Contrast Ultrasound Techniques in the Detection and Quantification of Patent Foramen Ovale: Myth Versus Reality—A Clarification

To the Editor:

We were pleased to see that our research was cited in a Letter to the Editor in Stroke, particularly in the context of paradoxical embolization and cryptogenic stroke.1 However, in both the Letter to the Editor and the Response to the Letter to the Editor, the results of our study were cited inaccurately.1,2 As such, we feel obliged to clarify some very important results from our study, so that misconceptions can be prevented.

Specifically, in the Letter to the Editor, Dr. Schuchlenz stated that: “…there is evidence that physiological arteriovenous intrapulmonary shunts do exist in most healthy humans.”3 While these arteriovenous intrapulmonary shunts appear to exist in most humans, it is important to point out they are not open when the subjects are resting quietly in the seated position, and were only recruited with exercise.3 Stickland et al report similar findings and also found that some (2 of 8) subjects recruit arteriovenous intrapulmonary shunts in the supine position.4 Thus, it appears that these intrapulmonary shunts are not recruited in the normal resting upright human, but are primarily inducible during hyperdynamic conditions, such as exercise.

In the Response to the Letter to the Editor by Anzola et al, the authors wrote that: “Physiological intrapulmonary shunts are activated after prolonged strenuous exercise...”3 First, a graded exercise protocol was used to examine intrapulmonary shunting, and shunting occurred at submaximal exercise intensities in 90% of subjects tested to date.3,4,5 As well, we found that some subjects demonstrated exercise-induced intrapulmonary shunting after only 3 minutes of exercise at workloads less than 100 watts. Finally, arteriovenous intrapulmonary shunts were not present in any subject 3 minutes following exercise. Accordingly, our results do not support the statement that prolonged strenuous exercise is required to induce intrapulmonary shunting in normal healthy human subjects, nor that these shunts remain open following exercise.

Without question, the opening of these arteriovenous intrapulmonary shunts has the potential to contribute to the gas exchange dysfunction during exercise.4 Furthermore, and possibly more importantly, these dynamic anatomic shunts may provide inducible conduits for the passage of embolic particles that may play a role in paradoxical embolization and thus, cryptogenic stroke and embolic heart disease. This is highlighted by the fact that cryptogenic stroke is more common among young people6–9 and is associated with exertion.10,11

Acknowledgments

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Risk of Thrombolysis-Associated Intracerebral Hemorrhage: The Need to Compare Apples With Apples

To the Editor:

We read with interest the dose-escalation safety study of tenecteplase (TNK) within 3 hours of stroke.1 Both this study and the pilot study of desmoteplase within 3 to 9 hours2 clearly demonstrate that higher doses of thrombolytic agents have increased rates of symptomatic intracerebral hemorrhage (sICH). Moreover, both studies revisit a hypothesis considered, but never tested with recombinant tissue plasminogen activator (rtPA), that lower thrombolytic doses may provide comparable efficacy with less sICH risk.

Lower rtPA doses (<0.9 mg/kg) were never adequately tested for their risk/benefit profiles in stroke patients. The initial rtPA pilot trial, in 1987, used 0.35 (n = 6), 0.60 (n = 12), 0.85 (n = 30), 0.95 (n = 25), and 1.08 mg/kg (n = 1) within 90 minutes after stroke.3 Notably similar to the desmoteplase and TNK pilot studies, no sICHS were seen until the 0.95 mg/kg tier. A second pilot study at 90 to 180 minutes after stroke, using 0.6 (n = 8), 0.85(n = 6), and 0.95 mg/kg (n = 6) rtPA, had 1 sICH in the 2
highest tiers. Subsequently, a small placebo-controlled trial of 0.85 mg/kg had no sICHs in the treated group (n=14). To maximize the potential benefit of rtPA, while accounting for a likely increased sICH risk, 0.9 mg/kg was chosen for the NINDS trial. There was no evidence of different efficacy at lower doses in these pilot trials. A proposed trial to compare 0.6 mg/kg with 0.9 mg/kg of rtPA in the mid 1990s was not approved for funding by the NINDS.

Cardiac studies clearly indicate that TNK is unlikely to be safer than rtPA, regarding sICH, when equipotent doses in humans are used. Specifically, the ASSENT-2 trial found 0.5 mg/kg TNK had almost identical clinical efficacy and sICH rates in acute myocardial infarction, compared with ∼1.1 mg/kg rtPA. Thus, 0.9 mg/kg rtPA may be bio-equivalent to 0.4 mg/kg TNK. Lower TNK doses would need to be compared against lower rtPA doses. Also, the baseline National Institutes of Health Stroke Scale score, a critical predictor of sICH, was lower in the TNK pilot stroke study than the NINDS rtPA stroke trial.

Moreover, the cardiac literature has not found any third-generation thrombolytic more effective than rtPA, suggesting that third-generation thrombolytics at bio-equivalent doses may have similar safety and efficacy profiles.

The TNK investigators assert the bio-equivalence of 0.1 mg/kg TNK to 0.9 mg/kg rtPA based on a rabbit model. However, models of young animals using human proteins are likely to give very different estimates of dosing safety and efficacy. This is illustrated by the fact that 0.1 mg/kg TNK showed no clinical efficacy in an ischemic stroke rabbit model.

We do not know if the current rtPA dose is the ideal balance of risk and benefit. The upcoming well-designed TNK trial is an excellent opportunity to examine whether a lower thrombolytic dose can offer similar efficacy with less risk of sICH.

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Response:

We thank Khatri et al for their interest in our article. We re-emphasize the preliminary nature of our observations with tenecteplase in acute ischemic stroke. With such preliminary data, there are many potential interpretations, and the one posed by Khatri et al is certainly one of them. However, whereas the cardiac experience has taught us much about thrombolytics, in general, and tenecteplase and alteplase, in particular, we would urge circumspection in directly extrapolating the cardiac experience to the ischemic stroke arena. The streptokinase experience is a cautionary tale in that regard. We also agree with Khatri et al that it is possibly hazardous to extrapolate dosing information directly from animal models to humans.

We continue to regard our preliminary tenecteplase experience in human stroke as encouraging. Future planned studies of tenecteplase in stroke will test a range of doses of tenecteplase compared with a concurrent control group treated with standard dose alteplase. These studies are carefully designed to guard against a reduction in efficacy in an effort to achieve an improvement in safety. Unfortunately, these studies will not answer the question of whether lower doses of alteplase might accomplish the same goals.

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For the TNK in Stroke Investigators

Microembolization During Carotid Endarterectomy and Diffusion Weighted Imaging

To the Editor:

We read with interest the recent article in Stroke by Wolf et al3 describing the relationship between transcranial detected microembolic signals (MES) and serial diffusion-weighted imaging (DWI) of the brain. The authors have studied 5 phases of the carotid endarterectomy (CEA) (dissection, clamping, shunting, de-clamping and wound closure). The authors observe microembolic signals detected during the dissection phase and clamping phase of CEA correlated significantly with the evolution of new DWI lesions and brain infarction on T1-weighted MRI. This study highlights the importance of good surgical technique especially in the dissection phase of the operation. However, MES detected in the dissection phase may be unavoidable because it also reflects the unstable carotid plaque,3 which even on minimal dissection may cause particulate embolization. It is of no surprise that no associations were found between DWI lesions and MES detected in de-clamping phase as microemboli in this phase of the operation tend to be gaseous in nature and therefore does not cause brain ischemia. In contrast, MES detected in the shunt phase tend to be a mix of particulate and gaseous microemboli and a nonsignificant correlation with DWI lesions in this study is consistent with previous studies.3
The wound closure phase of the operation tends to be short and gives us a glimpse of MES activity in the postoperative (or after restoration of blood flow) phase. MES detected in the postoperative and the recovery room period is particulate in nature and arises secondary to platelet aggregation and occasionally leads to thrombus formation on the denuded endarterectomized endothelium.\(^4\) Postoperative carotid thrombosis complicates 2% to 3% of CEAs and tends to occur within 4 to 6 hours of the operation. Patients who progress to this condition and subsequently brain ischemia have a 1- to 2-hour postoperative period of increased embolization.\(^5\) Approximately 12% of cases undergoing CEA are complicated by this postoperative MES and significant MES in this period is associated with ischemic changes on FLAIR brain images.\(^6,7\) Additionally, Payne et al\(^8\) have described that postoperative thromboembolism was significantly effected by a combination of antiplatelet agents acting on different pathways of coagulation.

Because Wolf et al\(^9\) only assessed MES in the short wound closure phase, the lack of association of MES with DWI lesions therefore does not allow to assess the contribution of the postoperative period to DWI evolution. It certainly would be of interest to elucidate the relationship of DWI lesion development and MES detected in longer postoperative periods, and to assess the efficacy of preoperative and postoperative pharmaceutical agents such as anticoagulants and dextran 40, respectively, in preventing subclinical and clinical brain ischemia detected by DWI.

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Response:
We appreciate the interest of Altaf et al in our work.\(^4\) As mentioned in our discussion, we confirm the statement of Altaf et al that microembolization during dissection is a function of plaque stability and good surgical technique with early clamping.

Because no reliable measurement of plaque stability exists up to now, other parameters like recent neurological symptoms were used as a kind of surrogate markers for stenosis activity and a significant correlation to the incidence of postoperative cerebral ischemia was found.\(^5\)

We agree with the statement that microembolic signals (MES) during shunting are a mix of gaseous and particulate microemboli and that MES during de-clamping seem to be harmless gaseous emboli.

New advances in MES detection using multifrequency Doppler sonography may allow to discriminate the nature of microemboli during the different phases of the carotid endarterectomy in the future.\(^1\)

We are aware of the results that evaluated microembolization in the early postoperative period.\(^2,3\)

Screening only during the procedure and not the early postoperative period may underestimate the relationship between diffusion-weighted imaging lesions and MES. We decided not to analyze the early postoperative period because of the limited ability to differentiate real MES from artifacts during this phase.

Transcranial Doppler as a monitor procedure is only reliable when an exact positioning of the probes can be realized and maintained.

Even during CEA, when the patient is in optimal position and under general anesthesia, this can be really challenging. During the early postoperative period when the patient recovers from anesthesia, it is difficult to get reliable MES data because continuous monitoring is often not possible because of movements of the patient.

If these difficulties can be resolved, the elucidation of the efficacy of postoperative pharmaceutical agents to prevent cerebral ischemia might be of great clinical value.

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Cognitive Function After Surgical Repair of Unruptured Intracranial Aneurysms

To the Editor:
Otawara et al. found no cognitive impairment or cerebral blood flow reduction in 42 patients submitted to surgical clipping of unruptured cerebral aneurysms. Two further patients of the series—supposed to be consecutive—were excluded from cognitive evaluation because of brain injuries caused by surgery, with Rankin Scale decrease >1. In other words, they had 0% mortality, 4.5% morbidity, and no cognitive impairment in the remaining 95.5%. These data favorably compare with 2.7% mortality and 9.9% morbidity resulting from the ISUIA study, as usually happens, for a series of reasons for single-center series in comparison with multicenter trials. The authors conclude that unruptured aneurysm surgery does not affect cognitive function, provided that the patient does not have brain damage sustained from the surgery. I wonder about the meaning of this statement for 2 reasons: first, it does not make sense to exclude patients with brain damage sustained from surgery; second, even uncomplicated surgery always requires a series of invasive maneuvers on the brain, making brain damage unavoidable. Clinical symptoms may appear or not, depending on the extent of the damage, on the region of the brain involved, and on the sensitivity of the applied tests. Neuropsychological and brain flow measurements are simply not sensitive enough to reveal subtle damages of the brain function.

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Response:
We appreciate the interest of Dr Bergui and colleagues in our article on safe surgery for unruptured intracranial aneurysms in patients without restrictions in postoperative lifestyle. Dr Bergui focuses our attention on the exclusion of two patients with surgical complications. We certainly agree with them that clinical symptoms may or may not appear, depending on the extent of the brain damage, the region of the brain involved, and the sensitivity of the tests applied. However, we maintain our conclusions for the following reasons.

The cognitive tests we applied can detect general intellectual function, visuospatial construction, and memory function. Although this test battery is not perfect, it can detect cognitive dysfunction if trans-Sylvian surgery affected the frontal and/or temporal lobes of the patient.

I do not agree that even uncomplicated surgery always requires invasive maneuvers in the brain, resulting in unavoidable brain damage. Surgery for unruptured intracranial aneurysm should not cause brain damage, although brain retraction is essential for this procedure. Our surgical procedure involved wide opening of the Sylvian fissure, intermittent use of self-retractors, and careful preservation of the cerebral veins. We believe that these surgical manipulations will preserve the cerebral blood flow and cognitive functions. Previous literature also supports the safety of unruptured aneurysm surgery based on cognitive tests and positron emission tomography.

We believe that surgery for unruptured intracranial aneurysm is safe if we exclude patients with restrictions in postoperative lifestyle. However, we must continue to improve our surgical results.

We thank Dr Bergui and colleagues for their insightful comments.

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Endothelial Progenitor Cells in Cerebrovascular Disease

To the Editor:
In their interesting article, Ghani and colleagues reported a reduction in endothelial progenitor cells (EPCs) in patients with cerebrovascular disease, when compared with healthy control subjects. However, the authors did not mention a recent article by Taguchi et al reporting that CD34+ cells and CD133+ cells, as an EPC-enriched population, provided a marker of cerebrovascular function, thus failing to consider their work as the first correlation between EPCs and cerebrovascular disease.

The study by Ghani et al took vantage from the large sample of subjects enrolled. However, they did not specify how many patients were included in the acute stroke, stable stroke and control group. Moreover, patient characteristics are not reported and it is not stated whether controls were matched for age, sex and concurrent risk factors, diseases, and medications. Given that cardiovascular and cerebrovascular diseases cluster together, the difference may be related to the overall cardiovascular risk rather than to the presence of stroke.

A growing amount of data suggests that EPCs are relevant to vascular homeostasis. Thus, the finding of reduced EPCs in the presence of altered cerebrovascular function is not surprising. What is unexpected is that the authors could not report higher EPCs in patients with acute stroke than in patients with stable stroke. Many articles have shown that tissue ischemia is a strong stimulus for mobilization of EPCs from bone marrow to peripheral blood. In their work, Taguchi et al demonstrated that circulating EPCs increased after the onset of stroke and peaked after 7 days. This inconsistency may be related to the different method used in the 2 works to identify EPCs. Indeed, it should be noted that in the work by Ghani and colleagues, EPCs are defined as CD31+/aWF+ cells in 7-day cultures of peripheral blood mononuclear cells. This technique identifies cells with a mature endothelial phenotype that may have an origin other than EPCs.

Currently, to identify the true EPC population, cultures should be prolonged for at least 15 days, allowing selection and outgrowth of
cells with actual progenitor properties. Alternatively, EPCs may be identified and counted by flow cytometry of fresh peripheral blood, looking for the parallel expression of both surface markers of immaturity (such as CD34 of CD133) and endothelial markers (such as VEGFR-2 or CD31). In the end, Ghani and colleagues may have specified whether the strokes were because of in situ intracranial thrombosis or to arterial atheroembolism. In the latter case, correlations between EPC levels and carotid atherosclerosis could be of some interest.

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Response

We thank Dr. Fadini and colleagues for their interest in our paper. There is a growing understanding that endothelial progenitor cells (EPCs) are involved in repairing damaged endothelium by forming a cellular patch at the site of injury or by serving as a cellular reservoir to replace damaged endothelium.1,2,3,4 The method that we followed in our studies is based on the isolation, culture and colony formation of EPCs. The method emphasizes the ability of EPCs to make colonies and the measurement of their numbers representing an indirect measure of their ability to repair endothelial damage. In contrast, the method described by Taguchi et al5 in their studies measures the level of circulating CD34+ and other cells by flow cytometry without culturing or determining their ability to make colonies. The 2 methods may measure the same cells but comparative work is lacking. Therefore, from a methodological perspective, we believe our work represents the first detailed study on the correlation of EPCs with cerebrovascular disease. We studied the progenitor cells in a large population of patients with acute and stable cerebrovascular disease (transient ischemic attacks and completed stroke).

The methodology for identification of endothelial cells is evolving and will hopefully improve as we better understand the behavior of EPCs. Phenotypic characterization of EPCs remains controversial.6 We identified EPCs by measuring CD31, vWF and CD133 markers. We are currently also evaluating the use of flow cytometry to better identify such cells. With regards to the culturing of EPCs, we included a preplating step in order to avoid the possibility of contaminating the cultures with mature endothelial cells. An initial preplating of cells was performed for 48 hours using human fibronectin-coated plates, and nonadherent cells were collected which were finally cultured for 7 days. Cells isolated in this manner are, in fact, EPCs which exhibit many endothelial characteristics as previously demonstrated by other investigators.7,8

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Who Will Care for Our Hospitalized Patients?

To the Editor:

Much debate has recently focused on who is best qualified to care for stroke patients.1,2 Arguments have been made for the certification of a neurology subspecialist—the “strokologist.”3 Care for the stroke patient is complicated now and only becoming more so. However, in an era when subspecialty coverage for emergency and inpatient care is scarce, the more appropriate question seems not who should care for these patients but rather, who will shoulder this responsibility. Neurologists have been...
accused of being “asleep at the wheel” in stroke prevention—the same may be true for stroke treatment.4

Even specialties that have traditionally provided after-hours emergency coverage are demanding payment or refusing to provide this service altogether. Now that stroke treatment involves emergent evaluation and treatment, there has been a significant change in what is expected. Low remuneration for a late night neurologic evaluation is not a great motivator, and neurologists are not used to canceling clinic appointments for emergencies. Neurologists perform few procedures and other sources of funding are few and far between. Cardiologists, nephrologists and gastroenterologists have developed rotations within their groups for 1 physician to perform the inpatient work for a period of time. The inpatient volumes for these specialties tend to be fairly high and are associated with well-reimbursed procedures.

As a result, others have stepped in to care for stroke patients. Hospitalists have come to the assistance of primary care physicians and have helped alleviate some of the workload for specialists. Internal medicine training is obviously an inadequate substitute for a neurology residency. In fact, on a national survey of hospitalists’ perceptions of their residency training needs, many felt that more training in neurology was needed.5 However, hospitalists are frequently called on to provide most, if not all, of the care of the stroke patient. In “straightforward” cases, perhaps this is appropriate. Hospitalists clearly have a different skill set than most neurologists—serving as experts in inpatient care and pathway development.

Neurologists then, are faced with a decision. General neurologists have not been perceived as interested, as a whole, in aggressive stroke care. Strokologists may help to fill some of this gap. Hospitalists, however, are likely to care for the majority of stroke patients in the United States—with or without neurology assistance. Hopefully neurologists will act to either help directly in caring for stroke patients, in the form of “Neurohospitalists,” or help to educate non-neurohospitalists in so doing. Hospitalists are looking for partners in caring for stroke patients—will neurologists be asleep at the wheel?

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Endothelial Progenitor Cells in Cerebrovascular Disease
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