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. 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 I and ECASS II, where, in the latter trial, the course of disease was much better despite similar inclusion criteria.5

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.

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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 Stroke1,2,3 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,3 clinical outcome can be forecasted,2 and a microbubble destructive approach decreases time of examination considerably. 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 with 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.4 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 CTT 5 days after clinical successful thrombolysis (NIHSS from 13 to 9) 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 semiquantitative marker of cerebral perfusion, since its variation is so small. In accordance with other technical approaches, we hypothesize that a delay of TPI forecasts hypoperfusion 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, 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.

### Response:

Eyding et al state that there is a growing body of evidence that ultrasonic 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 reference regions in middle cerebral artery (MCA) ischemia. The other statement that “quantification is only possible in a perfusion yes/no manner” does not match the results of three studies cited, 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 beside a missing signal.

In case of an MCA ischemia, the “bilateral approach” with an insonation depth of 15 cm covers the arterial territories of both sides. 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 calcified 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 the “bilateral approach” 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 conventional 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 injection, 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.
Quantitative Ultrasonographic Evaluation of Cerebral Perfusion in Acute Stroke Is Possible
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