Cerebral Perfusion Imaging with Bolus Harmonic Imaging

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ABSTRACT

Fast visualisation of cerebral microcirculation supports diagnosis of acute stroke. However, the commonly used CT/MRI-based methods are time consuming, costly and not applicable to every patient. The bolus perfusion harmonic imaging (BHI) method is an ultrasound imaging technique which makes use of the fact, that ultrasound contrast agents unlike biological tissues resonate at harmonic frequencies. Exploiting this effect, the contrast between perfused and non-perfused areas can be improved. Thus, BHI overcomes the low signal-to-noise ratio of transcranial ultrasound and the high impedance of the skull. By analysing image sequences, visualising the qualitative characteristics of an US contrast agent bolus injection becomes possible. The analysis consists of calculating four perfusion-related parameters, Local Peak Intensity, Time To Peak, Area Under Curve, and Average Rising, from the time/intensity curve and providing them as colour-coded images. For calculating these parameters the fundamental assumption is that image intensity corresponds to contrast agent concentration which in turn shows the perfusion of the corresponding brain region. In a clinical study on patients suffering from acute ischemic stroke it is shown that some of the parameters correlate significantly to the infarction area. Thus, BHI becomes a less time-consuming and inexpensive bedside method for diagnosis of cerebral perfusion deficits.

Keywords: Ultrasonography, bolus harmonic imaging, contrast agent, cerebral microcirculation, brain perfusion, cerebrovascular diagnostics, acute ischemic stroke.

1. INTRODUCTION

Successful treatment of acute ischemic stroke depends on early and reliable diagnosis of areas with critically reduced brain tissue perfusion. To diagnose such a perfusion disturbance visualisation of cerebral microcirculation is essential. Currently, the main diagnostic methods used for this purpose are high-technological methods such as CT, MRI, SPECT and PET. The drawbacks of these methods are multifaceted. First of all they are expensive and time-consuming. Furthermore they may require radioactive tracers and may be intolerable to restless or critically ill patients, since normally the patient has to be moved to the examination facility and lie steady during the imaging process.

Ultrasound, as a fast, inexpensive, and well-tolerated bedside method, has been introduced for the evaluation of myocardial perfusion.[1–3] New ultrasound technologies like conventional and phase inversion harmonic imaging, can detect perfusion deficits in the brain parenchyma by transcranial ultrasound.[4–6] To circumvent the low signal-to-noise ratio (SNR) of transcranial ultrasound, harmonic imaging (HI) is used.[7] It utilizes the fact that ultrasound contrast agents (UCA) are highly resonant at diagnostic ultrasound frequencies and produce harmonics of the fundamental frequency which are distinguishable from the tissue ultrasound response.[1,3,8] Thus, the SNR is increased and it becomes possible to track an UCA bolus within the human cerebral microcirculation providing the physician with perfusion-related parameters for diagnosis. This technology based on bolus kinetics is called bolus harmonic imaging (BHI).[9,10] Different harmonic imaging methods rely on a constant UCA infusion and measure the replenishment (RHI)[11–14] or diminution (DHI)[15,16] kinetics. This work describes how BHI parameters are provided as parametric images and uses this method to assess the diagnostic potential of BHI by comparing parametric images to cranial computed tomography (CCT) images in a clinical study.

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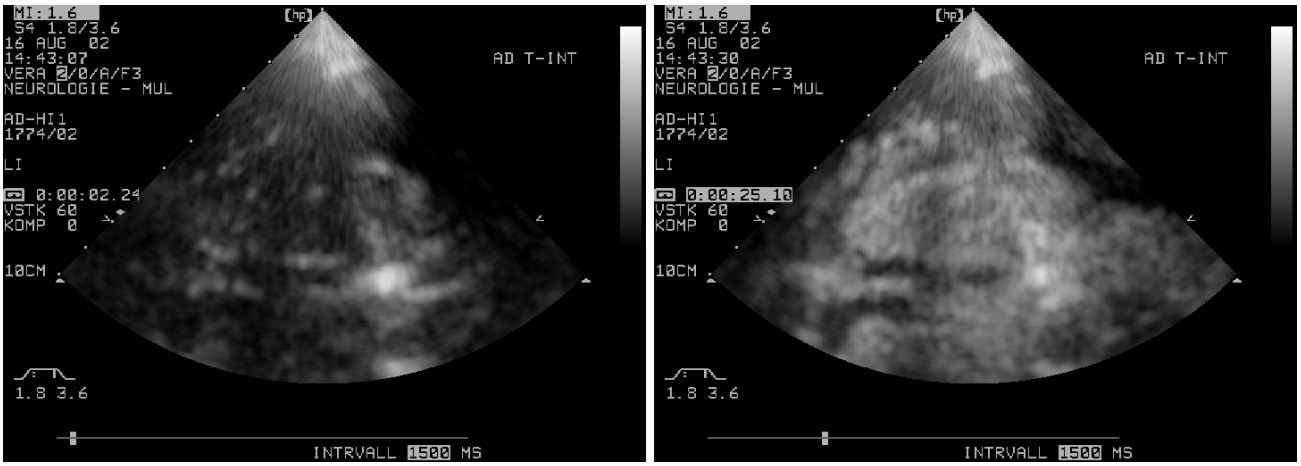


Figure 1. Temporal BHI images of a healthy left hemisphere. The left image is the first one taken in a BHI sequence. None of the administered SonoVue® contrast agent bolus has reached the brain region (baseline image). The right image is taken 23 seconds later at the peak of contrast agent influx and shows the improved SNR of harmonic imaging.

2. PERFUSION HARMONIC IMAGING BASED ON BOLUS KINETICS

Ultrasound images capture impedance differences of insonated tissues by backscattered soundwaves. The quality of diagnostic ultrasound images is limited by poor signal-to-noise ratios and granular speckle noise. In the case of transcranial B-mode sonography, image quality is additionally reduced by the high sound impedance of the skull. By using appropriate ultrasound contrast agents for signal enhancement, however, cerebral blood flow can be captured by harmonic imaging sequences and used to derive diagnostically relevant visualisations of human cerebral microcirculation.

In order to enhance the representation of blood vessels in ultrasound images, harmonic imaging is specialised to detect resonance phenomena of contrast enhancing microbubbles within the microcirculation after UCA injection. It utilises the fact that these bubbles are highly resonant at diagnostic ultrasound frequencies.[3] When a bubble vibrates near resonance, it produces harmonics or multiples of the transmitted frequency. Whereas insonated tissue responds primarily at the fundamental frequency band, the microbubbles respond at the fundamental and harmonic frequency bands. Harmonic ultrasound systems transmit soundwaves at the common diagnostic frequency band and receive only at multiples of that frequency (e.g. transmit at 1.8MHz, receive at mainly 3.6MHz, but also 7.2MHz). Since the harmonic frequencies result mainly from resonance phenomena of the microbubbles harmonic imaging prevents unwanted noise due to sound wave rejections by the tissue in the fundamentals frequency band. Therefore HI images have much better signal-to-noise ratios than ordinary ultrasound images (Fig. 1).

This improved SNR can be used to track the contrast agent kinetics by acquiring sequential images at a specific rate. Since the contrast agent is mainly present in the blood circulation a relationship from contrast agent kinetics to blood perfusion can be established.

The administered ultrasound contrast agent SonoVue® (Bracco/Altana Pharma, Konstanz, Germany) is a sulfur-hexafluoride-containing aqueous suspension of phospholipid microbubbles, which is capable of passing the pulmonary circulation. The diameter of the microbubbles is less than $8\mu m$ for more than 90% of the bubbles and the concentration is $5 - 8 * 10^8$ per ml suspension. The 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.

The grey-scale scans were adjusted in an axial diencephalic plane with the third ventricle as landmark. Due to the ultrasound signal attenuation, cerebral images of reasonable quality can be guaranteed for one hemisphere only. The investigation depth was set to 10cm with the focus on 8cm and hence, a second image sequence has to be taken from the opposite side to provide flow images of a full brain slice (Fig. 2).

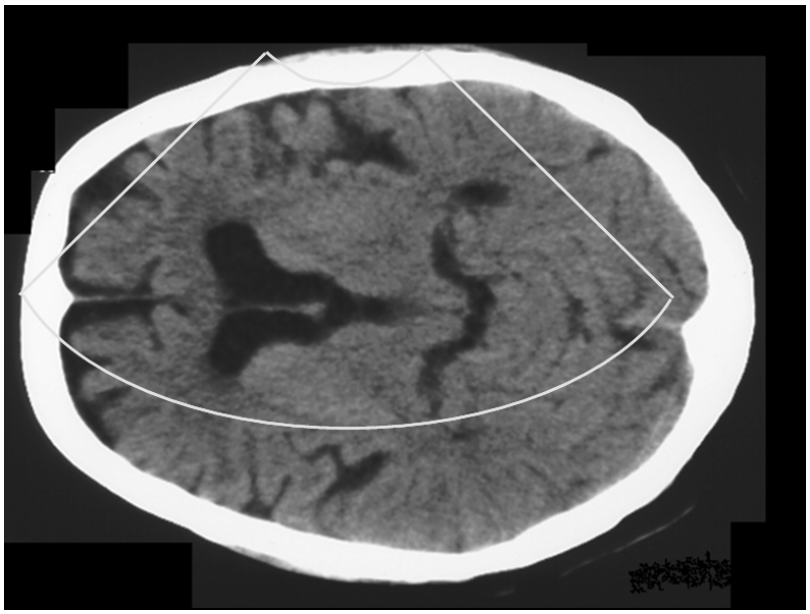


Figure 2. Illustration of the position of a temporal BHI image in a CCT brain slice.

A BHI sequence usually consists of 20 to 30 frames $f_0, \ldots, f_{n-1}$. With a pulse rate of $\frac{2}{3}$Hz, the image acquisition takes 30 to 45 seconds for one sequence. The acquisition is started as soon as the bolus is injected in the ante-cubital vein of the patient. Depending on the patient and the type of disease, a contrast agent response can be expected 5 to 10 frames, i.e. 7.5 to 15 seconds after injection. During the passage of the bolus through the perfused brain tissue, the UCA concentration and hence the intensity of the corresponding image areas quickly rise towards a maximum and decrease afterwards to reach a constant level slightly higher than the baseline level because of UCA recirculation.

The foremost limitation of BHI to date is that one contrast agent bolus must be applied for each set of parametric images. A technical solution is the so-called matrix probe, which scans multiple insonation planes within one investigation and one bolus applied.[17] Furthermore, the perfusion can not be measured quantitatively (cerebral blood flow or volume). It is just possible to characterize the time/intensity curve after contrast agent bolus injection with different parameters which are related to perfusion. Insonation artifacts occur in every BHI investigation, mainly at the edges of the insonation field. Due to their characteristic shape, these artifacts can be distinguished from perfusion deficits, but they decrease the area of proper BHI investigation.

2.1. Calculation of global parameters

For each image pixel $\mathbf{x} = (x_1, x_2)$ corresponding to a perfused tissue position, the time series of the corresponding values $f_j(\mathbf{x})$ of all images f_j of the HI-sequence yields the individual local time-intensity curve. The analysis of this curve results in four parameters which are provided in colour-coded images: Area under curve (**AUC**), local peak intensity (**LPI**), average rise (**Slope**) and time to peak (**TTP**).

Prior to calculating these four local parameters the global arrival time t_0 of the contrast agent in the brain has to be determined. The time t_0 is the earliest significant global intensity increase in the perfused brain area after the injection of contrast agent. It is estimated from the time series of the spatially averaged intensities of the ultrasound fan area of all frames f_j. Currently, the fan area is represented by a binary mask image prepared by a physician. To obtain the global arrival time t_0 from this series of intensity values, i.e. the frame number when the curve begins to rise, the maximum slope is determined as the maximum of the first derivative while the second derivative changes from positive to negative. Starting with this point, the curve is back-traced until the slope either becomes insignificantly small or negative. Since calculating the time derivative corresponds to a high-pass filter, the mean intensity values are low-pass filtered in time by an average filter to reduce noise.

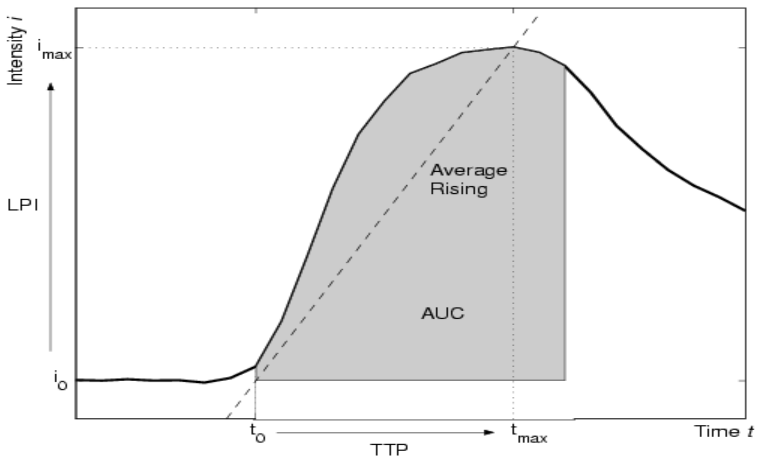


Figure 3. BHI parameters in a time/intensity curve after injection of an UCA bolus. The curve shown was computed globally from the US images of a stroke patient, while all described parameters except t_0 are calculated locally.

Figure 3 shows a time/intensity curve from a BHI examination. This curve originates from the spatially averaged intensity values of each image low-pass filtered with a sliding average filter of size 3. Together with the main parameters AUC, LPI, Slope, and TTP, the auxiliary parameters baseline intensity (i_0), maximum intensity (i_{max}), UCA arrival time (t_0) and time of local maximum (t_{max}) are shown in this figure. All frames before the time t_0 are used to calculate the baseline intensity for each pixel which is used for the parameters Area Under Curve and Local Peak Intensity.

2.2. Area Under Curve

The local parameter Area Under Curve (AUC) is obtained by summing up the intensities for each pixel starting with frame f_{t_0}. The baseline intensity $i_0(\mathbf{x})$ of each pixel is subtracted before the summation. The interesting part of the time/intensity curve for this parameter starts where the curve begins to rise and should include the peak. To be able to compare the sum within the parametric image, the summation must always include the same number of frames. It is not possible to let the summation stop at the peak frame since the number of this frame varies between different pixels. The solution is to let the summation stop at frame f_{t_0+r} with r set manually. The default value for r is 10 because it has been shown that the peak is reached latest after 15 seconds in every pixel. Since AUC is a local parameter it depends on $\mathbf{x}$:

$$\mathrm{AUC}(\mathbf{x}) = \sum_{j=t_0}^{t_0+r} f_j(\mathbf{x}) - i_0(\mathbf{x}) \qquad \text{with} \quad i_0(\mathbf{x}) = \frac{1}{t_0}\sum_{j=0}^{t_0} f_j(\mathbf{x}) \ . \tag{1}$$

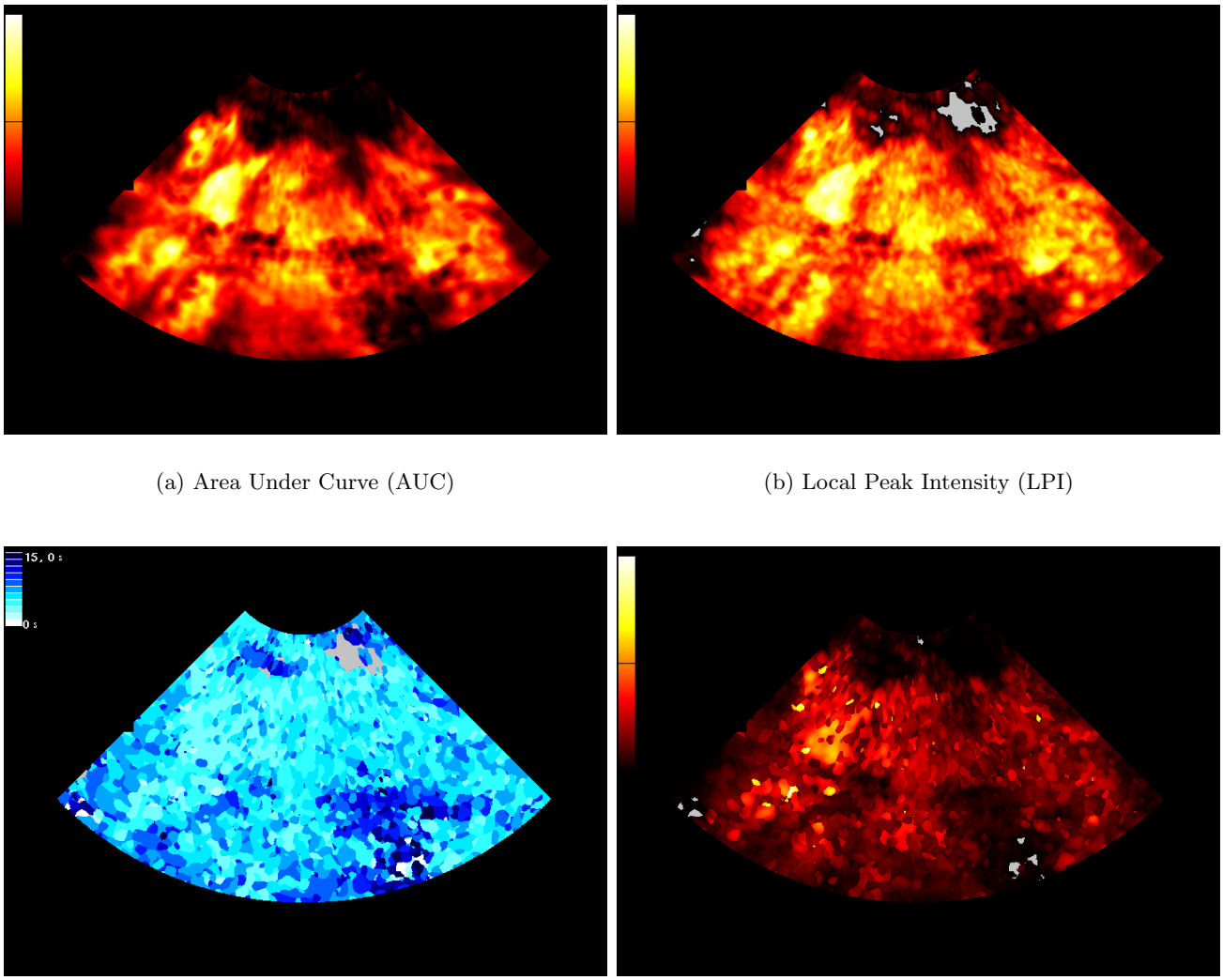
Subsequently, the obtained area values are normalized to 256 gray values. This ensures the comparability of parameter images of different patients. To support physicians quickly with their diagnosis, the AUC parameter is provided as a color-coded flow image, with light (white/yellow) and dark (red) colors representing little and high AUC values, respectively (Fig. 4, (a)).

2.3. Local Peak Intensity

The local peak intensity flow parameter is obtained by the intensity difference between the baseline intensity i_0 and the maximum intensity i_{max} at a point $\mathbf{x}$:

$$\mathrm{LPI}(\mathbf{x}) = i_{max}(\mathbf{x}) - i_0(\mathbf{x}) \qquad \text{with} \quad i_{max}(\mathbf{x}) = \max_{j=0\ldots n-1}\{f_j(\mathbf{x})\} \ . \tag{2}$$

Prior to the local peak intensity, the baseline image has to be calculated, containing the baseline intensity $i_0(\mathbf{x})$ for each image point. As equation (1) shows, it is estimated by the pixel-wise mean of all images acquired before



(a) Area Under Curve (AUC)

(b) Local Peak Intensity (LPI)

(c) Time To Peak (TTP)

(d) Average Rising (Slope)

Figure 4. BHI parameter images. The AUC image shows the area under the curve from f_{t_0} to f_{t_0+10} (a), i.e. the blood volume passing through the tissue while the LPI image (b) gives a measure for the maximum local perfusion in the corresponding tissue area in a frame $f_{t_{max}}$. The TTP image (c) visualizes the time delay of the contrast agent to reach its maximum local intensity and the Slope image (d) shows the average slope of the curve in a tissue point $\mathbf{x}$.

the global arrival time of the contrast agent in the patient's brain. The baseline intensity i_0 represents the pure tissue answers without any contrast agent response, i.e. the sound impedance of the tissue (Fig. 1). Since for LPI only the tissue response based on the contrast agent is of interest, it is obvious that the baseline intensity has to be a local parameter.

The maximum local intensity $i_{max}(\mathbf{x})$ represents the sum of sound impedances of the tissue and the highest contrast agent response. It is identified as the maximum of the intensity time series at each image position.

Again, the peak intensities are normalized to ensure comparability within different LPI images. The same colormap as in the AUC image (red-yellow-white, "hot" colormap in MatLab) is used to map gray values to colors (Fig. 4, (b)). Obtained LPI values without any information (e.g. negative) are displayed as grey. This method facilitates the comparison of the different flow parameter images.

2.4. Time To Peak

The local time to peak (TTP) is calculated as the duration from the first occurrence of the contrast agent in the cerebral microcirculation (arrival time t_0) to the time t_{max} when the maximum contrast agent concentration at a tissue point $\mathbf{x}$ is reached. Thus, it gives information about whether this region is directly supplied with blood or through revascularisation.

$$\mathrm{TTP}(\mathbf{x}) = t_{max}(\mathbf{x}) - t_0 \qquad \text{with} \quad f_{t_{max}}(\mathbf{x}) = i_{max}(\mathbf{x}) \ . \tag{3}$$

Equation 3 shows that t_{max} is the time when the maximum intensity i_{max} is reached in image position $\mathbf{x}$.

Unlike the other three parameters, TTP is a time parameter. Consequently, its values are mapped onto a different colormap with light (white) and dark (blue) colours representing fast and slow blood flow, respectively (Fig. 4, (c)). The values are normalized to better distinguish different time delays. Since the image acquisition occurs every 1.5 seconds and the peak is usually reached after 10 image frames there are only as many different colours in this parameter image. Again, TTP values without information are displayed grey.

2.5. Average Rising

The average rising (Slope) of the time/intensity curve is again a local parameter and thus calculated for each image position $\mathbf{x}$. It is related to the average blood flow velocity and is estimated by the ratio of LPI and TTP and thus joins temporal and intensity aspects in one image:

$$\mathrm{Slope}(\mathbf{x}) = \frac{\mathrm{LPI}(\mathbf{x})}{\mathrm{TTP}(\mathbf{x})} \ . \tag{4}$$

Again, the results for each pixel are normalized and mapped onto the white-yellow-red colormap (Fig. 4, (d)).

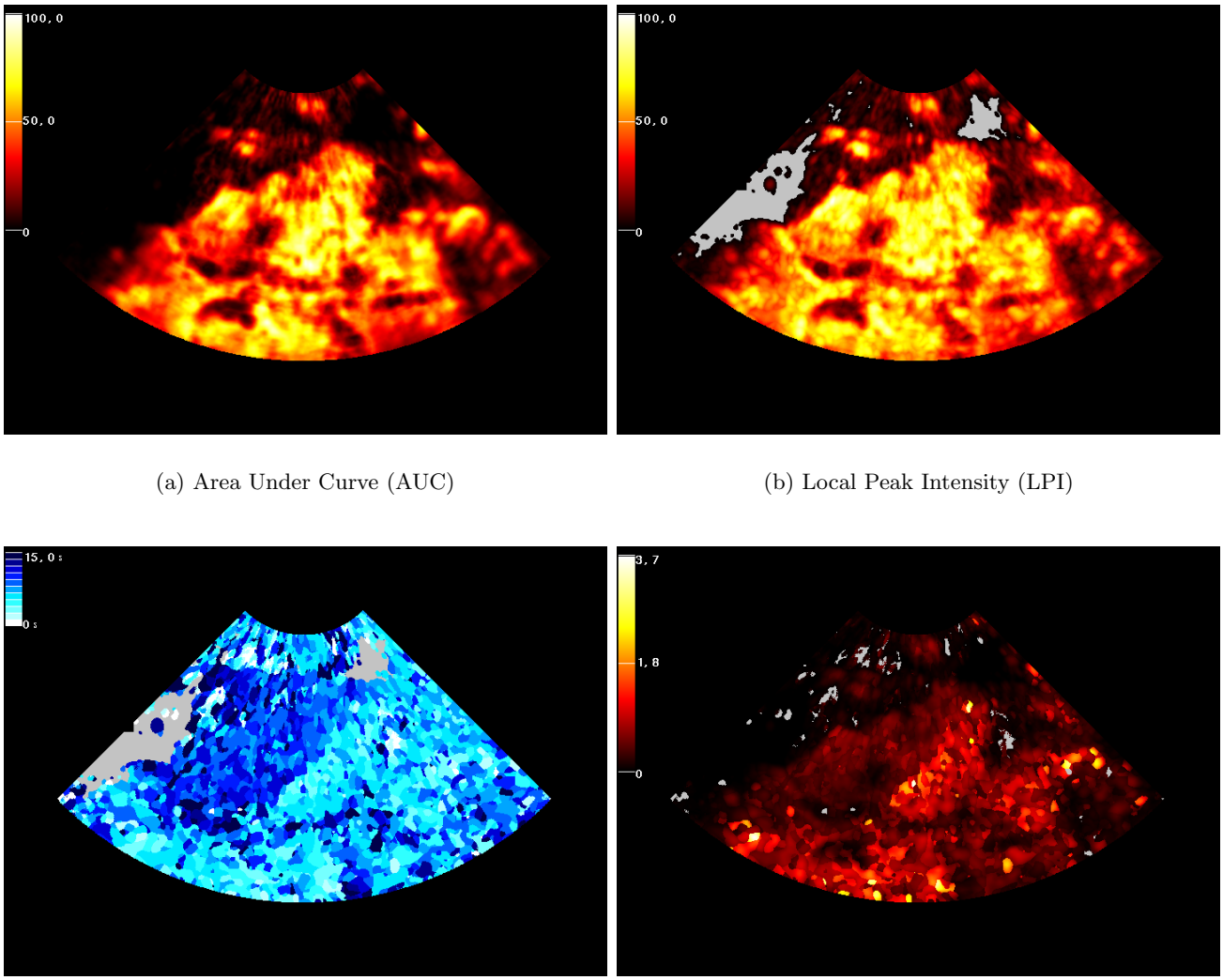
Our first approach for this parameter was to calculate the slope stepwise by finite difference ratios and take the maximum, because the blood flow velocity is assumed to be constant during the ultrasound examination while the UCA concentrations vary. However, a comparison of these two parameter images showed at once that the approximated slope image would correlate much better.

3. DIAGNOSTIC POTENTIAL OF BHI

A first look at the parameter images suggested a high diagnostic relevance of the BHI images. Figure 5 shows an extreme example of the four parameter images of a patient suffering from acute ischemic stroke due to middle cerebral artery occlusion. In comparison with figure 4 it is clear to see that a perfusion disturbance occured in the upper left area of the ultrasound fan. The AUC and Slope images are almost black in this area and the LPI image is also comparatively dark and shows quite a lot grey pixels as well indicating that the blood flow in this area does not match the assumption of a healthy time/intensity curve as shown in figure 3. The TTP image shows a larger area in dark blue colours indicating delayed perfusion. This area corresponds to the area of brain infarction as diagnosed by cranial computed tomography (CCT).

In order to assess the diagnostic potential of these ultrasound parameter images we have conducted a study on 14 patients suffering from acute ischemic stroke of the internal carotid artery circulation. Table 1 shows the descriptive statistics of these patients. Only 13 values are valid because one patient had an anterior (not middle) cerebral artery infarction so that no infarction could appear in the examination plane. The findings of the BHI images were compared to those of CCT.

Using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Score (mRS), the clinical status of the patients was assessed before the investigation. The initial ultrasound investigation consisted of extra- and transcranial color-coded duplex sonography (TCCS) as well as transcranial perfusion harmonic imaging using the bolus kinetics (BHI) with SonoVue® contrast agent. Two CCT scans (Aquilion; Toshiba Medical Systems Europe, Zoetermeer, The Netherlands) were performed as part of the routine protocol for stroke patients. Routinely, one CCT scan was done as first-line diagnostic approach before sonography and a



(a) Area Under Curve (AUC)

(b) Local Peak Intensity (LPI)

(c) Time To Peak (TTP)

(d) Average Rising (Slope)

Figure 5. BHI parameter images of a 67-year old patient with acute middle cerebral artery infarction (NIHSS 21 points) due to MCA mainstem occlusion. BHI was performed 6 h after symptom onset. Compared to the parameter images in figure 4 the perfusion disturbance is clear to see in the upper left part of the US fan in all images.

repeat CCT (CCT_FU) was performed to confirm localization and size of the infarction. No contrast agent was administered for CCT.

The BHI images were aquired with a SONOS 5500 ultrasound system (Philips Medical Systems, Best, The Netherlands) and a 1.8/3.6 MHz sector transducer (S4 probe; Philips). The ultrasound pulses were triggered with one pulse every 1.5 seconds, as described earlier. 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 symptomatic hemisphere was investigated after a bolus injection of 2.4 ml of SonoVue® followed immediately by a 10-ml saline bolus to flush the injection line. The sonographers (GS and KM), who were blinded as to the results of the initial CCT scans, were provided only with the clinical information of an ischemic stroke in the internal carotid

Table 1. Descriptive statistics of patients investigated in the study.

Property	# of patients	min	max	mean	std. dev.
Age (*years*)	14	48.0	75.0	64.07	8.03
NIHSS (*points*)	14	6.0	28.0	15.5	7.12
mRS (*points*)	14	3.0	5.0	4.43	0.76
CCT_FU (h)	13	12.0	225.5	69.79	68.05
BHI (h)	14	2.5	13.5	5.55	2.96

artery territory (exclusion of hemorrhage).

After the ultrasound parametric images had been calculated the actual areas of perfusion disturbance ($A_{AUC}, A_{LPI}, A_{Slope}$ and A_{TTP}) were determined manually for each image by a clinical expert. To make this decision reproducible the following definition was applied by the experts. A perfusion disturbance was defined as significant when a decrease of more than 50% of normalized intensity in the AUC/LPI/Slope images was visible and/or a delay of more than three seconds in a region compared with the surrounding tissue was seen in the TTP image.

Table 2. Correlation coefficient and significance (p) of comparison of A_{CCT} with perfusion disturbance area in BHI images and clinical parameters.

	Age	NIHSS	mRS	A_{AUC}	A_{LPI}	A_{Slope}	A_{TTP}
Correlation	0.27	0.7[a]	0.638[b]	0.559[b]	0.862[a]	0.455	0.65[b]
p (two-sided)	0.35	0.005	0.014	0.038	< 0.001	0.102	0.012

[a]Correlation is significant on 0.01 level.
[b]Correlation is significant on 0.05 level.

For the statistical analysis we used mean and median values as well as standard deviations for the description of the data. Calculation of correlation between the different variables was performed using non-parametric Spearman rank correlations. Correlation coefficients as well as two-sided p values are shown in table 2. A significant correlation was assumed for a p value < 0.05.

As the table shows the infarction area in the mid-thalamatic plane A_{CCT} correlates significantly in decreasing strength with:

- A_{LPI} (Intensity decrease over 50%),
- A_{TTP} (Delay of more than three seconds in a region compared to the surrounding tissue), and
- A_{AUC} (Intensity decrease over 50%),

whereas no significant correlation occurs for A_{Slope}.

4. CONCLUSIONS

The purpose of this prospective study was to demonstrate clinical relevance of the harmonic imaging method BHI. As a result, the area of significant amplitude decrease (A_{LPI}) detected by BHI in the early phase of ischemic stroke correlates significantly with the definite area of infarction shown by follow-up CCT. The parameters A_{TTP} and A_{AUC} correlate to the CCT area to some extent as well. LPI seems to be the best parameter to display the area of infarction in the early phase of ischemic stroke. Beside this signal amplitude dependent parameter, a time dependent parameter image like the TTP should be added as standard diagnostic protocol.

The advantage of BHI is that it can provide qualitative information regarding brain perfusion at the patient's bedside. It may prove to be a helpful extension of the conventional ultrasound examination of the basal

cerebral arteries. Up to now, a comparison between BHI and perfusion CT or MRI of the brain has not been performed in a considerable number of stroke patients[15] although promising results have been achieved with healthy volunteers.[18]

In conclusion, parametric imaging with BHI 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.

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