Ultrasound Cerebral Perfusion Analysis Based on a Mathematical Model for Diminution Harmonic Imaging

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Summary

Objectives: Cerebral vascular diseases are detectable by CT/MRI-based methods. Drawbacks of these methods are that they are expensive, time-consuming and intolerable to critically ill patients. Ultrasound, as an inexpensive bedside method, promises to become an alternative. Among other harmonic imaging methods, the diminution harmonic imaging (DHI) method is known, which determines perfusion-related parameters by analyzing ultrasound contrast agent (UCA) diminution kinetics based on constant UCA infusion. The shortcoming of DHI is that the used mathematical model can only determine these parameters by least squares fitting the model onto the data.

Methods: In this work, the underlying mathematical model is further developed such that it becomes possible to directly calculate the parameters from the image data. Furthermore, the new model offers an improved way to estimate the spatial distribution of the destruction coefficient necessary for accurately determining the destruction power of the ultrasound pulse on the contrast agent.

Results: The direct calculation of the perfusion coefficient is much faster than the former fitting of the model. Perfusion as well as destruction coefficients are displayed as color-coded images. In an example, a region with perfusion deficits (as shown in a MR image of the same patient) is clearly identifiable.

Conclusions: Displaying the parameters as color-coded images facilitates result interpretation for the diagnosing physician. The results are preliminary and still have to be validated, but they suggest that the new DHI model improves the significance of ultrasound as a diagnostic help.

Keywords

Ultrasound contrast agents, microbubbles, computer-assisted image interpretation, cerebrovascular circulation, diminution harmonic imaging

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1. Introduction

Successful treatment of cerebrovascular diseases mainly depends on early and reliable diagnostics of areas with critically reduced brain tissue perfusion. This diagnostic process can be supported by visualization of cerebral microcirculation. Currently, different high-technology methods are used to visualize and evaluate brain perfusion of patients with acute brain infarction, such as computed tomography (CT) [1] and magnet resonance imaging (MRI) [2]. The drawbacks of such methods are obvious: they are time-consuming, costly, and may be intolerable to critically ill or restless patients.

Since several attempts have been made in neurosonography and echocardiography to measure capillary blood flow and tissue perfusion by means of contrast-enhanced ultrasound (US) techniques, ultrasound imaging has turned out to be a fast and flexible alternative to established methods [3]. In spite of low signal-to-noise ratios (SNR) of transcranial ultrasound, it has been shown that it is possible to visualize and measure changes in ultrasound intensities in perfused areas of the brain through the intact skull by using harmonic grey-scale ultrasound imaging [4]. By using ultrasound contrast agents (UCA), the SNR can be further improved.

The first harmonic imaging method adapted for the assessment of cerebral microcirculation was bolus harmonic imaging [5]. This method analyzes the flow kinetics of an UCA bolus. Because image acquisition is done with interframe intervals of 1500 ms and covers a whole wash-in and wash-out phase, the procedure can take up to two minutes. The biggest difficulty with this method is to provide stable insonation conditions throughout the acquisition process. Nevertheless, it has been shown that this method is effective in predicting the patient's outcome [6, 7].

The diminution harmonic imaging (DHI) method has recently been adapted to the assessment of cerebral perfusion [8, 9]. It is based on continuous infusion of contrast agent resulting in a constant UCA concentration in the blood. By a series of fast high energy US pulses, the UCA concentration is decreased until a steady state is reached in which one pulse destroys as much UCA as flows into the imaging plane during one interpulse interval. This method is very promising, since an examination procedure of one imaging plane is done in 6-7 seconds, which reduces the artifacts originating from patient or examiner movements. Currently, two alternative analysis methods are in use with the DHI process. One calculates perfusion-related parameters directly from the time-intensity curve and displays these parameters as color-coded images [8]. The other one mathematically models the DHI process and estimates among other parameters the perfusion coefficient by fitting the model onto the data with least squares methods [12]. The results of both methods are used by a physician to diagnose perfusion deficits.

2. Objectives

The first approach with DHI modeled the process as an exponential decay function, only taking into account the destruction, and not the wash-in/wash-out kinetics [10]. By

fitting the model onto the data, the saturation, decay parameter, and half-life time were obtained and presented as color-coded images. The currently used mathematical model describing inflow, outflow, and destruction of contrast agent has been introduced by Wilkening et al. [11] and first applied to neurosonography by Eyding et al. [12], where the method is called Contrast Burst Depletion Imaging (CODIM). Still, the model is fitted onto the data to obtain the parameters describing the local perfusion.

The objectives of this work are to further develop the new DHI model introduced by [11], to be able to directly calculate the desired parameters from the image data. This would remove the necessity of the model fitting process, which usually is very time-consuming. Inaccuracies introduced by the fitting process could be avoided leading to better parameter determination. Displaying the parameters in color-coded images facilitates result interpretation for the diagnosing physician. Furthermore, the depth dependency of the perfusion parameter calculation is to be reduced. A method is introduced to better estimate the local destruction power of the ultrasound pulse.

Hence, by further developing the model from Wilkening et al. [11] and combining it with color-coded result presentation, better accuracy (also due to reduced depth dependency), increased calculation speed, and easy result interpretation are obtained.

3. Methods

Transcranial sonography suffers from a low SNR due to the high impedance of the skull. To improve the SNR, ultrasound harmonic imaging makes use of the fact that the ultrasound attenuation varies over frequency. The use of UCA amplifies this effect. UCA consist mainly of gas-filled microbubbles, that nonlinearly scatter ultrasound and hence improve harmonic imaging. Depending on the US pulse energy, the microbubbles are even destroyed, which also generates a nonlinear echo. While the US pulse is sent with a center frequency of 1.8 MHz, the probe also records harmonic frequencies which are mainly due to contrast agent.

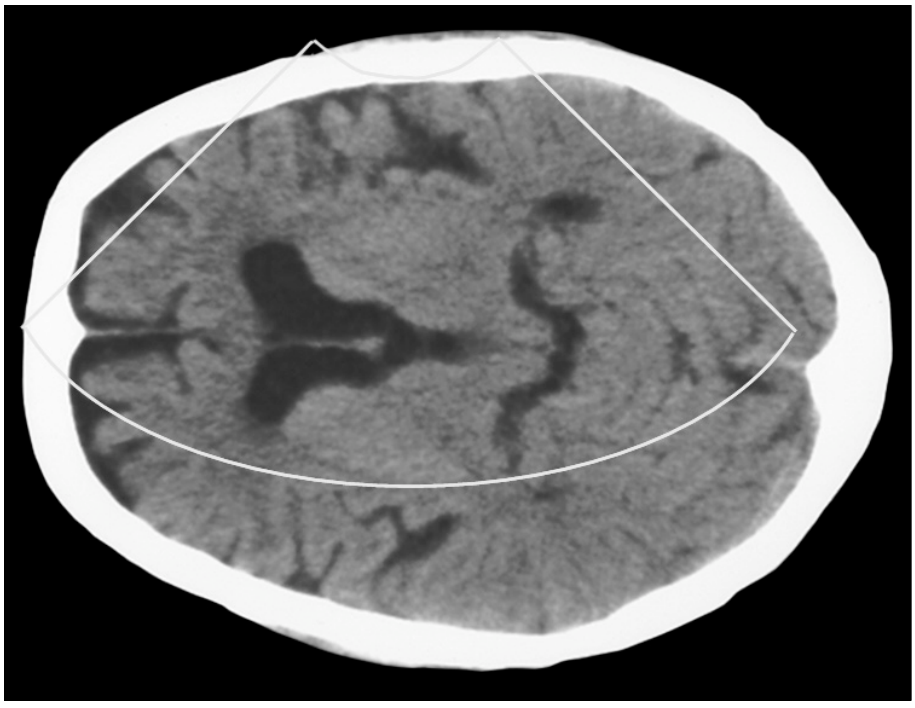


Fig. 1 CT scan of the diencephalic imaging plane. The field of insonation is marked within the white lines. An US frame covers slightly more than one side of the brain in the dedicated imaging plane.

Since contrast agent can only be found in the blood circulation, this procedure is well suited for perfusion imaging. Analyzing a varying contrast agent concentration in an US image sequence provides information about the actual perfusion in the imaging plane.

When acquiring a DHI sequence, the penetration depth of the ultrasound beam is set to 10 cm. Thus, two sequences are necessary to cover the diencephalic imaging plane from both hemispheres of a patient. Figure 1 shows the ultrasound imaging plane superimposed on a CT scan of the diencephalic plane. The most interesting part of the brain regarding pathological brain perfusion is close to the skull, i.e. close to the top in the US frame, because most perfusion deficits occur in this area. Since the lower part of the US image area already covers the opposite hemisphere, it can be ignored in the further analysis.

The DHI method is based on continuous contrast agent supply by intravenous infusion leading to a constant UCA concentration in the blood. Figure 3a shows the first image from an exemplary DHI sequence in which the US echo intensity is relatively high. A series of US pulses reduces the UCA concentration, since microbubbles are destroyed due to the high sound pressure used with this method. The US pulse series are acquired at two different interpulse intervals of 150 ms and 600 ms (6.67 Hz and 1.67 Hz) for each patient. In a healthy person the perfusion is usually

$$c(n+1) = c(n) \cdot \underbrace{d}_{Destruction} \cdot \underbrace{e^{-p\cdot\Delta t}}_{Outflow} + c(1) \cdot \underbrace{\left(1 - e^{-p\cdot\Delta t}\right)}_{Inflow}. \qquad (1)$$

Fig. 2 Model describing inflow, outflow, and destruction of contrast agent for every time step n

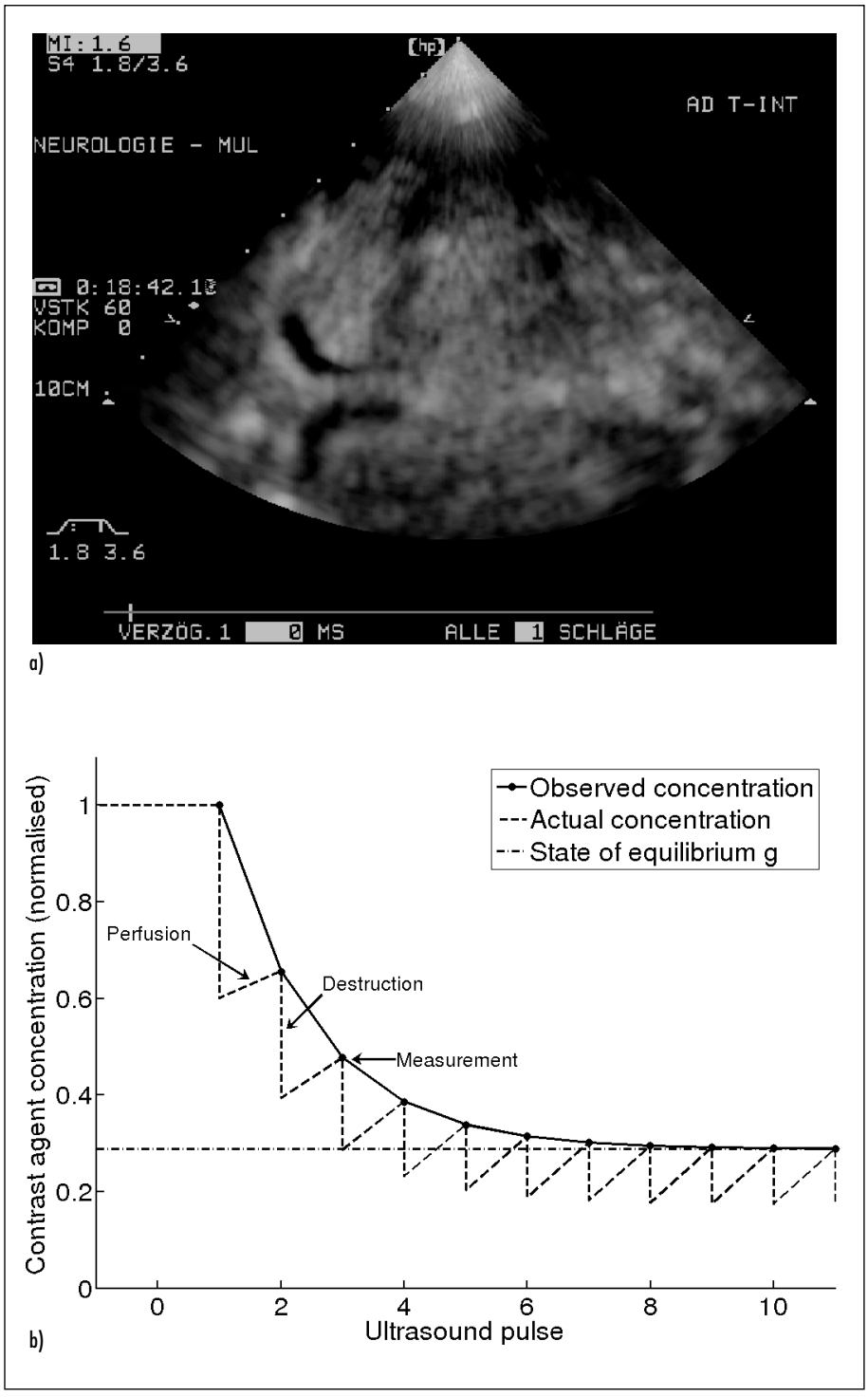


Fig. 3 Visualization of the DHI image acquisition procedure. a) Exemplary image of a DHI sequence (high contrast agent level). b) Actual and observed contrast agent concentration

faster than in a person with perfusion deficits. These acquisition speeds have empirically been proven to cover all possible perfusion conditions. After approximately ten pulses, a state of equilibrium is reached, in which an US pulse destroys as much contrast agent as is flowing into the image plane during one interpulse interval. This process is illustrated in Figure 3b. The basis for this graphical visualization is a mathematical model describing inflow, outflow and destruction of contrast agent for every time step and volume unit of the imaging area [11] (see Eq. 1 in Fig. 2).

Here, n is the number of ultrasound pulses, $c(n)$ the UCA concentration in the n-th step, Δt the time between two pulses, d the destruction coefficient ($0 \leq d \leq 1$) and p the perfusion coefficient. To calculate the concentration in the n-th step directly, the following closed form exists:

$$c(n) = c(1) \cdot \left(x^{n-1} + y \cdot \frac{x^{n-1} - 1}{x - 1} \right), \qquad (2)$$

with

$$x = d \cdot e^{-p \cdot \Delta t}$$

$$y = 1 - e^{-p \cdot \Delta t} .$$

Currently, this model is fitted with least squares methods onto the image data of the ultrasound sequence. This way the perfusion coefficient p is determined that is assumed to correlate best to the perfusion. The depth-dependent destruction coefficient d is determined the same way [13].

To reach our goal to calculate p directly, the aforementioned model is further developed. The state of equilibrium between inflow, outflow and destruction that is eventually reached, results in a constant intensity value in the ultrasound images. This value can mathematically be interpreted as the limit of the underlying model (with $n \rightarrow \infty$)(see Eq. 3 in Fig. 4).

This derivation shows the dependency of the limit g on the initial concentration $c(1)$, the perfusion coefficient p as well as on the destruction coefficient d. Hence, to calculate p, it is necessary to determine $c(1)$, d, and g first.

The initial concentration $c(1)$ is given by the first frame of the DHI sequence. For the calculation of d, the assumption is made that microbubble destruction only appears immediately after an US pulse. In the following interval until the next pulse only flow effects are then relevant. Thus, if the interpulse interval is chosen sufficiently short,

d can be estimated as the coefficient of two sequential concentration (i.e. intensity) values. To determine d, the DHI sequence with the highest frame rate is chosen (6.67 Hz). From this sequence the first two frames are taken for the calculation since the contrast agent level is still close to the saturation level, which means that flow effects are relatively small while the absolute destruction value is largest (see Eq. 4 in Fig. 4).

The limit g is calculated as temporal mean of the last three frames. This resembles a temporal low pass filter to reduce noise present in these images with low SNR. Having generated the limit g, the perfusion coefficient p can be calculated after conversion of Equation 3:

$$p = \frac{1}{\Delta t} \cdot \ln\left(\frac{g \cdot d - c(1)}{g - c(1)}\right). \qquad (5)$$

When all parameters are determined, the values are normalized and presented as color-coded images. Image pixels having a limit value of $g > \alpha \cdot c(1)$ (with α arbitrary, usually 1) are marked as invalid since the model assumptions do not apply in this region. The limit g has to be lower than the initial concentration, otherwise the UCA kinetics model is violated. A lot of regions are usually marked invalid however, since they are not supplied with enough blood or the perfusion is too low to be relevant.

Further parameters extracted from the time-intensity curve were the maximum amplitude as well as the half-life time of the contrast agent. These were also normalized and displayed as color-coded images. All calculations are done pixel-wise to allow pixel-based as well as region-based semi-quantitative analysis.

4. Results

Figure 5 shows sample parameter images of the perfusion coefficient p (Fig. 5a) and the destruction coefficient d (Fig. 5b). The brighter the intensity in the p image, the higher the perfusion. Invalid pixels are colored in gray. The high amount of invalid pixels in the lower part of the image is due to decreasing imaging quality with increasing depth. But this is not fatal as most of this area already belongs to the opposite hemisphere and is better imaged from the opposite side. In the image (Fig. 5b), a higher intensity corresponds to a lower destruction, i.e. the intensity corresponds to the fraction of contrast agent left after destruction. Here, invalid pixels are colored in black.

For comparison, Figure 5c shows a perfusion-weighted MR image of the same patient. It displays the time to peak (TTP) of the MRI contrast agent bolus. The brighter areas represent higher TTP values, i.e. the bright area close to the top is a perfusion deficit.

It is clear to see in Figure 5a that the parameter image of also displays a malperfused area close to the top. This is where the patient's ischemia was located. Parameter images of healthy persons do not show such large dark areas close to the top.

Depending on the number of frames acquired and parameters selected for fitting the DHI model to the data (especially the number of iterations), this process can take a long time, since every image pixel is fitted seperately. The time needed for parameter calculation with the newly developed model is much shorter, since it requires only a small number of calculations for each pixel. The accuracy of the parameters determined by the fitting process is retained, if not even improved by the new calculation method.

$$g = \lim_{n\to\infty} c(n) \overset{(2)}{=} \lim_{n\to\infty} c(1)\cdot x^{n-1} + \lim_{n\to\infty} c(1)\cdot y \cdot \frac{x^{n-1}-1}{x-1} \qquad (3)$$

$$\overset{p>0}{=} c(1)\cdot \lim_{n\to\infty} y\cdot\frac{x^{n-1}-1}{x-1} = c(1)\cdot\frac{-y}{x-1} = \frac{c(1)\cdot e^{-p\cdot\Delta t} - c(1)}{d\cdot e^{-p\cdot\Delta t}-1}.$$

$$\lim_{\Delta t\to 0}\frac{c(2)}{c(1)} \overset{(2)}{=} \frac{1}{c(1)}\lim_{\Delta t\to 0}\left[c(1)\cdot d\cdot \overbrace{e^{-p\cdot\Delta t}}^{\to 1} + c(1)\cdot\overbrace{\left(1-e^{-p\cdot\Delta t}\right)}^{\to 0}\right] = d. \qquad (4)$$

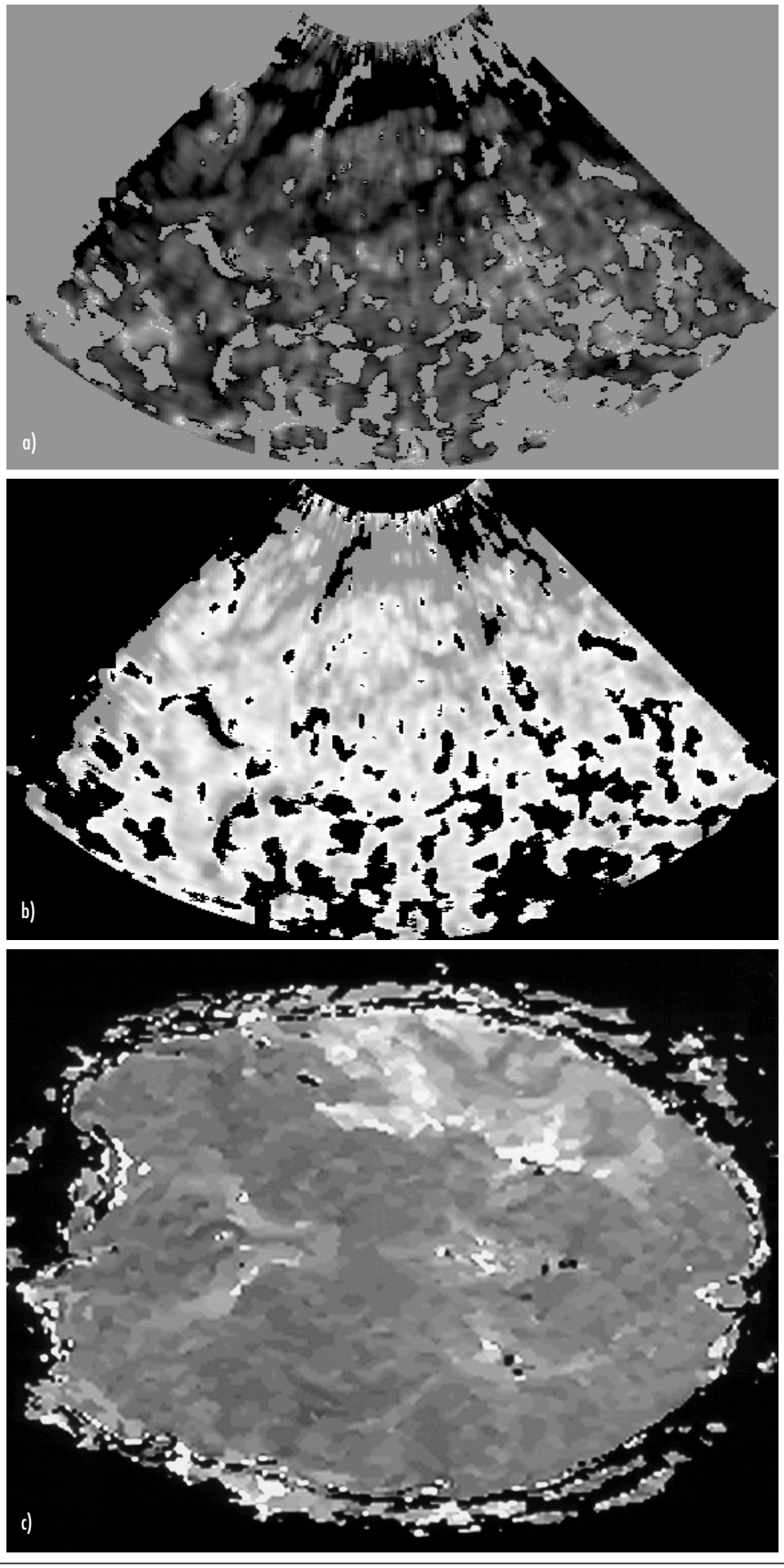
Fig. 4 Limit construction of the mathematical model (3). Estimation of d from the first two image sequence frames (4)

5. Discussion and Conclusions

Compared to currently used diagnostic procedures our presented method features fast and inexpensive diagnostics of cerebral perfusion by means of ultrasound image sequences. An examination can be performed directly at the patient's bedside under minimal strain for the patient. Especially noteworthy is the short examination time of the DHI method compared to other harmonic imaging methods like bolus or replenishment harmonic imaging. Besides further stress reduction for the patient it helps the examiner in providing stable insonation conditions and thus makes it the most promising method among its competitors [6, 8, 12].

From the presented results, it can be strongly presumed that our further development of the underlying mathematical model has improved the DHI method and allows a more exact calculation of the perfusion coefficient p. The depth-oriented estimation of the destruction coefficient d also increases the method's accuracy since the depth-dependency of p is reduced.

A shortcoming of our method is the determination of perfusion deficit regions which is currently done manually by clinical experts. Although the physicians do not know the findings of other diagnostic modalities they often see the patient (inevitably when the physician is also the examiner)



who sometimes already shows stroke symptoms which biases the decision on the parameter images. Furthermore, some experts tend to mark larger regions as perfusion deficits while others tend to restrict the region of interest on a smaller area. A solution to this problem would be an automatic or at least standardized system that by objectively marking perfusion deficits would remove the examiner-dependency. Ideally, this system would combine the information from all parameters to make a final statement about possible perfusion deficit regions. Since our method works pixel-wise, an extension towards region-based evaluation is possible. Further emphasis should also be put towards examining invalid pixels. These are marked invalid because the limit g is larger than the initial concentration $c(1)$ (by factor α). Pixels with strong perfusion defects, i.e. almost no perfusion, could also fulfill this criteria due to (speckle) noise present in the ultrasound images. Hence, some of the invalid pixels could also be perfusion deficits.

To summarize, our method is very promising but should be considered work in progress. The results are preliminary and should be validated by a clinical trial. Furthermore, some methodical extensions have been identified. Once this is done, the ultrasound-based diminution harmonic imaging method provides a fast and inexpensive alternative among different modalities for microcirculation evaluation. Because of the general approach it is not restricted to cerebral microcirculation but can be applied to every organ that is reachable by ultrasound.

Fig. 5 Sample parameter images of the perfusion and destruction coefficients. The brighter the intensity, the stronger the perfusion and the weaker the destruction respectively. The values are normalized and color-coded to be best interpretable for the adjudging physician. c) shows a MR image of the same patient with the perfusion deficit visible as the brighter area. a) Perfusion coefficient p, invalid pixels gray. b) Destruction coefficient d, invalid pixels black. c) Perfusion-weighted MR image of the same patient

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