Update on ultrasound brain perfusion imaging

Günter Seidel* 

Department of Neurology, Asklepios Klinik Hamburg Nord — Heidberg, Tangstedter Landstrasse 400, D-22417 Hamburg, Germany

Summary Several studies have demonstrated the value of ultrasound perfusion imaging to visualize the area of perfusion deficit in patients with acute ischemic stroke. Triggered high mechanical index (MI) imaging, which uses contrast microbubble destruction to analyze bolus contrast kinetics in the brain parenchyma, was used in these studies. Recently high sensitive, low MI imaging was introduced. With this new technology real-time bolus kinetics as well as refill kinetics could be analyzed without triggering. In the early phase of ischemic stroke, ultrasound perfusion imaging is useful in detecting the area of perfusion deficit and to assess outcome prognosis of the patient. This bedside technology is available for use in the stroke unit when patients with acute ischemic stroke undergo a color-coded duplex work-up to evaluate their vascular status.

Technical background

Several studies using trigger high mechanical index (MI) techniques for visualization of cerebral perfusion after ultrasound contrast agent (UCA) injection have been published in the last 13 years [1–6]. The studies were mostly performed with triggered harmonic gray scale imaging techniques (conventional, power modulation or pulse-inversion) analyzing the bolus kinetics in healthy subjects to find out the best way for the detection of UCA in the cerebral microcirculation. Recently low mechanical index gray scale imaging was introduced. With this new real-time technology bolus kinetics as well as refill kinetics could be analyzed. Refill kinetics is based on the reappearance of echo contrast in tissue after complete microbubble destruction using a high MI pulse. After destruction of the contrast agent within the scanning plane new microbubbles enter the volume with a certain velocity, thus allowing calculation of regional cerebral blood flow (Fig. 1). Refill kinetics to measure regional cerebral blood flow was first studied in dogs after craniectomy [7]. Recent technological advances in ultrasound equipment with improved sensitivity for detection of microbubbles in the cerebral microcirculation through the acoustic bone window in humans now enable real-time ultrasound perfusion imaging [8,9]. This new real-time refill technology has several advantages over the triggered high MI techniques. First refill kinetics could be recorded and analyzed within seconds (Fig. 2); therefore, several insonation planes could be evaluated with one contrast bolus injection. Second software tools like microvascular imaging (display of the...
amount of contrast signals over time [8]) help in visualization and documentation of perfusion deficits. On the other hand there are some disadvantages like the limited maximal insonation depth and the high rate of insonation artifacts.

As of yet, it is not evident which method is superior for the analysis of brain perfusion, because studies with a direct comparison are missing.

Figure 2  Microvascular imaging: captured contrast signals over 8s after destruction pulse using low MI real time contrast imaging (iU22 ultrasound system) in a 41-year-old female patient suffering from middle and anterior cerebral artery infarction 11.5 h after symptom onset. We used 2.4 ml SonoVueTM as a bolus. MRI scan (DWI, below) was performed 20min after the ultrasound perfusion study. Notice the insonation plane within the yellow margins. The area of diffusion disturbance in the MRI (white area) showed no contrast signal in the ultrasound perfusion study (dark area).

The commercially available ultrasound contrast agents LevovistTM (Schering), OptisonTM (Amersham Health), and SonoVueTM (Bracco) proved to have contrast enhancing properties in human brain perfusion imaging. No severe adverse events were documented in numerous volunteer studies published on brain perfusion analysis using these contrast agents including more than 200 subjects.

Various curve parameters have been described for the analysis of the different contrast kinetics (bolus and refill). To date (12/2011), it is not evident which kinetics or which parameter is the most valuable for the analysis of brain perfusion in healthy subjects. Theoretically, time-dependent parameters like time to peak intensity (bolus kinetics) or the \( \beta \)-value (refill kinetics) should be more useful than amplitude-dependent parameters, because the latter depend also on insonation depth. Parametric images of certain properties of the time–intensity curves have been generated, which facilitate the evaluation of regional brain perfusion (Fig. 3) [6].

Several studies were reported on ultrasound perfusion imaging in healthy volunteers using perfusion weighted MRI as reference for ultrasound perfusion imaging (Contrast Burst and Time Variance Imaging as well as high MI harmonic imaging) [5,10]. In these studies the time to peak intensity and in one study [5] the area under the time–intensity curve of ultrasound perfusion imaging showed a good correlation to the time to peak intensity as measured in perfusion weighted MRI.

Stroke studies

In most clinical studies on ischemic stroke patients contrast bolus kinetics was analyzed using different high MI harmonic imaging modalities (harmonic imaging, power modulation, and pulse inversion imaging). LevovistTM, OptisonTM, and SonoVueTM were used as contrast agents [12–16]. With new, more sensitive multi-pulse ultrasound technologies it is possible to analyze brain perfusion not only in the ipsilateral but also in the contralateral hemisphere within one investigation improving the geometry of the insonation plane and overcoming near-field artifacts [16]. When using this approach, additional artifacts (calcification of pineal gland
Figure 3  Ultrasound perfusion study using parametric imaging (high-MI imaging, 2.4 ml SonoVue™ bolus kinetics). Ultrasound (SONOS 5500, Philips) was performed 6 h after symptom onset in a 70-year-old male patient suffering from MCA occlusion (M1-segment). Upper row: Time-to-peak image (TTP) and peak signal increase image (PPI—pixelwise peak intensity). Notice the area of delayed contrast arrival in the TTP image (within the red line), which showed in the anterior section a decrease of contrast amplitude in the PPI image. CCT follow-up in the same imaging plane as investigated by ultrasound is shown in the lower row. In the follow-up 180 h after symptom onset a complete middle cerebral artery infarction was displayed, which fits with the initial delay of contrast arrival in the TTP image.


Some more investigations based on contrast bolus kinetics were performed on smaller populations using Xenon-CT [20] and MRI [14] as reference methods. These case reports demonstrate the potential of different contrast-specific modalities for the assessment of pathologic brain perfusion using contrast ultrasound imaging. In a small study analyzing local correlations of ultrasound perfusion parameters of bolus kinetics with the occurrence of a perfusion-diffusion mismatch on Stroke MRI (penumbra) thresholds were calculated. Penumbra could be assumed if the relative time delay exceeded 4 s and the relative signal amplitude exceeded 1/3 [21]. These preliminary data should be verified by a prospective study.

Besides the high potential of ultrasound perfusion imaging as a fast, semi-invasive bedside method to evaluate supratentorial brain perfusion in acute ischemic stroke patients, there are some drawbacks like the insonation artifacts, which occur in most of the patients and the inability to scan the whole brain. Besides these technical limitations there are potential side effects of the new contrast agents, which restrict the employment of these substances in severe cardiac or pulmonary disease.

Disclosure statement
Prof. Seidel is employed by Asklepios Kliniken Hamburg GmbH and is professor of Neurology at the University of
Luebeck, Germany. He has previously received unrestricted educational grants from Schering, Bracco Imaging SpA, Philips Medical Systems, Boehringer Ingelheim, Solvay, Bayer HealthCare, Biogen idec, Desitin, Merck Serono, Meda, MSD, Novartis Neuroscience, Talcetis, UCB, Grunenthal, Lundbeck, Merz, Teva and Sanofi Aventis. He has worked together with Bracco Imaging SpA and Philips Medical Systems in research projects funded by the European Union.

References


