even from a qualitative assessment of cortical perfusion. There is no need to replace the standard methods; on the contrary, insonation of the large vessels and spectroscopic investigation of cortical perfusion will be complementary. Ideally it will be combined with the high spatial resolution of perfusion weighted MR imaging performed at larger intervals.

**Functional Stimulation**

There is no reason why the large number of functional stimulation studies performed with near infrared spectroscopy should not be directly transferred to a bedside assessment in patients suffering from neurovascular or neurodegenerative diseases. The major problem here rather is the reluctance of clinical practice to focus on functional rather than structural brain imaging. The traditional exception is electroencephalography (EEG) and the assessment of visually, somatosensory, and acoustically evoked potentials (VEP/SSEP/AEP), which have been used for decades. The slow introduction into clinical practice is by no means specific to optical methods; Functional magnetic resonance imaging (fMRI) and positron emission tomography share a similar problem. Because spatial resolution of optical topography will most probably not reach that of fMRI techniques, primary cortical areas (motor and visual) may serve as indicators of a normal or disturbed neurovascular coupling. Much like evoked potentials, this will help link evidence of structural lesions (as seen in routine imaging approaches) to the clinical examination (which by no means is objective but still the gold standard when therapeutic success is evaluated).

**Neurovascular Coupling**

It has been suggested that a number of neurological diseases interfere with the physiologically tight coupling between neuronal and vascular response.6,7 This can be assessed with low-cost, undemanding set-up and at the bedside when EEG-techniques and optical topography are combined.8 Again, the major obstacle is the fact that clinical studies require a longer and potentially very tedious approach, and as yet few representative studies have been published. This again is a limitation, which necessitates adequate funding rather than shedding doubt of the versatility of optical methods as such.

Our impression is that the state of the art methodological approaches of noninvasive optical imaging techniques presently do allow for studies relevant to clinical practice. The major shortcoming is the reluctance to challenge the method in larger studies, with representative numbers of patients included. At the same time, the research into physiological mechanisms of functional activation has been established. In cooperation with physicists and a practice-oriented engineering effort, cortical functional activation is bound to reach much higher topographical and depth resolution in the very near future.

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The Need to Recognize the Difference Between a Quality Register and a Randomized Controlled Trial

To the Editor:

In the pursuit of new data on thrombolysis with recombinant tissue plasminogen activator (rtPA) in patients with acute ischemic stroke, clarity is needed on what information can be obtained from different methods; ie, observational methods, like a quality register, and experimental methods, like a randomized controlled trial (RCT).

Apart from treatment in a stroke unit that benefits all stroke patients, thrombolytic therapy for acute ischemic stroke is at present the only medical treatment available, and is by far the most promising.1 To date 2955 patients have been randomized into trials with intravenous rtPA.2 Systematic reviews of the trials showed that, despite the hazards of intracranial hemorrhage and early death, there is scope for benefit from thrombolysis up to 6 hours.2,3 Based on the first positive thrombolysis trials in 1995,2,3 treatment with rtPA has been licensed in USA and Canada for use within 3 hours of stroke onset for a selected group of patients. Since 2002 there is a provisional license in the European Union for treatment within 3 hours in even more selected patients, 80 years of age or younger.4 The licensing will be renewed after 3 years if (1) a further randomized trial (ECASS 3; in patients at 3 to 4 hours after onset) is performed by the manufacturer; and (2) safety (as recorded in the quality register SITS-MOST) is satisfactory among patients treated within the license. These conditions highlight the need to appreciate that an RCT must have adequate statistical power to give reliable answers5 and whether a treatment register can give valid answers to safety issues.6 The difference between a quality register and an RCT seems important to elucidate. Quality registers are based on registration of data on patients treated in ordinary clinical practice according

Main Uncertainties for Intravenous Thrombolysis With rtPA up to 6 Hours in Patients With Acute Ischemic Stroke

1. Estimations of effect in the individual trials
2. Effect of rtPA on death from all causes
3. Effect on functional outcome, heterogeneity, and imprecise estimates
4. Effect in older people
5. Safety in older people
6. Clinical selection criteria
7. CT features reliably predicting response to thrombolysis
8. Potentially maximal, or individual, time window between onset of stroke and treatment
9. Patients already on antithrombotic therapy at stroke onset
10. Implication of the type of ischemic stroke
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 occurred over time. For example, today a much larger proportion of patients are already on antiplatelet treatment, and refinement 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.

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 Stroke 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. With parametric imaging, the diagnosis becomes quick and easy, but clinical outcome can be forecasted, 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. 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. 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 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.
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