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,8 we hypothesize that a delay of TPI forecasts hypoperfused 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.

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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 insolation depth, insolation 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 insolation 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,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 insolation 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 insolation 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 (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 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.4

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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 endarterectomy for the treatment for vertebral artery disease, the recog-
nition of vertebral artery disease has not progressed like its carotid artery counterpart. Rocha-Singh insightfully attributed this to the nonspecific symptoms associated with posterior cerebral ischemia, difficulties imaging proximal vertebral artery stenosis with ultrasound, and the absence of a standard surgical therapy for vertebral artery disease.2

The relationship between vertebral artery insufficiency and posterior circulation ischemia is now becoming clear. In a review over 400 cases evaluated for posterior circulation stroke or transient ischemic attack, Wityk et al determined that 20% of patients with posterior ischemia had occlusive disease in the proximal vertebral artery (V1 segment); in 9% of patients a lesion in the V1 segment was the only defined cause of stroke.3 Similarly, the role of vertebral artery disease and other neurological pathologies is now better understood (ie, the relationship between isolated vertigo without other neurological symptoms and vertebral insufficiency). Welsh et al found in a review of patients suffering from long-standing vertigo that 52% of patients demonstrated abnormal configurations or diminished vertebrobasilar flow, 76% of these having the pathology of the vertebral artery.4

Magnetic resonance technology has been used successfully to noninvasively identify vertebral artery disease.5 Similarly, vertebral artery stenting has demonstrated successful procedural outcomes in case series and in this before-mentioned trial.1,2 Should there be an increased awareness of the relationship between posterior ischemia and vertebral artery disease, the absence of an acceptable surgical treatment, and the potential vertebral artery stent-supported angioplasty may offer. Ultimately, large-scale randomized trials are necessary to accurately determine the future role of stent-supported angioplasty in the long-term management of vertebral artery disease.

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**Carotid Artery Stenting With and Without Cerebral Protection**

*To the Editor:*

We note with interest the finding from the EVA-3S Trial of carotid stenting that the rate of stroke within 30 days of treatment appeared to be higher in patients who were stented without the use of protection device.1 However, we are surprised that the Safety Committee recommended that all patients should be treated with a protection device, although the difference between treatment with and without protection did not reach statistical significance. Moreover, the report does not state whether there were any differences between the two groups in the indications for stenting, the nature of the stenosis, or difficulty of access. Any of these could have led to the decision to stent without protection and at the same time increase the risk of procedural stroke. In the EVA-3S report, age was significantly different between patients treated with and without cerebral protection (66.0 versus 72.7 years, P = 0.013).1 Age has been reported to be a risk factor for carotid stenting2 and this could explain the worse outcome in patients treated without a protection device. There was also a threefold increase in the proportion of patients treated by predilation in the protected group, which might contribute to their better outcome. Only strokes at the time of the procedure would be expected to be prevented by protection devices. In the EVA-3S, only 2 strokes occurred on the day of the procedure without protection, compared with 3 strokes in those treated with cerebral protection. Such a difference could well have arisen by chance. For all these reasons, we believe the recommendation of the EVA-3S Steering Committee was premature. On the other hand, we accept that ethical and research governance considerations may make it difficult to continue a treatment that appears to have a greater risk before the difference reaches statistical significance.

No protection devices were used in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) where the rate of stroke within 30 days of treatment was 10% in patients treated with angioplasty or stenting.3 In the EVA-3S report, the same measure in patients treated with cerebral protection was 10.3%.1 There is therefore no clear evidence that protection reduces the rate of stroke. Thus, we are not convinced that the evidence presented mandates the use of protection devices. Moreover, there are those who argue that protection devices are unnecessary and may increase the risks in some patients.

The protocol for the International Carotid Stenting Study (ICSS or CAVATAS 2) states that when a patient is having stent placement “a cerebral protection system should be used whenever the operator thinks one can be safely deployed.”4 The editorial accompanying the EVA-3S report recommends that ICSS should do an interim analysis of protected versus unprotected patients.1 The ICSS investigators have subsequently presented confidential data on the outcome of stenting with and without protection devices in ICSS to the Data Monitoring Committee. The Data Monitoring Committee acknowledged the need to keep monitoring this issue in future annual reports, but did not recommend any protocol modifications. At present the ICSS investigators have complete data returns for 78 completed stenting procedures of which 66 (85%) were carried out with some form of cerebral protection. The sample of unprotected procedures is very small1,2 and this fact alone can bias any safety data. To take a theoretical example, in an existing series of 10 procedures with 1 stroke, a single stroke in the next procedure would almost double the apparent rate of complications.

In conclusion, we believe that the data from the EVA-3S Trial should be treated very cautiously because of the small numbers of patients analyzed. We do not believe that the current protocols of the other carotid stenting trials need modification.

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3. The CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Trans-
The Often-Neglected Vertebral Artery
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