Re: Randomized Controlled Study of Stroke Unit Versus Stroke Team Care in Different Stroke Subtypes

To the Editor:

We have read with interest the article by Evans et al., which presents a post hoc analysis of a previously published randomized controlled trial comparing a stroke unit, a stroke team, and domiciliary care. The demonstration that the stroke team could not provide sufficient stroke management can be considered the most important conclusion of this trial. This finding confirms our previously reported study comparing a stroke unit with a stroke team within the same neurological department, demonstrating that a stroke unit is better than the stroke team in terms of reduction of mean hospital stay, systemic and neurological complications, and hospital costs, in addition to an improvement of functional state at discharge with an increase in the number of independent patients and a decrease in long-term hospitalization. Besides, we also demonstrated that cerebral hemorrhage and territorial infarction patients (both atherosclerotic and cardioembolic stroke subtypes) get more benefit from a neurological stroke unit care than lacunar or transient ischemic attack patients, a finding that could help us to optimize the stroke unit results, taking into account the limited stroke unit resources, and the preliminary data of this analysis were communicated in the 10th European Stroke Conference that took place in Lisbon, Portugal, in May 2001. In this report Evans et al., in a post hoc analysis of a randomized trial, found no differences in outcome in the stroke unit versus the stroke team in terms of mortality, mortality or institutionalization, level of neurological recovery, or dependence, confirming our observations about lacunar stroke.

In our study, the data of 285 lacunar stroke patients admitted in a neurological department during 3 consecutive years, 78 attended by a stroke team (first year) and 206 in a stroke unit (second and third years), were analyzed. There were no differences in vascular risk factors or comorbidity between the 2 samples. Stroke unit care was associated with a decrease in both systemic and neurological complications, 54.7% and 84.4% reductions, respectively, as well as a decrease of 61.8% in the percentage of lacunar stroke patients with any complication. Only 1 patient in the stroke unit (0.49%) and no patients in the stroke team group died. No patient required institutionalization. There was a trend to an improvement in functional status (modified Rankin Scale).

Moreover, we found that lacunar stroke patients in the stroke unit had a significantly lower length of stay than in the stroke team group (7.17 versus 12.83 days; P=0.000 Bonferroni post hoc test). However, in the report by Evans et al, lacunar stroke patients had a longer length of stay in the stroke unit (27.4 versus 18.5 days; P<0.01). The shorter length of stay in our study (whether stroke team or stroke unit) is easily explained by the different stroke unit design as compared with the design by Evans et al. Our stroke unit is an acute neurological stroke unit, attending patients within the first 48 hours from stroke onset, and does not include the rehabilitation ward stay. In addition, although early physiotherapy and rehabilitation are important features of our stroke unit, when a stroke patient has been clinically stabilized, the diagnostic procedures have been finalized, and the patient has a modified Rankin Scale <2, the rehabilitation treatment can continue in an appropriate poststroke rehabilitation ward. On the other hand, Evans et al’s stroke unit is a combined acute and rehabilitation stroke unit settled in a geriatric medicine ward, with no limit of time in unit, although with a program of discharge, usually to final placement (home or institution).

It has been suggested that an early start of physical therapy and stabilization of blood pressure are probably the most significant aspects of care at the stroke units, in addition to a reduction in the number of patients with a temperature >38°C in the first 5 days, that contribute to the positive results of stroke units as compared with a general medicine ward. A possible explanation for the lesser benefit of a stroke unit in lacunar stroke is that in this stroke subtype, located in subcortical white matter, the prognosis is probably not as sensitive to changes in blood pressure, temperature, or glucose blood levels than in large vessel infarctions with cortical damage.

In our opinion, all stroke patients should be admitted to an acute stroke unit. However, the data of Evans et al’s study as well as ours, showing that large vessels infarctions get more benefit from a stroke unit than lacunar strokes, are useful to improve stroke unit resources, taking into account that there are not always enough available beds.

Finally, although we agree with Hacke that it is difficult to understand the design of this randomized study on stroke units, considering the amount of evidence about their benefit from previous randomized studies at the time of the beginning of this study when stroke unit care was a level of evidence I, grade A recommendation, it is true that an adequately powered prospective, randomized, controlled trial in patients with lacunar syndromes to compare the benefits and cost-effectiveness of stroke unit care with organized care in other settings could have no ethical problems, because of the lack of evidence in this stroke subtype both on outcome and in costs. Although this study observed a longer length of stay in the stroke unit group, in our study we found benefits in lacunar stroke in terms of reduction of length of stay and consequently a decrease in hospital costs, and better clinical outcome. However, a randomized trial would clarify the efficacy of the stroke unit in lacunar stroke patients.

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Response

Thank you for forwarding the letter by Fuentes and Diez Tejedor. Their studies support our findings on the differences between stroke unit and stroke team care, both in the acute and the postacute phases of stroke management. Their experience, similar to ours, is that patients with large-vessel stroke benefit more than those with lacunar stroke, probably because of a lower probability of death and fewer rehabilitation needs.

The difference in the length of stay between the study by Diez Tejedor and Fuentes and our study are of interest and are probably due to differences between healthcare systems in Spain and the United Kingdom. As highlighted in the letter, the unit in their study was an acute neurological unit rather than the combined acute and rehabilitation stroke unit described in our study. It is likely that the process of comprehensive multidisciplinary patient assessment by medical, nursing, therapy, and social service professionals and assessment of home environment, social support, and caregiver needs prior to discharge were responsible for longer stays. The practice of discharging patients from the stroke unit only when community support and continuing rehabilitation systems were in place may also have contributed. Many of these processes were not undertaken in patients on the general wards managed by the stroke team.

We agree with Fuentes and Diez Tejedor that all suspected stroke patients should be admitted to a specialist stroke unit for comprehensive assessments, investigations, and acute management, regardless of the type of stroke. It is probable that patients with lacunar infarcts may not be disadvantaged by postacute management in other settings, as long as they receive specialist stroke care. However, only mortality and basic functional abilities were assessed in our study; it is possible that patients managed on the stroke unit may have had better outcome if assessments for higher functional abilities and quality of life were included. The evidence presented in our article is not robust enough to change practice because of the post hoc nature of the analysis, small sample size, and limited outcome measurement. However, it does suggest that an adequately powered definitive trial on this aspect of stroke care may be justified.

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Re: Randomized Controlled Study of Stroke Unit Versus Stroke Team Care in Different Stroke Subtypes

To the Editor:

In a recent article in Stroke, Evans et al examined the effect of stroke unit care by subtype and concluded that stroke units improve the outcome in patients with large-vessel infarcts but not in those with small-vessel disease. However, this conclusion appears to be based on a misinterpretation of the analysis and lack of essential details in the presentation of results.

The authors conclude that in small-vessel occlusions, “mortality and institutionalization … were influenced by age and stroke severity but not by management strategy.” This is based on an odds ratio for stroke unit care of 4.9 (95% CI 9.0 to 25.0) and probability value of 0.06. In contrast, for large-vessel infarcts, the conclusion is “the odds for dying or being institutionalized were also increased nearly 3-fold in stroke-team patients.” This is based on an odds ratio for stroke unit care of 2.8 (95% CI 1.3 to 6.2) and probability value of 0.01. The actual effect size for stroke unit care at 12-month follow-up is larger for patients with small-vessel disease, and yet because the probability value is larger than the arbitrary cut-off of 0.05, the authors conclude that the effect of stroke unit care in this subgroup is not clinically important.

The authors’ conclusion depends heavily on the arbitrary distinction between “significant” and “nonsignificant” results (based on whether $P<0.05$ or $P>0.05$). As recommended recently, the description of differences based on “statistical significance” is not acceptable—estimates (with 95% CIs) and exact probability values should be given for all comparisons. This would include all those in Table 3 in their article, where the odds ratio and 95% CI are omitted and the probability value merely described as “NS.”

The correct analysis is to use the complete data set (including both subtypes) to examine the strength of the evidence for interaction, ie, to examine whether the effect of stroke unit really differs between the 2 subgroups. The evidence for this interaction should be presented in the article, and only if this evidence is strong should claims be made about different effects of stroke unit care for those with large- and small-vessel disease.

Given the clinical importance of the conclusion that stroke unit care offers no “significant” advantages for those with small-vessel disease, it is vital that these conclusions are based on good scientific practice. It is also crucial that adequate information be provided in every published article for the reader to be able to judge the clinical significance of the results and to assess the validity of the conclusions drawn.

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Response

The letter by Tilling and Wolfe raises some important issues on the subgroup analysis and interpretation of data as well as on the delicate balance between presenting details of statistical analysis versus presenting a clear clinical message. We believe that relevant details have been presented in the results and the interpretation of data are accurate and appropriate.

We agree that statistical significance should not be assessed on the grounds of a probability value alone, and more so in the case of a borderline probability value like that of 0.06. The subgroup analyses (small-vessel and large-vessel) presented in this article followed appropriate tests of interactions between strategy and vessel subtype in the complete data set as recommended. These interactions were significant, with the strength of significance decreasing across time. For example, strategy for the small-vessel group was not significant at 3 months, with no deaths on the stroke unit and only 1 death in stroke team (Fisher’s exact test $P>0.40$). The odds ratios for the strategy (stroke team versus stroke unit) by vessel-subtype interaction were 6.5 at 6 months and above 2.0 at 12 months (95% CI 0.7 to 61; $P=0.10$). (Considering the low power of the test of interaction, the threshold value for its significance is around 10%.) Hence the conclusion that stroke units may have
limited effectiveness in patients with small-vessel disease was based not on isolated subgroup comparisons but on preliminary tests for interaction between strategy and subtype in the whole data set. Such tests should always precede subgroup analysis, as was done in this article.2

The style of writing the article reflects the aim to present relevant data and clear analyses in a familiar and "user friendly" format, which enables readers (mostly stroke practitioners) to judge the clinical significance of results, rather than to overburden them with precise details of all statistical analyses undertaken, many of which would be of little interest to clinicians. Hence, corresponding pair-wise comparisons of data and important comparisons with both CIs and probability values were presented in the article. We disagree with Tilling and Wolfe that enough information has not been given in Table 3 of the article. With the exception of the 12-month mortality, all estimates (with 95% CIs) and precise probability values have been given for all variables that were relevant to the model presented. The odds ratio and CIs for mortality at 12 months were 7.2 (95% CI 0.8 to 60; P=0.06), similar to those for mortality or institutionalization. The term nonsignificant has been used only when the probability approached unity.

We believe it is important that significant clinical messages are clearly presented and do not get lost in a morass of statistical computations, which detract from the main message and are of little interest to most clinicians. Tilling and Wolfe’s letter also appears to imply a concern that the findings of the article may deprive patients of specialist stroke care. They apparently have missed the fact that comparisons were undertaken between a stroke unit and a specialist stroke team, hence both groups were receiving specialist stroke care. This may be one of the reasons for the lack of difference in outcome in patients with small-vessel disease, in whom mortality and need for rehabilitation are limited, as discussed in the article. Furthermore, it is important to recognize the limitations of proven interventions to ensure that they are used appropriately and in the most cost-effective way. No one will argue that stroke unit care in the acute phase reduces mortality and specialist stroke care facilitates recovery.3 However, an unquestioned belief that stroke units may be the only method of providing specialist stroke care in the postacute phase to patients with low probability of death and limited disability may be misplaced and prove detrimental to the development of high-quality and cost-effective services for stroke patients.

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Re: Role of Endothelial Nitric Oxide and Smooth Muscle Potassium Channels in Cerebral Arteriolar Dilation in Response to Acidosis

To the Editor:

The article by Horiuchi et al1 in the March issue of Stroke contains potentially important data implicating both nitric oxide (NO) and the K_{ATP} ion channel in the dilation of rat cerebral parenchymal arterioles produced by acidosis. The authors employ 2 different inhibitors of NO synthase (NOSI) and demonstrate partial impairment of the response. To demonstrate a role for K_{ATP} channels, they demonstrate impairment by glibenclamide, a selective inhibitor of the channel. Unfortunately, the authors fail to cite articles by Kontos and Wei,2,3 which demonstrated that hypercapnic acidosis of rat (same species) pial arterioles was mediated by K_{ATP}.

Like Horiuchi et al, Kontos and Wei also showed that NOSI inhibited the response to acidosis. However, Kontos and Wei also found that the same NOSI had a second, previously unreported action: under their experimental conditions these NOSI also prevented opening of K_{ATP}. Unless Horiuchi et al have tested the NOSI against an opener of K_{ATP} channels (eg, against pinacidil), we cannot say whether NO was really involved in the dilation of the parenchymal arterioles. The authors showed that glibenclamide plus NOSI produced significantly greater inhibition than NOSI alone. This was further evidence for a role of K_{ATP} channels. However, we are not told whether a maximally effective dose of NOSI was used. If it was, then it was warranted to conclude that 2 different mechanisms of impairment were superimposed. But if a maximally effective dose of NOSI was not used, then the possibility exists that both the NOSI and the glibenclamide were acting on K_{ATP}, as shown by Kontos and Wei.

Horiuchi et al demonstrated that endothelial injury impairs the response to acidosis. This implied that some endothelium-derived substance, such as NO, was involved. However, such substances might also affect the resting potential of the vascular smooth muscle, and the function of K channels is known to be highly dependent on resting potential. Thus the effect of endothelial injury in this study does not necessarily mean that NO or any other endothelium-derived material acted as a true mediator of the dilation produced by acidosis.

Until these issues are resolved, it may be that the data of Horiuchi et al, as presented in their article, simply supports a role for K_{ATP} as shown by Kontos and Wei.

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Response

We agree with Dr Rosenblum’s assertion that, if a maximally effective concentration of NOS inhibitor was used, we have to conclude that 2 mechanisms must be involved in the acidosis-induced vessel dilation: (1) a nitric oxide–dependent component and (2) a K_{ATP}-dependent component independent of a possible effect of the NOS inhibitor on K_{ATP}.

We have shown that a number of NOS inhibitors significantly constrict isolated, cannulated, and pressurized rat cerebral penetrating arterioles.1,2 We also demonstrated that an increase of the NOS inhibitor concentration above 100 μmol/L causes vessel dilation and as such a pharmacological effect of the drug.2 The NOS inhibitor–induced constriction is reversed by L-arginine, while the D-arginine as well as D-NAME had no effect.1 This conclusively demonstrates that the NOS inhibitors and concentrations chosen have a significant physiological effect and specificity that are related to the conversion of L-arginine and production of NO by NOS without causing pharmacological side effects.
In the present letter to the editor, the work of Kontos and Wei is cited.3,4 Of the 2 articles, only one5 presents data obtained in the rat model while the majority of results in both articles were obtained in the cat model. However, when studying the results presented, 20 μmol/L LNNA causes either no constriction (control diameter of 48 μm versus 48 μm after L-NNA) or a small dilation (average 2 μm after L-NNA) in rat pial arterioles.4 We find that 10 μmol/L L-NNA significantly constricts our vessel preparation by 24% (23% with 10 μmol/L L-NMMA),3 demonstrating the efficacy and potency of NOS inhibition in our experiments.

KATP inhibition significantly reduced acidosis-induced dilation both after initial NOS inhibition (18%) as well as after KATP inhibition alone (23%).5 We reanalyzed the 2 data sets and did not find them to be different (t test). Thus, we can only conclude that in our preparation, NOS inhibition did not directly affect KATP.

Dr Rosenblum indicates that after air embolism, the loss of endothelium-derived factors such as NO or others may cause smooth muscle depolarization with subsequent potassium channel inactivation. We cannot exclude that air embolus-induced endothelial damage causes smooth muscle depolarization. However, our data already exclude the participation of endothelial factors such as prostaglandins (inhibitable by indomethacin) or EDHF (inhibitable by MS-PP2H) in both resting and acidic conditions.5 Air embolism caused a modest but significant vasoconstriction (6%) in our study.5 Previously, we reported that smooth muscle cells in our preparation have on average a resting membrane potential of 44 mV,6 raising the membrane potential to 31.5 mV. Thus, it is not likely that air embolus-induced membrane depolarization inactivated any potential sensitive potassium channels, but it is likely that an endothelial factor, notably NO, is involved.

We thank Dr Rosenblum for his interest in our article and allowing us to clarify and substantiate our conclusions drawn.5

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# Timeless

To the Editor:

We were pleased to see that Quilliam et al1 elected to use their number needed to harm (NNTH) in case-control studies2 to express the estimates of bleeding risks they obtained from their case-control study in elderly stroke survivors. However, in reporting their NNTHs, they omitted one crucial element, namely time. This is essential to the interpretation of NNTHs: it makes a vast difference whether the NNTH of 467 reported for serious bleed and aspirin refers to an exposure period of 1, 6, or 12 months—or 12 years.

The authors reported their estimate of the unexposed event rate (UER) as event rates per person-year of follow-up: however, this is not sufficient: an NNHT for case-control studies should always be expressed in terms of the duration of exposure in the case-control study at issue, unless the exposure is a 1-time event with lasting effects, such as in the case of vaccination.

Furthermore, the authors do not specify whether their UER estimate was derived from data applying to a 1-year period or whether it was derived by extrapolation or interpolation from data applying to shorter or longer time periods. This is important because making UER estimates based on interpolations or extrapolations assumes that the risk of events in unexposed persons is constant over the chosen time period. This may or may not necessarily be the case, and therefore every interpolation and extrapolation used to estimate a UER should be justified based on substantive knowledge.

Finally, there are some calculation errors in the 95% CIs reported by the authors for their NNTHs (page 2301 of their article): 2 of the CIs (those for aspirin and “combination”) have infinity as a limit. It is unclear to us how the authors arrived at this result, as this can only occur when the odds ratio (OR) is exactly zero, which was not the case, or when the UER is equal to zero, which was also not the case and is a situation that almost never arises. When calculating CIs for NNTHs, it should be kept in mind that a modified version of the NNTH formula is to be used if the lower limit of the CI for the OR is less than 1.6 We recalculate the NNTHs and their CIs. Correct values are as follows (NNTH given first, CI in parentheses; bold type indicates elements that were erroneous or missing in the Quilliam study report):

- NNTH for a any serious bleed, given treatment with: (1) warfarin: 126 (76 to 297) per year; (2) aspirin: 467 (182 to 817) per year; (3) combination: 96 (40-3268) per year.

We hope that other authors will follow suit and use the NNTH for case-control studies. In doing so, however, it is crucial that they pay due attention to congruency between the duration of exposure in the case-control study and the time period over which the incidence was calculated to obtain the UER, lest their results lose their meaning and interpretability.

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2. Bjerré LM, LeLorier J. Expressing the magnitude of adverse effects in case-control studies: “the number of patients needed to be treated for one additional patient to be harmed.” BMJ. 2000;320:503–506.

Response

We thank Bjerré and LeLorier for their helpful letter regarding our presentation of the number needed to treat to harm (NNTH).1 We recognize the apparent controversy in how to estimate the upper boundary of the 95% CI when the interval includes the null value of 1.2,3 As opposed to suggesting the upper bound of the confidence interval is infinity, Bjerré and LeLorier suggest an alternate formula for calculating the upper boundary.2 Yet to our knowledge, this article does not offer either a discussion or a
derivation of this formula to allow the reader a better understanding of the utility of this estimating procedure. Despite this, we appreciate the clarification of the proposed methodology and hope that it will initiate further discussion. Nevertheless, we feel the NNTH we estimated for bleeding among aspirin or combination users remains clinically significant whether the upper boundary was reported as infinite (as we did) or as 817 and 3268, respectively, as estimated by Bjerre and LeLorier.2

We also regret omitting the element of time when interpreting the NNTH, although this information could be obtained from both the methodology and discussion sections of the article. We hypothesized that the exposures of interest would occur approximately 6 months prior to hospitalization for a bleeding event.1 We agree with Bjerre and LeLorier state that this should be reinforced in the interpretation of the measure. We do, however, believe that the assumption of a relatively constant rate of hospitalization for bleeds used in our estimation of the unexposed event rate (UER) hold up in our data and appear to in previous reports, as well.4

Finally, we support the use of any measures, including the NNTH, that may help physicians and other clinicians make difficult decisions when enumerated by large amounts of technical information. As Bjerre and LeLorier state, the odds ratios derived from case-control studies assessing adverse effects “... are not intuitively understandable estimates of risk.”22 We hope that by our example, others can learn to appreciate both the utilities and the intricacies of this methodology and ultimately advance the dissemination of research results to clinicians and other healthcare professionals.

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Re: Does Acupuncture Have Additional Value to Standard Poststroke Motor Rehabilitation?
To the Editor:

The results of Sze et al1 are surprising because they show virtually no placebo effect of acupuncture. This intervention is regularly associated with powerful placebo effects. In fact, the most conclusive interpretation of the earlier studies is that the positive effect of acupuncture was to a large extent due to nonspecific effects of acupuncture.2–3 The finding of a total absence of a placebo response in the study by Sze et al thus contradicts all previous trials. The authors do not address this contradiction, but I think it cries out for an explanation.

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Can Microembolic Signals Identify Unstable Plaques Affecting Symptomatology in Carotid Stenosis?
To the Editor:

We read with interest the article by Liapis et al1 on factors affecting symptomatology in carotid stenosis and agree that factors other than the degree of stenosis are important in determining increased risk of neurological events. Authors observed that ultrasonically echolucent plaques show a trend toward higher frequency of neurological events likely due to an increased lipid content, rendering them more vulnerable to rupture. Nevertheless, ultrasonographic evaluation of plaque morphology may fail to identify unstable plaques showing embolic activity likely due to inflamma-
tory factors2 able to determine from time to time fluctuations of the risk of neurological events. Previous small studies have suggested that asymptomatic microembolic signals (MES) detected by transcranial Doppler (TCD) in middle cerebral arteries may predict symptoms occurrence,3,4 and a large multicenter study was planned to determine whether MES are an independent predictor of neurological events in patients with asymptomatic ≥70% carotid stenosis.5

We evaluated 21 patients (13 males and 8 females, mean age 75.2 years, range 62 to 84 years) with asymptomatic ≥70% carotid stenosis documented by selective angiography according to NASCET criteria. Echocardiography was performed to exclude cardioembolic sources, and antiplatelet treatment (acetylsalicylic acid 100 mg daily in 15 cases and ticlopidine 500 mg daily in 6 cases) was administered. All the patients were submitted to TCD monitoring (DWL MultiDop X TCD7 FRG device) prolonged for 60 minutes to detect MES in middle cerebral arteries. MES were identified according to the criteria of the Ninth International Cerebral Hemodynamic Symposium6 and the recommendations of the International Consensus Group on Microembolus Detection.7 Monitoring was repeated with the same method after 6, 12, 18, and 24 months, and clinical follow-up aimed to identify onset of symptoms (amaurosis fugax, transient ischemic attack, stroke) related to carotid stenosis was performed during such period. Six of 21 (28.6%) patients showed MES in the middle cerebral artery on the same side as carotid stenosis during at least one of the monitoring times, and 5 of these 6 (83.3%) patients became symptomatic (transient ischemic attack in 2 cases and stroke in 3 cases). MES occurrence was intermittent at different monitoring times but always preceded symptoms onset and in 3 cases occurred also during the following monitoring (Table). No change of carotid stenosis degree was assessed by the NASCET criteria. Echocardiography was performed to exclude emboli detected by transcranial Doppler (TCD) were more frequent in the presence of low plaque echolucency. This finding, however, is in contrast to the results of a previous study by Droste et al,8 according to which echolucency of the plaque was not related to the presence or number of MES. Whatever the case may be, factors such as the degree of carotid stenosis, plaque echolucency, and surface morphology should be included in any multivariate analysis aiming to determine the independent prognostic significance of MES in the development of future stroke.

With respect to the time-course of the increased risk of neurologic events, echoluent plaques are associated with a high long-term risk due to the fragility of the lipid-rich plaque. On the contrary, microemboli most probably originate from already ruptured plaques with resultant surface ulceration and luminal thrombus and are related to an increased risk of neurologic events within the following few days or months. In the study of Siebler et al,4 neurologic events occurred within 2 days to 6 months in 4 of the 5 patients who became symptomatic, while in the study of Molloy and Markus psychologic events in previously asymptomatic patients occurred within 3 to 4 months of the positive TCD recording. This fact may represent a major advantage of the method but at the same time it may be a drawback in terms of using TCD as a screening tool in patients with asymptomatic carotid stenosis. Indeed, it seems that very frequent monitoring by TCD is required in order to timely detect plaque destabilization periods. In the series of Orlandi et al, for example, only 1 of the 5 patients, who eventually showed MES in the middle cerebral artery, had a positive TCD recording on his first scan. The appropriate frequency as well as the cost-

### Letters to the Editor


### Response

We thank Orlandi et al for their interest in our study.1 Their comments give us the opportunity to address several issues with regard to the detection of microembolic signals (MES) in patients with asymptomatic internal carotid artery stenosis.

Echoluent plaques and MES may actually be correlated, with echolucency representing the ultrasonographic picture of unstable plaques and MES their result. In support of this theory, Tegos et al2 recently showed that emboli detected by transcranial Doppler (TCD) were more frequent in the presence of low plaque echogenicity. This finding, however, is in contrast to the results of a previous study by Droste et al,3 according to which echolucency of the plaque was not related to the presence or number of MES. Whatever the case may be, factors such as the degree of carotid stenosis, plaque echolucency, and surface morphology should be included in any multivariate analysis aiming to determine the independent prognostic significance of MES in the development of future stroke.

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Arrows indicate the interval between monitoring times. Microembolic signals number and *symptoms onset time.
effectiveness of this technique are questions that need to be answered by large-scale multicenter studies that are currently underway.

Given the above-mentioned reservations, we believe that a negative predictive value of 100%, as that described by Orlandi et al, is somewhat optimistic and rather due to the small number of patients in their series. As Molloy and Markus remark, a sample size of approximately 600 patients is required for a study to determine the predictive value of Doppler embolic signals in patients with asymptomatic carotid stenosis. Level 1 evidence deriving from such a study will give the technique the place that it deserves in the diagnostic armamentarium of carotid disease. We would like to share with Orlandi et al the hope that this study will verify the existing promising data.

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Diagnosis of Basilar Artery Vasospasm

To the Editor:

I read with interest the recent article in Stroke by Soustiel et al1 regarding improvement in the diagnosis of basilar artery vasospasm by transcranial Doppler (TCD) sonography. The article describes normative and patient-derived data pertaining to a BA/EVA ratio, defined as the ratio between the highest recorded basilar artery (BA) flow velocities (insonation depth >80 mm) and the average of the flow velocities from the 2 extracranial vertebral arteries (EVA) (insonation depth 45 to 55 mm). The purpose of the study was to learn if this ratio could help discriminate between BA vasospasm and BA hyperemia, given that BA flow velocities may be difficult to interpret in this setting.2,3 In fact, a previous study2 showed that 5/6 false-positive TCD examinations for BA vasospasm were of unknown cause. It has recently been hypothesized that this observation may be due to dysautoregulation or hyperemia.3–5 The present authors showed (1) a strong linear correlation between BA diameter measured by computed tomographic angiography and the BA/EVA ratio, (2) that a BA/EVA ratio >2 has 100% sensitivity for BA vasospasm, and (3) that a BA/EVA ratio >3 identified severe angiographic BA vasospasm.

While these data are useful for the interpretation of BA flow velocities patients with subarachnoid hemorrhage, there are a number of methodologic concerns about the work of Soustiel et al.1 First, the definition of the BA/EVA ratio bears a striking resemblance to the Vba/Vva ratio described 5 years ago.6 In that article, normative data and patient-derived data using the same rules for insonating the vessels and calculation of the so-called posterior circulation flow index7 were presented. Using a Vba/Vva ratio >2.5, the specificity of TCD for BA vasospasm was substantially improved from 42.3% to 87.5%, suggesting that the Vba/Vva ratio can eliminate most false-positive TCD examinations attributable to BA hyperemia. As such, the present data1 confirm and extend the value of a posterior circulation flow index that may adjust for hyperemia or increased intracranial pressure when interpreting BA flow velocities. However, it is not clear why the present authors believe that an insonation depth of 45 to 55 mm corresponds to the extracranial portion instead of the proximal intracranial portion of the vertebral arteries, since the TCD probe is typically placed immediately inferior to the occipital protuberance to insonate the vertebrobasilar circulation. Second, it is not clear why the authors chose computed tomographic angiography as the “gold standard” against which TCD was compared, especially since reference to a study showing the comparability of computed tomographic angiography and catheter angiography was not provided. Were all the computed tomographic angiograms of high quality? Use of an imperfect gold standard often magnifies measurement error, leading to misclassification bias, with unpredictable effects on calculation of sensitivity and specificity. In addition, what was the time interval between performance of the TCD and computed tomography examinations? Given the dynamic nature of the vasospastic process over time, a 24-hour interval between studies has typically been used.2,6,7 Third, the study population was heterogeneous and included patients with spontaneous and traumatic subarachnoid hemorrhage and 1 patient with an arteriovenous malformation. Thus, the presence, location, and grade of subarachnoid clot, as well as resultant hemodynamic aberrations, may have varied between subgroups in the study population. As a result, it may be more appropriate to split the study population into homogeneous subgroups (ie, spontaneous and traumatic subarachnoid hemorrhage, excluding arteriovenous malformations), perform this type of analysis in each subgroup, and develop disease-specific diagnostic criteria using the appropriate gold standard.3,4,5 Fourth, were the sonographers or clinicians blinded to the angiogram results when selecting which TCD result was used to compare with the angiogram? If not, then bias may have been introduced into all reported calculations. Fifth, selection of the computed tomographic angiogram with the smallest BA diameter for correlation purposes in patients who had multiple angiograms introduces a biased assessment of test accuracy, since only the “best” data are used. It is preferable to use all available data, ie, multiple correlations in patients with multiple gold standard examinations, when evaluating test accuracy. Sixth, it appears that a BA/EVA ratio >2 only slightly improves the specificity (85% to 95%) of TCD for the diagnosis of BA vasospasm in this data set. Whether this is a reflection of different study populations, differences in study methodology, variation in pathophysiologic derangements, differences in cerebral perfusion pressures, different concomitant treatments, or other reasons may be determined by further research.

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Response

I read with interest the comments made by Dr Sloan in his letter to the editor. In general, I found in these comments some puzzling contradiction as they directly dispute the reliability and the accuracy of the findings presented in our article, while at the same time the author claimed to have obtained similar findings using a method bearing “a striking resemblance” to that described in our article. Although I was not aware of the existence of the quoted article since it was not published in a peer-reviewed journal and does not appear in medical publication listings, I think that this would only add to the clinical value of the presented BA/EVA velocity ratio, especially when similar findings based on a similar protocol were obtained by a different team using different imaging methods.

The first question raised by Sloan addressed the insonation depth chosen for the extracranial segment. Three different and simple arguments stood behind this. The first relates to depth measurements that were made in numerous CT scans and averaged, leading to a range of 45 to 50 mm in most instances. Second, most authors would agree on an average minimal insonation depth of 60 mm for the intracranial segment of the vertebral artery. Last but most important, we found that a progressive reduction of the insonation depth resulted in an abrupt decrease in the flow velocity that is most likely consistent with the larger diameter of the vertebral arteries in their extracranial segment. I would agree, however, that unlike the extracranial segment of the internal carotid artery, the distinction may be difficult, just as it is for the basilar and the vertebral artery.

The second question related to the CT-angiography technique that was used in our study. Although it is indisputable that the conventional digital subtraction angiography remains the gold standard for vessels imaging, high-resolution CT angiography has gained a wide acceptance, and there are numerous studies that the reader may refer to easily. Furthermore, since the purpose of CT angiography in our study was not interventional or surgical in nature, the obtained resolution was high enough for the evaluation of vessel diameters. Unless papaverine or balloon dilatation is contemplated, it would have been difficult to justify an arterial angiography for the mere diagnosis of vasospasm, especially in critically ill patients, as were some of our head-injured patients. Clearly, the improvement in the resolution of CT angiography offers a more flexible diagnostic attitude in such indications. TCD in all patients was performed immediately before the CT angiography in all instances.

The third concern addressed the heterogeneity of our patients’ population. Although it is a widely accepted convention to deal with a homogeneous population, this is not immediately relevant to the present study. On the contrary, it is most likely that different kinds of pathologies may raise different clinical situations. Hyperemia, for instance, is uncommon following aneurysmal rupture. Consequently, it is not surprising, as specifically discussed in our article, that the issue of false-positive TCD was mostly overlooked in the article by Sloan et al,1 as they evaluate patients suffering from spontaneous subarachnoid hemorrhage. Furthermore, should a velocity ratio be reliable enough, it should apply to any situation where hyperemia is to be differentiated from vasospasm. Similarly, the Lindegaard index is applied to postradiotherapy as well as to aneurysmal subarachnoid hemorrhage and, as such, has gained wide acceptance.

The fourth concern has been actually addressed in detail in the methods section of our article.

The fifth comment relates to the choice of the narrowest location for the measurement of vessel diameter. The answer is dictated by simple hydrodynamic considerations. The flow in a stenotic tube would be rather determined by the point of higher resistance and smallest diameter (“bottle neck”) than the contrary. Furthermore, the increase in flow velocities is a direct consequence of the decrease in the vessel diameter. It is therefore only logical to correlate to highest recorded flow velocity to the narrowest stenosis. A correlate and good example of this would be the fundamental principles of ultrasonographic diagnostic of carotid stenosis. However, I agree, as most would, that any particular study should better rely on the “best data” than on the worst.

The sixth point is the essence of our article itself. The most important outcome of the use of such a ratio is an improved differential diagnosis between hyperemia and vasospasm, which may be potentially useful in head injury. In the present series, despite the selection of the “best data” (narrowest diameter), 3 patients had elevated flow velocities in the basilar artery without concurrent radiological evidence of vasospasm. Two had a BA/EVA ratio suggestive of hyperemia, hence the potential clinical value of such a parameter.

In conclusion, I think that there is no such clinical study that is not subject to some degree of criticism, and I hope that the methodological limitations of the present study will eventually trigger the design of improved research tools rather than skepticism.

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Vascular Complications of Cocaine Use

To the Editor:

In their article on the neurovascular complications of cocaine use, Conway and Tamargo concluded that vessels narrowing and delayed clinical deficit after aneurysmal subarachnoid hemorrhage were due to cocaine-induced vasospasm. However, cerebral thromboangiitis obliterans (TAO), which is often unrecognized, may have the same clinical and angiographic presentation. Many cases of peripheral arteritis very similar to TAO have recently been reported with cocaine use.4,5 Platelet activation and microvascular lesions can be observed in cerebral and coronary arteries of patients exposed to cocaine.5,6
aggregation formation have also been reported, explaining the beneficial effects of antithrombogenic agents such as aspirin on cerebral blood flow in chronic cocaine users. Cerebral TAO is therefore probably more frequent than supposed and must be considered in the differential diagnosis of the cerebrovascular complications of cocaine use.

The vascular effects of impurities and adulterants found in cocaine are probably also underestimated. They are sometimes more dangerous than the psychoactive substance. Arsenic, for example, which is a frequent contaminant of recreational drugs, is suspected to be an important trigger of TAO. Interestingly, a more dangerous than the psychoactive substance. Arsenic, for example, which is a frequent contaminant of recreational drugs, is suspected to be an important trigger of TAO. Interestingly, a dose-response relationship between the prevalence of cerebrovascular disorders and arsenic ingestion has also been found among populations at risk of arsenic poisoning. The mechanism of arsenic toxicity on endothelial cells seems to involve the activation of plasma membrane NADPH. Platelet aggregation and reduction of cAMP level have also been observed.12

In conclusion, additional studies are warranted to determine more precisely which substances and what kind of vascular lesions are responsible for the cerebrovascular complications of cocaine use. Early use of platelet-inhibiting agents such as aspirin and smoking cessation must be considered in suspected cases.

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Response
We have read with interest the letter by Dr Bernard Noël. In his letter, Dr Noël discusses thromboangiitis obliterans and its possible relationship to cocaine exposure. He then suggests that the cerebral vasospasm experienced by patients after aneurysmal subarachnoid hemorrhage (aSAH) associated with acute cocaine exposure may be due to a cerebral variant of thromboangiitis obliterans. In addition, Dr Noël notes that adulterants found in some illicit drugs may be associated with cerebrovascular complications.

In our opinion, cerebral vasospasm after aSAH associated with recent cocaine exposure is identical to that experienced after aSAH in general. Cerebral vasospasm in cocaine users has the same clinical course as vasospasm experienced by patients suffering aSAH without cocaine exposure. The onset of vasospasm; its response to hypervolemic, hypertensive therapy; and reversibility are similar in the 2 patient populations.

To our knowledge, there exist no data suggesting that vasospasm after aSAH is a cerebral variant of thromboangiitis obliterans caused by cocaine or adulterants. Vasospasm experienced after aSAH is clinically different than the vasculopathy seen with thromboangiitis obliterans. Vasospasm after aSAH has a distinct and limited time course; is often responsive to hypervolemic, hypertensive therapy; and is reversible. By contrast, thromboangiitis obliterans has a prolonged, progressive course with acute attacks and remissions; is not responsive to therapy; and is not reversible.

We and other authors have investigated the role of inflammation in the pathogenesis of cerebral vasospasm after aSAH.1–5 While we agree with Dr Noël that an inflammatory response is involved in the pathogenesis of cerebral vasospasm after aSAH, we do not feel that it is unique to those patients with acute cocaine exposure or a variant of thromboangiitis obliterans.

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MRI: The New Gold Standard for Detecting Brain Hemorrhage?

To the Editor:
Computed tomography (CT) is widely considered as the gold standard to image brain hemorrhage. The main argument not to use MRI in acute stroke patients is its assumed low sensitivity for intracranial blood. Kidwell et al and Nighoghossian et al are to be congratulated for contributing important observations to the discussion about the capabilities of MRI in acute stroke.1,2 Using T2*-weighted MR sequences, Kidwell et al found small deposits of hemosiderin in 5 of 41 acute stroke patients (12%, 95% CI 5% to 26%). Nighoghossian et al found traces of microbleeds in 20 of 100 of their prospectively examined stroke patients (20%, 13% to 29%). Higher incidences of cerebral microbleeds were seen in patients with primary intracerebral hemorrhages compared with CADASIL.3

The hemosiderin deposits of cerebral microbleeds remain undetected by CT and may represent a risk for clinically relevant hemorrhages if the patients are treated with antithrombotic agents. Because of the small numbers of patients, both studies could not determine the clinical relevance and the impact of these findings on thrombolytic therapy.
Nighoghossian et al may have missed another important aspect of their findings: in their Figure 1, they presented the CT scan of an acute stroke patient with hypoattenuation of the right lenticulostriate arteries (hardly visible, because of the very low quality of image reproduction). The MRI of this patient was obtained immediately after the CT and showed a signal loss of the affected brain region on a T2*-weighted sequence indicating acute hemorrhage. CT and MRI confirmed a middle cerebral artery infarct with hemorrhagic transformation of the right lentiform nucleus during follow-up.

This observation suggests that MRI detects acute brain hemorrhages earlier than CT. It appears as if an acute stage of brain hemorrhage, e.g., small amounts of unclotted blood, does not cause an increase in x-ray attenuation but can be detected by MRI because of the susceptibility effect of deoxyhemoglobin. If this impression is confirmed by other studies, MRI and not CT should serve as the gold standard for cerebral hemorrhages. MRI has the capacity to show hemorrhages in different stages, enabling the assessment of bleeding onset, whereas CT is positive only for acute and subacute hemorrhages. As shown by these previous studies, MRI shows whether a stroke patient has a disease that is prone to cerebral microbleeds and whether the patient has an acute hemorrhage that may be missed by CT. This information could be highly relevant if a treatment with thrombolytic agents or antithrombotic drugs is planned. Consequently, MRI should be the imaging modality of first choice for acute stroke patients who may receive antithrombotic treatment.

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**Crossed Nonaphasia in a Dextral With Left Hemispheric Lesions: Handedness Technically Defined**

To the Editor:
The article by Hund-Georgiadis et al on crossed nonaphasia in a “dextral” with left hemispheric lesion1 deserves attention because of the light it and similar cases throw on the subject of laterality and hemispheric dominance in humans. However, this requires abandoning certain conventionalism, which is the cause of the puzzlement they expressed as to the laterality of the results they obtained, i.e., ipsilateral activity of motor cortex on moving the ostensibly dominant hand (as opposed to the neurologically dominant, as I explain below). In this light, their result is a reaffirmation of the findings of high-resolution EEG experiments of Kristeva et al,2,3 Barrett et al,4 and others. More recently, similar observations have been made using functional MRI,6,7 positron-emission tomography,8 transcranial magnetic stimulation,9,10 and Doppler11 techniques. These observations require an anatomical substrate, depicted below.

One source of confusion of the respectable authors is their complete reliance on an inventory-based methodology in ascertaining a subject’s laterality. The other is lack of appreciation of the anatomical significance of absence of apraxia in the subject’s (ostensibly nondominant) left hand. Cognizance of these 2 critical points as well as intimate familiarity with 2 other laterality indexed clinical syndromes are essential ingredients in grasping the issues involved.

The twin entities to which I referred are syndromes of ipsilateral weakness involving the nondominant hand in certain lesions affecting the dominant hemisphere,12,13 and that of weakness involving nondominant hand after callosotomy, whether natural (such as in Marchiafava-Bignami disease or trauma)14–16 or iatrogenic17 (and my own unpublished data). The fact that these twin syndromes are laterality indexed clearly denotes that the callosum mediates the symptoms and signs observed in both. Only electrophysiologic methods have the temporal resolution necessary to discern which hemisphere controls the other through the callosum via an excitatory synapse (evidenced by occurrence of diaschisis symptomatology ipsilateral to the minor hemisphere on interruption of its excitatory connection from the major hemisphere, in the twin syndromes mentioned above). The older techniques of bilateral simultaneous measurement of reaction times in right- and left-handed subjects,18 the more sophisticated recent techniques for detecting movement-related cortical potentials, and other approaches19,20 support temporal priority of activation of the cortex related to the (neurologically) dominant hand by an amount equal to that of interhemispheric transfer time in comparison to the activity detected over the other hemisphere related to the nondominant hand. Thus, the earlier activation of the dominant hand in bilateral, simultaneous key pressing or other tasks18–20 as well as bilateral activation of the motor cortex when moving the nondominant fingers indicate the existence of a central command for initiating all voluntary movements, located in the major hemisphere. Such findings are common to all these studies, providing a technical definition of handedness and a satisfactory answer to the authors’ query in their article and to that of earlier investigators, including the 2 neurosurgeons who decades earlier commented on the “amazing [fact] that in all our cases [of ipsilateral hemiplegia] the left hemisphere was involved. Surprisingly, the same holds true in the cases of... and Kernohan and Woltman and... where clinical data are available”.

To recap, the validity of self-declared laterality is only statistical in nature and cannot guarantee the same on an individual basis, especially among those who consider themselves left-handers. The occurrence of crossed aphasia and crossed nonaphasia cases reflects the validity of the above statement. The lack of left-hand apraxia and absence of aphasia in their subject indicated that the patient was neurologically left-handed. The fact that he had gone through life masquerading as a right-hander is something many subjects do, the majority of them ostensibly left-handers. We now know that the role of family history in handedness is obscure21 (see below) and that the introduction of it into the subject of cerebral dominance by Foster Kennedy22 was an improvisation to rescue Paul Broca’s fledgling cerebral localization theory from collapsing under a barrage of similar cases (of crossed aphasia or crossed nonaphasia), which were threatening the survival of Broca’s claim. By declaring that all right-handers with family history of left-handedness were “real” sinistral left-handers with no such history were “real” dextrals, Kennedy successfully fought off the challenges—but at the cost of delaying an understanding of motor control in humans that required not an arbitrary but a technical/anatomical definition of handedness, as provided here.

To summarize, there is nothing odd about the brains of real left-handers, except with regard to which side controls the other compared with right-handers (see above), and the fact that they
have been a ubiquitous minority of humanity. Here comes the dividend of the explanatory power of the above scheme: Since the callusom is the path through which the axons of the neuronal aggregate that underlie laterality traverse, the lopsidedness of laterality distribution in humans must be related to an unfavorable event related to the development of the same structure in utero (allowing a role for imitation and social factors in certain circumstances). We know that anomalies of corpus callusom (e.g., holoprosencephaly)\(^{23}\) are the most common finding among aborted fetuses in humans. Therefore, the vast majority of those destined to become left handers die before birth. Moreover, it is known that such life-threatening anomalies are sometimes genetic in nature.\(^{24,25}\)

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Response

We would like to thank Dr Derakhshan for his detailed comments concerning our article. Focusing on the main point, he apparently implies that our patient was actually left-handed, at least as far as “neurological dominance” is concerned. The absence of apraxia is used to undermine this hypothesis. We, in contrast, had clearly stated that (1) the patient was right-handed by all means of behavioral testing and history, and moreover that (2) he was evaluated only in the chronic phase (4 years after stroke onset). Thus, initial presence of apraxia cannot be fully ruled out; the statement of Derakhshan is at best speculative.

Dr Derakhshan implies that a number of patients go through life masquerading as right-handers. Furthermore, these patients would be unaware of their actual handedness, would never have presented a left-handedness, and could not be identified by most commonly used examination techniques. Declaring a patient as “neurological sinistral” without any hard evidence, as Dr Derakhshan suggests in our reported case, certainly requires abandoning conventionalism. We are not convinced, though, that such an approach would really help to reduce the confusion on the topic of laterality.

Moreover, it is rather questionable whether the arbitrary attribution of a masked left hand dominance—as suggested by Dr Derakhshan—could really help to “grasp” the whole issue of hemisphere dominance in this particular case. According to previous laterality research,\(^{3,27}\) only a very small portion of “phenotypical” left-handers (2%) show exclusive right-hemisphere association activated with language tasks. On the whole, left-handers are much better characterized by a left-hemisphere preponderance of language function (76%) or by a mixed laterality to different degrees. Hence, we still end up with the central question of why a phenotypical right-hander (or, more speculatively, a masked left-hander) did not exhibit aphasia following stroke in the territory of the left middle cerebral artery and exclusively employs the right hemisphere in a motor, language and alertness task. And most likely we will return to the concepts of a mirrored brain organization.

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Re: Randomized Controlled Study of Stroke Unit Versus Stroke Team Care in Different Stroke Subtypes

B. Fuentes and E. Diez Tejedor

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