SHORT REPORT

Detection of cerebral perfusion abnormalities in acute stroke using phase inversion harmonic imaging (PIHI): preliminary results

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Phase inversion harmonic imaging (PIHI) with newer contrast agents can display parameters of cerebral perfusion either using the established ipsilateral approach, or the novel bilateral approach in which both hemispheres are assessed in one examination. The aim of this study was to evaluate the potential of PIHI in detecting pathological perfusion in acute stroke, using the bilateral approach. Patients with a hemispheric syndrome presenting within 12 hours after symptom onset were examined with PIHI (SonoVue®; bolus kinetics, fitted model function) using the bilateral approach if possible. Semi-quantitative perfusion related parameters (time to peak intensity (TPI) and peak width (PW)) were evaluated, and results correlated to follow up cerebral computed tomography (CCT) scans. In these four preliminary cases (one ipsilateral, three bilateral), PIHI was able to identify the ischaemic region because the function could not be fitted to the data. In one case, there was a difference between a core region where no perfusion was seen, and a surrounding region where hypoperfusion was detected (prolonged TPI and reduced PW). PIHI was able to predict the localisation and size of the eventual infarction even if no early CCT signs were seen. Furthermore, in one case, a surrounding hypoperfused region was identified, where tissue survived after recanalisation of the initially occluded middle cerebral artery. Using the bilateral approach, two advantages in comparison with the ipsilateral approach were obvious: cortical structures could be evaluated, and only one examination was needed to compare unaffected (ipsilateral) with affected (contralateral) tissue. These results should be confirmed by more cases, and should also be correlated to acute perfusion/diffusion weighted MRI data.

Phase inversion harmonic imaging (PIHI) makes use of the fact that harmonic frequencies generated by the non-linear effects (oscillation or destruction) of applied contrast agents in the microvascular space can be separated very sensitively from the fundamental frequency if two transmit pulses are sent out with “inverted” over and under pressure characteristics¹—that is, with a 180° phase shift of the carrier phase. Up to now, cerebral ultrasound perfusion imaging has generally been performed using an ipsilateral approach, which displays only the ipsilateral hemisphere and parts of the contralateral thalamus.^{2–4} The main drawbacks of this approach are that it is not possible to evaluate the “near field” (the 2–3 cm closest to the probe) comprising the cortical structures, and that the evaluation of both hemispheres necessitates two separate examinations because of the limited examination depth of 10 cm. However, evaluation of the contralateral hemisphere is possible.^{7–8} Furthermore,

pathological perfusion imaging has only been demonstrated with second harmonic imaging without any semi-quantitative, reproducible, and validated indicator of tissue perfusion.^{5–6}

In our method of PIHI, an algorithm fits a function that models a typical bolus curve to the measured time–intensity curve (TIC) in order to confirm the presence of contrast agent and then to extract semi-quantitative parameters such as time to peak intensity (TPI) and peak width (PW), and the qualitative parameter peak intensity (PI) from specific regions of interest (ROI; for details see Eyding *et al*⁸). We describe four preliminary cases that demonstrate the potential of PIHI in detecting perfusion deficits both ipsilaterally and contralaterally to the probe and the potential advantages of the bilateral approach.

METHODS

Design of the study

Patients with a hemispheric syndrome who presented within 12 hours after symptom onset were included in this protocol. Informed consent was obtained from patients before entering them into the study, which was approved by the local ethics committee. Procedures were in accordance with institutional guidelines.

Initial extra- and trans-cranial ultrasound (US) examination followed previously described guidelines.¹⁰ In the PIHI examination, a bilateral approach from the side contralateral to the supposed pathology was performed, using a Siemens Sonoline® Elegra system (field of view 150 mm, 2.5 MHz phased array transducer, PIHI mode, sector angle of 90°, mechanical index >1, focal zone placement 8 cm, transmit frequency 2.0 MHz). If there was no temporal bone window, the established ipsilateral approach was attempted. Using the bolus kinetic approach, examination with a frame rate of 0.5 Hz started once the diencephalic plane was adjusted (compare Eyding *et al*⁸) with injection of 2.5 ml of a sulphurhexafluoride dispersion (SonoVue®; Bracco International BV, Germany) followed by 10 ml of saline in an antecubital vein, and was terminated 90 seconds later. Data were transferred to a PC and evaluated using the previously described model function.⁸ It was hypothesised that once the algorithm was not able to fit the model function to the measured TIC, this region could be regarded as ischaemic. Furthermore, areas close to the ischaemic region were evaluated, where hypoperfusion defined by delayed TPI and shortened PW could possibly be found. In perfusion weighted MRI examinations, first results had

Abbreviations: ASA, acetylsalicylic acid; CCT, cerebral computed tomography; MCA, middle cerebral artery; PCA, posterior cerebral artery; PI, peak intensity; PIHI, phase inversion harmonic imaging; PW, peak width; ROI, region of interest; TIC, time–intensity curve; TPI, time to peak intensity; US, ultrasound

suggested that time to peak abnormalities (a delay of 6–8 s) may be a good predictive factor concerning eventual size of infarction,¹¹ and furthermore, we knew from our own work that less perfused tissue (white matter compared with grey matter) shows a shortened PW.⁸ It is, however, not yet possible to define cutoff values for both parameters for US perfusion analysis owing to a lack of data.

Case reports

Patient 1

A male patient aged 75 years presented 7 hours after acute onset of a left sided severe hemiparesis (NIHSS 12). Initial cerebral computed tomography (CCT) exhibited no signs of acute pathology. Initial US examination revealed stenosis of the right middle cerebral artery (MCA). There was no adequate temporal bone window on the left side, thus we

Figure 1 (A–D) CCT scans and peak intensity parameter images of PIHI examinations with time–intensity curves (TIC) for displayed regions of interest (ROI; white squares on the colour scans). CCT scans were shifted to correspond to the ipsilateral and contralateral areas of PIHI examination. In the PIHI parameter images (colour), a white star marks the midline structure (third ventricle). Black arrows mark a wedge like shadowing artefact that is known to occur in these scans. White arrows mark apparently pathological areas in posterior middle/posterior artery (MCA/PCA) regions. TICs are equally scaled in each patient. (A) Ipsilateral PIHI examination with follow up CCT (50 hours). PIHI shows an area of pathological perfusion (area outlined in black). Parameter extraction from the ROI within the infarcted tissue is shown by the left white square; the algorithm could not fit a function to the TIC, but a typical function could be fitted to unaffected ipsilateral thalamic structures (right white square). Note that cortical structures close to the probe could not be evaluated, even though there is an older infarction on CCT. (B) Bilateral PIHI with MCA infarction in follow up CCT (24 hours). Note that in the infarcted area (area outlined in black with parameter extraction of ROIs shown by the two lower white squares) no bolus curve could be fitted to the measured data, whereas in the unaffected thalamic structures (upper white square) a normal bolus curve was found. (C) Bilateral PIHI with haemorrhagic transformation in follow up CCT (36 hours). Note that in the infarcted area (area outlined in black with parameter extraction of ROIs shown by the two lower white squares), PIHI examination could not detect perfusion, whereas in the unaffected thalamic structures (upper white square) a normal bolus curve could be fitted to the data, indicating tissue perfusion. (D) Bilateral PIHI with follow up CCT (13 days). Note that the area of eventual infarction did not match the initial pathological perfusion as seen on the PIHI parameter image (area outlined in black) and that two ROIs within this area displayed different results: the middle white square where no function (bolus curve) could be fitted to the data, and the lower white square where a function could be fitted, with marked delay of TPI and shortened PW compared with unaffected grey matter areas (see text). The latter region may correspond to tissue still salvageable at the time of PIHI examination, as clinical presentation improved after thrombolytic therapy in this patient. Upper white square is the ROI in healthy thalamic structures.

performed an ipsilateral PIHI examination an hour later, which demonstrated an area of pathological perfusion in the frontal parts of the MCA area without involvement of thalamic structures and with distinct lateral demarcation (shown by an absence of PI as displayed in fig 1A). The algorithm was not able to fit the function to the extracted data in the region marked by the black outline in fig 1A, indicating ischaemia, whereas in thalamic regions, a reasonable curve could be fitted. Follow up CCT 50 hours later (NIHSS 11 treatment: acetylsalicylic acid; ASA) confirmed a demarcated infarction in the areas detected with initial PIHI.

Patient 2

An 83 year old woman presented 8 hours after onset of an acute left sided hemiparesis (NIHSS 11). Initial CCT showed obscuration in the right caudate nucleus. Initial US examination revealed occlusion of right distal ICA and proximal MCA, which were not reperfused within the first 3 days. Bilateral PIHI examination 2 hours after CCT revealed an area of pathological perfusion (no increase of PI as illustrated in fig 1B) in the right MCA region (indicated by the outlined area in fig 1B). Within this region, the function could not be fitted, whereas in surrounding thalamic structures a normal function could be derived. Follow up CCT after 24 hours (NIHSS 11, treatment: iv ASA) revealed an infarcted area corresponding to initial PIHI examination (fig 1B).

Patient 3

A female patient, 70 years old, presented 8 hours after onset of a severe hemiparesis of the right side with mixed aphasia (NIHSS 12). CCT showed an obscuration of basal ganglia of the left side and sulcal effacement. Initial US examination revealed proximal MCA occlusion of the left side, which was not reperfused within the first 2 days. Bilateral PIHI examination, an hour after CCT, yielded normal parameter values in the unaffected right hemisphere and in thalamic structures on the affected side. In the region marked with the black outline in fig 1C, no typical curve could be extracted from the data. Owing to atrial fibrillation, heparin was given intravenously. Follow up CCT after 36 hours (NIHSS 14) discovered a haemorrhage with mass effect of the infarcted area corresponding to the area initially presenting with signs of pathological perfusion in PIHI examination (fig 1C).

Patient 4

An 81 year old male patient presented 2 hours after onset of a severe acute right sided hemispheric syndrome (NIHSS 13). CCT displayed a hyperdense middle cerebral artery sign and obscuration of anterior parts of the lentiform nucleus of the left side. Initial US examination suggested distal left sided MCA occlusion. Bilateral PIHI examination was performed before systemic therapy with rt-PA. A perfusion abnormality was seen in the region indicated by the black outline in fig 1D. Here, TPI was delayed (33.0 s) and PW was shortened (7.0 s) compared with a mean (range) of 22.0 s (21.1–23.1 s) and 11.4 s (10.2–13.1 s) in the other uninvolved grey matter regions such as thalamic structures (upper white square, fig 1D). In a sub-region, the algorithm could not detect perfusion (middle white square, fig 1D; TIC displayed as infarction); laterally to this, a delayed TPI and shortened PW could be shown (lower white square, fig 1D; 35.6 s/6.6 s, TIC displayed as cortical tissue). MCA had been reperfused in the 24 hours follow up US examination. Follow up CCT 13 days later (NIHSS 7) displayed an infarcted area (fig 1D). Some parts of the cortical structures did not decay. In accordance with the initial PIHI examination, these regions corresponded to the region described as cortical tissue in fig 1D, where only a delay of TPI and a shortening of PW could be recognised compared with healthy grey matter regions.

DISCUSSION

In all cases, initial PIHI examination could predict the eventual localisation and size of the infarction. Using the ipsilateral approach (patient 1), spatial resolution is better, because the depth of examination is limited to 10 cm, and identification of morphological structures is easy; however, evaluation of the “near field” is not possible. Consequently, information about cortical structures is not obtained with this examination, as illustrated by all of our cases. All patients presented pathology involving cortical structures. Using the bilateral approach through the unaffected temporal bone window, this pathology could be demonstrated (patients 2–4). With this approach, it also became possible to compare regions of both sides in one examination. In patient 4, the evaluation of unaffected grey matter regions of both hemispheres gave a mean TPI of 22.0 s and PW of 11.4 s. In the core of the final infarction, the algorithm could not fit the model function to the measured TIC, indicating the absence of perfusion. In the region that eventually survived (possibly due to collateralisation) the algorithm found a delayed TPI of 35.6 s and reduced PW of 6.6 s. The question remains if this responds to the penumbra of the ischaemic area, as suggested by other groups.⁹ Even though it is not yet possible to clarify this question, this differentiation promises to be a major improvement over the present perfusion analysis without a fitted model function, where no such differentiation can be shown.⁶ More patients and a comparison with perfusion/diffusion weighted MRI with follow up are needed to learn which parameter changes first and whether cutoff scores for normal variation, salvageable tissue, and primarily irreversible ischaemic tissue can be described.

One limitation of the bilateral approach becomes obvious when viewing the parameter images in fig 1. There is a region of missing contrast enhancement in the posterior parts of the field of view (white arrows in fig 1B–D). This region is located within a well known wedge like shadowing artefact (black arrows in fig 1A–D) that occurs in all ultrasonic perfusion imaging modalities, which has not yet been satisfactorily explained. Furthermore, anatomically this area probably consists of both MCA and PCA regions. Even though typical TICs can be derived from these regions, we would recommend that evaluation of perfusion related parameters should be limited to the MCA area until it is shown that reliable data can be derived from these regions.

To our knowledge, this is the first study employing PIHI with the ipsilateral and bilateral approach in acute stroke. This combination promises to identify localisation and size of acute brain infarction and possibly to differentiate areas of different pathology in acute ischaemia. The fact that only one investigation is needed to assess information about both hemispheres with the bilateral approach reduces examination time significantly.

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