to criteria derived from completed randomized trials. A quality register gives the means to identify rare side effects and to monitor the uptake of a new treatment. In theory, it may be of interest to compare findings in a quality register to findings in earlier trials (historical controls). However, such comparisons have very limited scientific value because the lack of randomization will inevitably introduce bias.5 By necessity there will be a long delay between the trials and the analysis of the quality register. Hence, there is no way of adjusting for case mix or for the many immeasurable changes in treatment that may have occurred over time. For example, today a much larger proportion of patients are already on antiplatelet treatment, and refinement of diagnostic tools may influence the type of patients who are entered in the register. An example of the effect of changes over time is the difference between the placebo-treated patients entered in ECASS I2,3 and ECASS II2,3 where, in the latter trial, the course of disease was much better despite similar inclusion criteria.

Despite the positive effect of thrombolysis shown in the systematic reviews, there are prevailing, definite, and important uncertainties (Table). We believe that these questions can only be answered validly and reliably by large RCTs, and not by observational studies and quality registers.

Veronica Murray, MD, PhD
Division of Medicine
Danderyd Hospital
Karolinska Institutet
Stockholm, Sweden

Eivind Berge, MD, PhD
Department of Medicine
Ullevål University Hospital
Oslo, Norway

Peter Sandercock
Professor, Department of Clinical Neurosciences
Edinburgh University, Western General Hospital
Edinburgh, United Kingdom

Bo Norrving
Professor, Department of Neurology
Land University Hospital
Lund, Sweden

Per Wester
Department of Medicine
University Hospital of Northern Sweden
Umeå, Sweden

Andreas Terent, MD, PhD
Department of Medical Sciences
Uppsala University Hospital
Uppsala, Sweden


Quantitative Ultrasonographic Evaluation of Cerebral Perfusion in Acute Stroke Is Possible

To the Editor:

With much delight we have read in the issues 2, 5, and 7 of Stroke1–3 that ultrasonic perfusion imaging of the brain achieves more and more recognition in the community. In these very well conducted studies, the authors have proven the ability of the method of predicting localization and size of final infarction in the acute state. Even though of different technical background, there are now 5 studies with a considerable cohort of about 120 patients altogether suffering from acute stroke examined by ultrasonic perfusion imaging.1,2,3,4,5 With parametric imaging, the diagnosis becomes quick and easy,1 clinical outcome can be forecasted,2 and a microbubble destructive approach decreases time of examination considerably.3 However, two main drawbacks of the different methods remain: only 1 hemisphere is examined so that quantitative comparison with healthy referential tissue is only possible with a second (contralateral) examination; the evaluation of the microbubble kinetic is performed in a way that quantification is only possible in a “perfusion yes/no” manner.

Since visualization of perfusion deficits has obviously improved so much since the early days, we propose that future studies should gain for a semiquantitative bilateral examination the aim of differentiating ischemia and hypoperfusion in the acute state. A bilateral examination (having both hemispheres in the field of view) using the bolus kinetic yields stable parameters throughout the field of view, where regions of one hemisphere can be compared with the same regions of the other hemisphere.6 Interindividual ranges of the resulting parameters are considerable due to various cardiovascular reasons. However, intraindividual ranges of eg, the time-to-peak intensity (TPI) are very small.7 In 20 healthy volunteers, the mean quartile deviation of TPI values in individual 14 regions throughout both hemispheres was 0.68 seconds, and there was no case in which any TPI exceeded the individual mean for more than 2 seconds.

Initial TPI parametric image with a visible TPI delay in the reddish and white encircled area and no detectable perfusion kinetic in the pinkish and black encircled area (white arrow: frontal ventricular horns; black star: 3rd ventricle, midline; black arrow: posterior ventricular horn; dotted lines: near field and side field artifacts); follow up CCT 5 days after clinical successful thrombolysis (NIHSS from 13 to 5) with an infarction in the area corresponding to initial black encircled area in ultrasonic perfusion imaging; Phase Inversion Harmonic Imaging, bolus kinetic, Sonovue 2.5 mL, fitted model function, field of view 150 mm.
Our conclusion is that TPI might be a reliable semiquanti-
tative marker of cerebral perfusion, since its variation is so
small. In accordance with other technical approaches,8 we
hypothesize that a delay of TPI forecasts hypopерfused and
potentially still salvageable tissue, whereas regions without
detectable perfusion kinetic forecasts ischemia, ie, the core of
the infarction. As a cut-off for a significant TPI delay we
determined the double of the maximum variation in the
healthy cohort, ie, 4 seconds. These considerations were
supported by preliminary cases of acute stroke patients
examined by the same protocol,9 in one of which we could
demonstrate a region without a perfusion kinetic (where
eventually infarction occurred) and a region with a delayed
perfusion kinetic, where eventually tissue stayed viable after
clinically successful thrombolytic therapy (Figure).

Thus, we propose that for future ultrasonic perfusion imaging
protocols using the bolus-kinetic, the bilateral approach should be
applied with settings optimized for a quantitative evaluation of the
kinetic parameters in order to differentiate “penumbra” and core of
infarction.

Jens Eyding, MD
Christos Krogias, MD
Saskia Meves, MD
Horst Przuntek, MD
Department of Neurology
St. Joseph Hospital
Ruhr-University Bochum, Germany

Thomas Postert, MD
Department of Neurology
St. Vincenz-Krankenhaus
Paderborn, Germany

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abnormalities in acute stroke using phase inversion harmonic imaging (PIH):

Response:
Eyding et al state that there is a growing body of evidence that
ultrasound perfusion imaging with the bolus or the diminution
approach expands the diagnostic potential of ultrasound from
the cerebral macrocirculation to the microcirculation. As discussed,
there are several limitations of these new approaches like the
limited insonation depth, insonation artifacts and, of course, the
fact that brain perfusion (cerebral blood flow or cerebral blood
volume) cannot be assessed quantitatively.

The statement that “quantitative comparison with healthy
referential tissue” is not possible with the conventional technique
is not entirely correct because at 10 cm insonation depth
ipsilateral and contralateral thalamus can be reliably investigated
and, being supplied by the posterior circulation, serve as refer-
ence regions in middle cerebral artery (MCA) ischemia. The
other statement that “quantification is only possible in a perfu-
sion yes/no manner” does not match the results of three studies cited,1,2,3 which showed very reliably that a delay (>3 seconds to
the surrounding tissue) and a decrease (>50% of normalized
signal amplitude) of the contrast signal predict the area of
infarction besides a missing signal.

In case of a MCA ischemia, the “bilateral approach” with an
insonation depth of 15 cm covers the arterial territories of both
sides.4 The advantage of this approach would be a direct
comparison of both MCA territories after one bolus injection.
Yet, because of the known depth dependence of the ultrasound
signal, a comparison of the signal amplitude (the strongest
predictor of infarction) remains impossible. Only time dependent
parameters of the time-intensity curve could be compared,
provided that the extracranial vascular status is normal. This is
likely the case in healthy volunteers, but not in elderly ischemic
stroke patient. Another limitation of the “bilateral approach” is
the increase of insonation artifacts which occur because of
calculated structures in the midline of the brain like the pineal
gland and the choroid plexus as shown in the figure given by
Eyding et al (notice the small window of proper insonation and
the shadowing artifacts at the left lower margin of the image).
Because of these theoretical limitations and the limited number
of published cases (n=4) the “bilateral approach”4 may be a
promising new feature which should be further investigated but,
by now, cannot be considered state of the art for ultrasound
perfusion imaging. This approach should be evaluated with new
ultrasound technologies like power modulation or contrast pulse
sequencing which increase the sensitivity for contrast agent
detection in deeper regions of the brain, compared with conven-
tional harmonic imaging or phase inversion harmonic imaging.

The conclusion of the letter that, by using parameters of the
time-intensity curve after ultrasound contrast agent bolus injec-
tion, the detection of ischemic core and penumbra could be
predicted seems an over-interpretation of a study with four
clinical cases authored by Eyding et al.4

Günter Seidel, MD
Karsten Meyer-Wiethe, MD
Department of Neurology
University of Schleswig-Holstein
Lübeck, Germany

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Ultrasound perfusion imaging in acute middle cerebral artery infarction


abnormalities in acute stroke using phase inversion harmonic imaging (PIH):

The Often-Neglected Vertebral Artery
To the Editor:
The SSYLVIA trial’s results clearly add to the nascent body of
literature evaluating vertebral artery stenting.1 Even in the
absence of ‘gold standard’ surgical procedures such as endarter-
ectomy for the treatment for vertebral artery disease, the recog-

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