 %), AUC (100 %/90 %), FAMIS (89 %/89 %), PG (84 %/94 %) und TTP (47 %/100 %). Die Flächen der fünf parametrischen Darstellungen korrelierten jeweils signifikant mit der jeweiligen Infarktfläche des Verlaufs-CCT. Bilder, berechnet nach dem FAMIS-Algorithmus, und PPI-Bilder hatten die höchsten Spearman-rank-Korrelationskoeffizienten (beide $r = 0{,}76$, $p < 0{,}001$), die übrigen Bilder korrelierten wie folgt: PG: $r = 0{,}62$ ($p = 0.003$), AUC: $r = 0{,}53$ ($p = 0.014$), TTP: $r = 0{,}50$ ($p = 0.021$).
Schlussfolgerung: Parameterbilder der sonographischen Hirnperfusion prädizieren die Infarktentwicklung bei akuten Hirninfarkten. Darstellung der Kontraststärke (Intensität) und die FAMIS-Analyse haben hohe Sensitivitäten, die TTP-Darstellung hat eine hohe Spezifität und ein hohen PPV.

Abstract

Purpose: Cerebral perfusion deficits in acute ischemic stroke can be detected by means of transcranial harmonic imaging after ultrasound contrast agent bolus injection. We evaluated five different parameters of the bolus kinetics as parametric images and correlated areas of disturbed perfusion with the area of definite infarction.
Materials and Methods: Perfusion harmonic imaging after SonoVue® bolus injection (BHI) was used to investigate 22 patients suffering from acute internal carotid artery infarction. For each subject, we calculated five different images based on the following parameters from the time-intensity curve in each pixel: pixelwise peak intensity (PPI), area under the curve (AUC), positive gradient (PG), time to peak (TTP), and a three factor image from the factor analysis of medical image sequences (FAMIS). The findings in the diencephalic imaging plane were compared with the definite area of infarction, as diagnosed by cranial CT.
Results: In predicting the definite area of infarction in follow-up CT, we found the following sensitivities and positive predictive values (PPV): PPI (100 %/95 %), AUC (100 %/90 %), FAMIS (89 %/89 %), PG (84 %/94 %) and TTP (47 %/100 %). The areas of disturbed perfusion in all five types of parametric images correlated significantly with the area of infarction in CT. Images from the FAMIS algorithm and PPI images showed the highest Spearman rank correlation with the area of definite infarction as displayed in CT (both $r = 0.76$, $p < 0.001$). Images from the other parameters correlated as follows: PG: $r = 0.62$ ($p = 0.003$), AUC: $r = 0.53$ ($p = 0.014$), TTP: $r = 0.50$ ($p = 0.021$).
Conclusion: BHI can detect disturbed perfusion in acute hemispheric stroke. In their ability to predict the development of an infarction, intensity-based parameters and FAMIS were determined to have a high sensitivity, and TTP was found to have a high PPV and specificity.

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Aim

Successful treatment of ischemic stroke mainly depends on early and reliable diagnostics of areas with critically reduced brain tissue perfusion. New ultrasound technologies (e.g., conventional and phase inversion harmonic imaging) can detect perfusion deficits in the brain parenchyma [1 – 5]. Transcranial sonography seems to be a more suitable, less time-consuming, less expensive, and better tolerated bedside method for critically ill patients than other neuroimaging methods, such as brain CT, MRI, SPECT, or PET.

By using transcranial harmonic imaging, it is possible to track an ultrasound contrast agent (UCA) bolus within the human cerebral microcirculation. Studies on parametric imaging of the signal amplitude and the time to peak in each image pixel after an ultrasound contrast agent bolus injection demonstrated the potential of this new method in predicting the size and the location of a definite brain infarction [6 – 8].

The purpose of our study was to evaluate the diagnostic potential of the different parametric images using parameters that can be extracted from the time-intensity curve (TIC).

Subjects and Methods

Patients

We investigated 22 patients suffering from acute infarction in the internal carotid artery circulation (7 women, 15 men; mean age 64.8 [SD 7.6] years). Inclusion criteria were as follows: acute onset of sensorimotor hemiparesis, neglect or incomplete aphasia within 24 h before sonography, and early stroke signs on brain CT (focal hypoattenuation or focal brain swelling in the territory of the internal carotid artery, obscuration of basal ganglia or hyperdense middle cerebral artery [MCA] sign) as well as a sufficient acoustic bone window for conventional transcranial color-coded sonography [9]. Exclusion criteria were as follows: intracranial hemorrhage detected by CT as well as complete aphasia, pregnancy, and severe cardiac, pulmonary, or renal disease. All patients gave informed consent.

The clinical status was rated using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). The initial ultrasound investigation consisted of extra- and transcranial color-coded duplex sonography as well as transcranial perfusion harmonic imaging using the bolus kinetics with SonoVue®. Two CTs (Aquilion; Toshiba Medical Systems Europe, Zoetermeeer, The Netherlands) were performed as part of our routine protocol for diagnosing stroke patients. Routinely, one CT was done as a first-line diagnostic approach before sonography. A repeat CT was performed to confirm the localization and the size of the infarction. No contrast agent was administered for CT. Parts of the data from a patient subgroup (n = 16) were published previously [8].

Ultrasound contrast agent

The ultrasound contrast agent SonoVue® (Bracco/Altana Pharma, Konstanz, Germany) is a sulphur-hexafluoride-containing aqueous suspension of phospholipid microbubbles, which is capable of passing through the pulmonary circulation [1 to 5] × 10^8 microbubbles/ml; diameter less than 8 µm in more than 90 % of microbubbles). This agent has been approved for neurosonology purposes by the European authorities and is routinely administered for the assessment of basal cerebral arteries in patients with insufficient insonation conditions.

Ultrasound examination

We performed conventional ultrasound methods (extra- and transcranial color-coded duplex sonography) and bolus harmonic imaging (BHI) images with a SONOS 5500 ultrasound system (Philips Medical Systems, Best, The Netherlands).

Extracranial color-coded duplex sonography of the brain-supplying arteries (carotid and vertebral arteries in all segments) was performed with a 7.5-MHz linear array scanner (L7540; Philips) and a 12-MHz sector scanner (S12 probe; Philips). For conventional transcranial color-coded sonography of the basal cerebral arteries, we used a sector transducer (S4 probe; Philips) with a fundamental frequency of 2 to 4 MHz in the frequency-based mode [10]. We classified the Doppler flow in the MCA of the symptomatic hemisphere using the Thrombolysis in Brain Ischemia (TIBI) score [11]. The Doppler waveforms are graded as follows: 0 indicates absent; 1 = minimal; 2 = blunted; 3 = dampened; 4 = stenotic; 5 = normal.

Perfusion harmonic imaging was performed at 1.8/3.6 MHz (S4 probe; Philips). The ultrasound pulses were triggered with a frame rate of 0.67 Hz, as described previously [8]. The investigation was performed in a standardized axial diencephalic plane (landmarks: third ventricle, thalamus, and the anterior horn of the ipsilateral ventricle) with a maximum depth of 10 cm (focus on 8 cm) on the symptomatic hemisphere in each patient. Gain and transmit power settings were optimized for each patient at the beginning of the initial investigation. The digitized grayscale images of the brain were stored in a continuous-loop review memory and were then recorded on an optical disc for later offline analysis. The symptomatic hemisphere was investigated after a bolus injection of 2.4 ml of SonoVue®, which was followed immediately by a 10-ml saline bolus injection. The sonographers, who were blinded as to the results of the initial CT, were provided only with clinical information pertaining to an ischemic stroke in the internal carotid artery territory (exclusion of hemorrhage).

Data analysis

We used a custom-made PC software (BHI-View) program, which is a Linux® command-line tool implemented in C language using the TIFF-library to stack-process image data and create color-coded parametric images (Seidel et al. 2004). In a bolus kinetics image series, four different parametric images (**Fig. 1**) were calculated from each pixel localization: 1. pixelwise peak intensity (PPI) image, 2. area under the curve (AUC) image, 3. positive gradient (PG) image and 4. time-to-peak (TTP) image.

To calculate the PPI images, the maximum intensity at each pixel localization was identified. After normalization to the maximum signal increase and background subtraction, a color-encoded PPI image was received. A disturbed perfusion was diagnosed in an area with a signal increase below 50 % of the maximum increase. The local parameter AUC was obtained by summing up the intensities for each pixel, starting at the point of UCA arrival time minus the baseline intensity in the TIC. The data were normalized to the maximum value of AUC and then provided as a color-encoded flow image. A pathological decrease was assumed when a reduction of more than 50 % compared to the maximum value occurred. The PG of the TIC is a local parameter

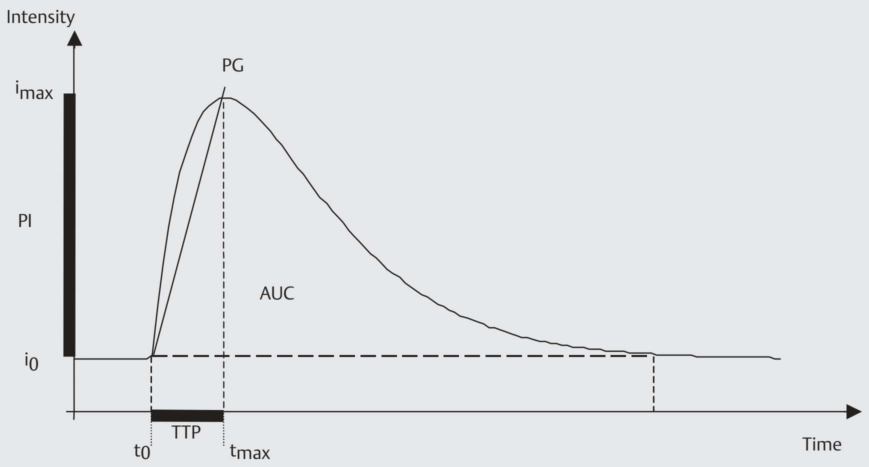

Fig. 1 Scheme of a time-intensity curve after ultrasound contrast agent (UCA) bolus injection. PI (peak intensity), AUC (area under the curve), PG (positive gradient), TTP (time-to-peak), i_{max} (maximum intensity), i_0 (baseline intensity), t_0 (time of peak onset), t_{max} (time of peak maximum).
Abb. 1 Schema einer Zeitintensitätskurve nach Ultraschallkontrastmittelbolusinjektion. PI (peak intensity), AUC (area under the curve), PG (positive gradient), TTP (time-to-peak), i_{max} (maximale Intensität), i_0 (Ausgangsintensität), t_0 (Zeit bis zum Beginn der Kontrastzunahme), t_{max} (Zeit bis zum Intensitätsmaximum).

that represents the influx velocity of the UCA (i.e., blood into the tissue).

The PG was calculated for each pixel by dividing the maximal intensity increase by the time-to-peak value. Again, the results for each pixel were normalized and a color-encoded image was provided. A pathological decrease was assumed when a reduction of more than 50 % compared to the maximum value occurred. The time, corresponding to the frame number of the image containing a certain pixel's maximum, was represented by color and was set into the TTP image. A pathologic delay of the contrast bolus peak was assumed at a delay of more than 3 seconds compared to the surrounding tissue. Pixels that remained black in the whole gray-scale image loops represented regions without any recognizable blood flow and were displayed as gray.

The fifth parametric image was calculated with the factor analysis of medical image sequences (FAMIS) algorithm using Pixies software (Apteryx, Issy-les-Moulineaux, France). This approach allows for the decomposition of an image sequence into parametric images and kinetic curves [12, 13]. It is based on a principal component analysis, followed by a constrained oblique analysis to extract physiologically related curves (factor curves) and their spatial localization (factor images). Each TIC can be finally considered as the linear combination of these factors. Positivity on factor curves and images and exclusivity on factor images constraints are applied to extract physiologically related kinetics. The maximum of each factor curve is set to the maximum of the TIC, where the factor has the highest contribution. For this application, the following three factors were selected: The first factor (in red) represents the earliest contrast uptake kinetic and corresponds to the arterial areas, the second (in green) represents the intermediate kinetics in parenchymal areas, and a late kinetic (in blue) represents the delayed contrast uptake areas such as venous areas or pathological areas.

A pathological parenchymal component was assumed when a delayed factor was located in a parenchymal or arterial area (with exclusion of venous regions) (▶ **Fig. 2e** and **f**) or in the case of a low amplitude tissular component (in green). The area of perfusion disturbance in the diencephalic plane was manually calculated for each parametric image (PPI, AUC, PG, FAMIS, TTP) with a graphics software tool (Image J 1.30v, National Institutes of Health, USA) and statistically compared with the area of definite infarction in the follow-up CT.

Statistical analysis

We used mean and median values as well as standard deviations and interquartile ranges (between 1. and 3. quartile) to analyze the data. Statistical testing for linear dependence between the different variables was performed using non-parametric Spearman rank correlations. Correlation coefficients as well as two-sided p-values are shown (SPSS 11.5; SPSS, Chicago, IL, USA). A significant correlation was assumed for $p < 0.05$.

Results

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This study investigated 22 patients suffering from acute infarction in the internal carotid artery circulation (7 women, 15 men; mean age 64.8 [SD 7.6] years). The time between the onset of infarction and the initial CT-scan was no more than 9 hours (mean 2.4 [SD 2] hours, median 1.5 [interquartile range 1.75]); median NIHSS score before the ultrasound investigation 16.4 [interquartile range 10.5] points; median mRS before the ultrasound investigation 5.0 [interquartile range 1]). Lesion patterns were as follows: 17 cortico-subcortical, 1 subcortical, 1 cortical, and 2 lacunar MCA infarctions. One patient suffered from an infarction in the anterior cerebral artery (ACA) territory. In three patients, the area of infarction in the follow-up CT was not located in the diencephalic plane. One patient suffered from a space-occupying MCA infarction, with enlarged early signs of infarction. A follow-up CT was not performed on this patient, and she later died of cerebral herniation. All BHI investigations (mean 7.1 [SD 5.25] hours, median 5.4 [interquartile range 4.05] hours after symptom onset) showed contrast enhancement and were of sufficient quality for further analysis. Follow-up CT was performed (mean 54.5 [SD 58.3] hours, median 28.8 [interquartile range 33.6] hours after symptom onset).

Pixelwise peak intensity (PPI)

In 20 patients, the PPI images showed a perfusion deficit (▶ **Fig. 1**). Hypoperfusion was not detected in the diencephalic plane in two patients: One patient suffered an ACA infarction, and the other one had a lacunar lesion in the MCA territory. Both lesions were located outside the insonation plane. One patient had a false-positive result in the PPI study. The sensitivity of PPI in the diencephalic plane was 100 %, and the positive predictive value (PPV) was 95 % (▶ **Table 1**).

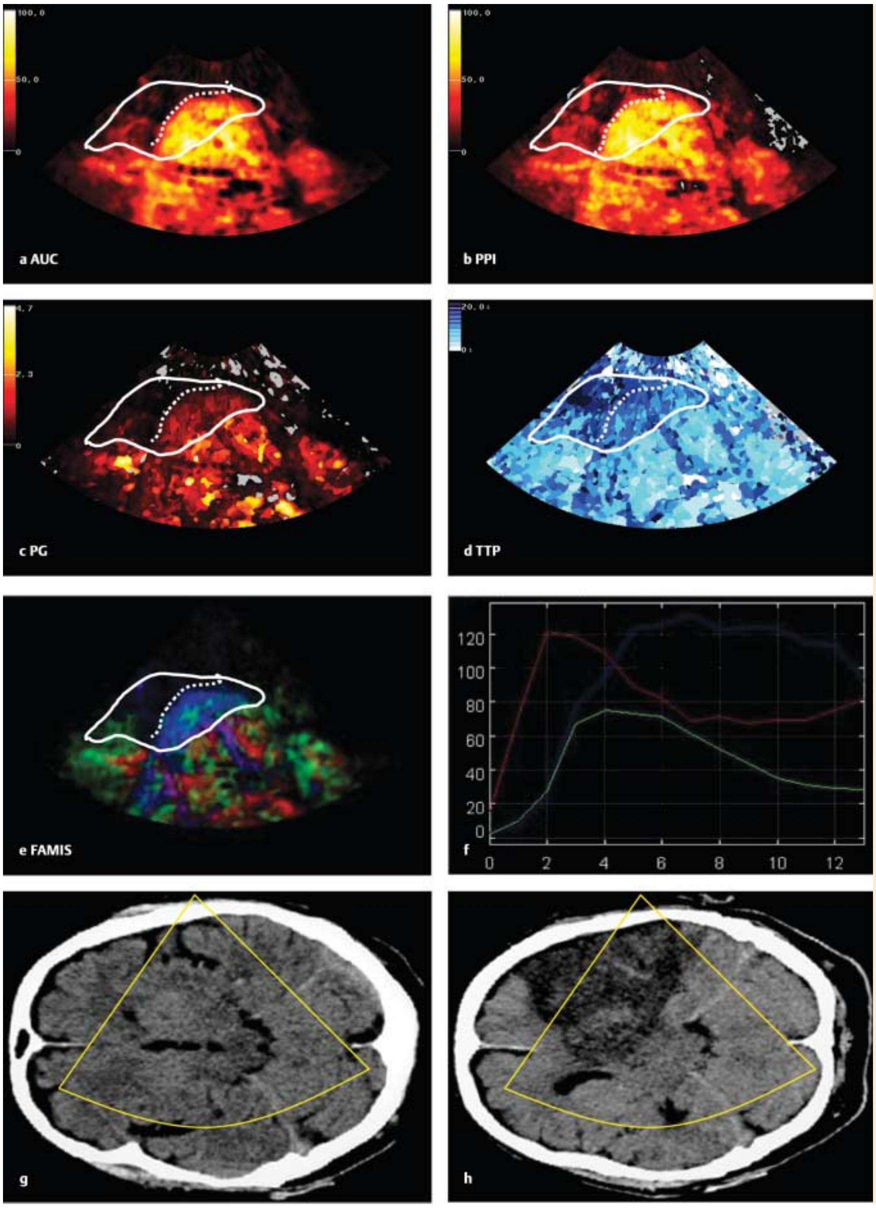

Fig. 2 Parametric and CT images of the axial diencephalic plane of a 70-year-old patient suffering from middle cerebral artery occlusion. Bolus harmonic imaging (BHI) was performed 4.5 h after symptom onset. **a** Area under the curve (AUC) image. **b** Pixelwise peak intensity (PPI) image. **c** Positive gradient (PG) image. **d** Time-to-peak (TTP) image. **e** Factor analysis of medical image sequences (FAMIS) image. **f** Factor curves of FAMIS image in **e**. **g** Initial CT scan, 2.5 h after symptom onset. **h** Follow-up CT, 180 h after symptom onset with clear depiction of the infarcted area in the middle cerebral artery territory. The white line indicates the area of significant perfusion delay in TTP. The dashed line tags the border between the pathologic areas in PPI and TTP. The yellow line on the CCT scans represents the insonation plane. Note that the whole area of TTP delay (even with normal PPI) turned to infarction in the follow-up CT.

Abb. 2 Sonographisches Parameterbild und CT in der dienzephalen Ebene eines 70-jährigen Patienten mit einem akuten Infarkt im Versorgungsgebiet der A. cerebri media durch einen Verschluss der A. cerebri media. Die Sonographie wurde 4,5 Stunden nach Symptombeginn durchgeführt. **a** Area-under-the-curve(AUC-)Bild. **b** Pixelwise-peak-intensity (PPI-)Bild. **c** Positive-gradient-(PG-)Bild. **d** Time-to-peak-(TTP-)Bild. **e** Factor-analysis-of-medical-image-sequences-(FAMIS-)Bild. **f** Faktorkurven des FAMIS-Bildes aus **e**. **g** Initiales CCT 2,5 Stunden nach Symptombeginn. **h** Verlaufs-CCT 180 Stunden nach Symptombeginn mit Demarkation eines ausgedehnten Mediainfarktes. Innerhalb der weißen Linien sind perfusionsverzögerte Areale dargestellt, die unterbrochenen Linien trennen amplitudengeminderte und perfusionsverzögerte Areale. Innerhalb der gelben Linien auf den CCT-Bildern befindet sich die sonographische Untersuchungsebene. Man beachte, dass das gesamte perfusionsverzögerte Areal im Verlauf infazierte.

Table 1 Analysis of parametric imaging in predicting the development of an infarction in the diencephalic plane of follow-up CT[1]

parametric image	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
PPI	100	67	95	100
AUC	100	33	90	100
FAMIS	89	33	89	33
PG	84	67	94	40
TTP	47	100	100	23

[1] n = 21 patients. Sens. = indicates sensitivity; Spec.= specificity; PPV = positive predictive value; NPV = negative predictive value; PPI = pixelwise peak intensity; AUC = area under the curve; FAMIS = three factor image from the factor analysis of medical image sequences; PG = positive gradient and TTP = time to peak.

We found a highly significant positive correlation between the area of infarction in the follow-up CT and the area of perfusion disturbance in the PPI image ($r = 0.76$, $p < 0.001$) (**Table 2**). A highly significant positive correlation between the area of PPI-reduction and the severity of stroke symptoms was also apparent (NIHSS: $r = 0.63$, $p = 0.002$ and mRS: $r = 0.72$, $p = 0.001$ before BHI) (**Table 2**).

Area under the curve (AUC)

In 21 patients, the AUC images showed an area of pathological perfusion. A perfusion disturbance was not detected in only one patient suffering from a lacunar lesion outside the insonation plane (sensitivity 100%). Two patients (one lacunar lesion and one ACA infarction) were wrongly classified as patients with an ischemia in the diencephalic plane (PPV 90%). The correlation between the area of infarction in the follow-up CT and the area of perfusion disturbance in the AUC image resulted in a moderate relationship ($r = 0.53$, $p = 0.014$).

Factor analysis of medical image sequences (FAMIS)

A perfusion disturbance was identified in 19 patients. One patient suffered from a lacunar lesion outside the insonation plane and was correctly classified with FAMIS. In two patients, the FAMIS method did not reveal any perfusion deficits

Table 2 Spearman rank correlations between the area of infarction in the follow-up CT (diencephalic plane) and several variables[1],

variable	coefficient	p
NIHSS before BHI	0.72	< 0.001
mRS before BHI	0.56	0.010
TIBI score	– 0.39	0.089
PPI	0.76	< 0.001
FAMIS	0.76	< 0.001
PG	0.62	0.003
AUC	0.53	0.014
TTP	0.50	0.021

[1] n = 21. NIHSS indicates National Institutes of Health Stroke Scale before the bolus harmonic imaging (BHI) ultrasound investigation; mRS = modified Rankin Score before BHI; TIBI = Thrombolysis in Brain Ischemia score; PPI = area of pathologic pixelwise peak intensity; FAMIS = area of pathologic three factor image of factor analysis of medical image sequences image; PG = area of pathologic positive gradient; AUC = area of pathologic area under the curve and TTP = area of pathologic time to peak.
Abbreviations: AUC = area under the curve; BHI = bolus harmonic imaging; CT = computed tomography; FAMIS = factor analysis of medical image sequences; MCA = middle cerebral artery; MRS = modified Rankin Score; NIHSS = National Institutes of Health Stroke Scale; PG = positive gradient; PPI = pixelwise peak intensity; PPV = positive predictive value; TCCS = transcranial color-coded sonography; TIBI = thrombolysis in brain ischemia score; TIC = time intensity curve; TTP = time to peak; UCA = ultrasound contrast agents.

within the area of definite infarction as depicted by follow-up CT. Two other patients without infarction in the diencephalic plane of follow-up CT had false-positive results. Compared with the area of definite infarction, the sensitivity and the PPV of the FAMIS image were both 89%. We found a highly significant positive correlation between the area of infarction in the follow-up CT and the area of perfusion disturbance in the FAMIS image ($r = 0.76$, $p < 0.001$). A significant positive correlation between the area of perfusion disturbance in FAMIS and the severity of stroke symptoms (NIHSS: $r = 0.65$, $p = 0.001$ and mRS: $r = 0.62$, $p = 0.002$ before ultrasound investigation) was also determined.

Positive gradient (PG)

PG images revealed a perfusion deficit in 17 patients (including the patient with an ACA infarction). Those patients without a perfusion deficit in the PG image included two patients with lacunar lesions outside the insonation plane and three patients with a false-negative result (sensitivity: 84%, PPV: 94%). A comparison between the area of infarction in the follow-up CT and the area of perfusion disturbance in the PG image showed a significant positive correlation ($r = 0.62$, $p = 0.003$).

Time to peak (TTP)

TTP images indicated a perfusion delay in 9 patients. All patients with a perfusion disturbance in the TTP image developed an infarction in this area. Three patients without a perfusion deficit were correctly classified. In 10 cases, TTP imaging failed to show a perfusion delay in the area of infarction; therefore, the sensitivity was 47%, but the PPV was 100%. We found a moderate correlation between the area of infarction in the follow-up CT and the area of perfusion disturbance in the TTP image ($r = 0.50$, $P = 0.021$).

The evaluation of the vascular status of the brain-supplying arteries (TIBI score) did not reveal any significant correlation with the area of infarction in CT (**Table 2**).

One patient died because of a space-occupying infarction. No adverse effects attributed to the contrast agent application were observed during the study.

Discussion

Ultrasound bolus perfusion imaging techniques have proved capable of displaying normal and hypoperfused regions in the human brain [1 – 5, 15, 16]. The ability of parametric imaging after UCA bolus injection to identify hypoperfused brain areas in the early phase of ischemic stroke that turned to infarction in the follow-up CCT scan has been demonstrated recently [6, 7]. In a study published by our group with the ultrasound technology used in this paper [8], we could show that in the early phase of acute ischemic stroke, BHI after SonoVue bolus injection is useful to analyse cerebral perfusion deficits and that BHI data correlate with the definite area of infarction and outcome after 4 months. In this study we used just the PPI and TTP images. Therefore, the question arose which TIC parameter can predict the area of infarction most accurately.

In our prospective study, we generated different parametric images (AUC, PPI, PG, TTP, FAMIS images) using sequences of harmonic images after SonoVue® bolus injection. For PPI, AUC, FAMIS, and PG images, we could calculate high sensitivities and PPVs, indicating that these perfusion modalities may predict the development of an infarction. In predicting the area of infarction, the TTP image (100%) provided the highest PPVs, but the sensitivity was only 47%. A significant correlation between the area of disturbed parameter display and the area of definite infarction in the diencephalic plane was found in descending order for FAMIS, PPI, PG, AUC, and TTP.

In conclusion, PPI seems to be the best parameter to display the area of infarction in the early phase of ischemic stroke with a high sensitivity and PPV as well as a high correlation with the area of infarction. An additional time-dependent parameter, such as TTP or FAMIS, is necessary to assess delayed perfusion areas with sufficient contrast uptake amplitude (**Fig. 2**).

When comparing the high correlation of parametric imaging with the low correlation of the TIBI score to the area of infarction, it is evident that ultrasound perfusion imaging provides substantial information on the cerebral perfusion status of the patient as compared to the isolated evaluation of the blood flow velocities of the basal cerebral arteries. All patients with sufficient insonation conditions for transcranial color-coded sonography showed successful perfusion harmonic imaging studies after SonoVue® bolus injection, indicating a strong signal increase with this contrast agent. Earlier studies showed that transcranial harmonic imaging after Levovist® bolus injection could visualize perfusion deficits and predict an infarction with a sensitivity of 75 to 86.4% and a specificity of 96.2 to 100% [2, 4]. The rate of successful investigations with Levovist® bolus injection ranges from 76.7 to 84%.

Contrary to studies using perfusion CT or MRI, we investigated only the axial diencephalic insonation plane rather than the whole volume of ischemic brain tissue. Nevertheless, BHI can assess the vascular territories of the main basal cerebral arteries (middle, anterior, and posterior cerebral artery) in this single investigation plane, thus providing information on the severity of brain perfusion disturbance. The detection of small ischemic territories outside the well defined diencephalic imaging plane is possible, but frontoapical and frontoparietal regions could not be insonated because of the geometry of the temporal bone window. The main advantage of BHI compared with other neuroimaging methods is its suitability at the patient's bedside.

There are some limitations associated with BHI. First of all, we could not measure perfusion quantitatively (regional cerebral blood flow or volume). Because the parameters calculated from the signal amplitude are depth dependent, they are only qualitative markers of the perfusion status, whereas time-dependent parameters are less sensitive [14]. Insonation artifacts also occur in every BHI investigation, mainly at the edges of the insonation field [7]. These artifacts can be separated from perfusion deficits by their characteristic shape, but they minimize the area of proper BHI investigation.

Minimally invasive bedside analysis of brain perfusion is becoming more and more important in routine diagnostics. This preliminary study is encouraging as a basis for further efforts (e.g., comparison between ultrasound BHI methods and perfusion-weighted MRI or perfusion CT technologies, which are the most promising assignments that will follow in this field). The combination of different ultrasound modalities (extra- and transcranial color-coded sonography and BHI parametric imaging) expands the diagnostic potential of ultrasound techniques from macrocirculation to microcirculation of the brain.

In summary, this study showed that parametric imaging after UCA bolus injection increases the diagnostic impact of neurosonology by providing additional information on the distal vascular bed of the brain in the early phase of ischemic stroke at the patient's bedside.

Acknowledgement

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