Cerebral Venous Thrombosis: Nothing, Heparin, or Local Thrombolysis?

To the Editor:

I really must object to the recent editorial in your journal reviewing trials in cerebral venous thrombosis (CVT).1 As someone who tries to practice evidence-based medicine whenever possible, I cannot understand how Dr Bousser can suggest that although treatment with heparin offers no statistical benefit over treatment with placebo, it should be used as the treatment of choice for all CVT. She even suggests that further placebo-controlled trials would be unethical. This is a complete nonsense! Further properly conducted, placebo-controlled trials are just what are needed to answer the questions associated with the management of CVT.

I suspect some of the difficulty with this issue comes from the fact that, as physicians, we find it very difficult to do nothing. If, for example, the trial had been comparing an established treatment with a new treatment and had produced the figures this trial produced,2 we would not even be having a debate as to whether the new treatment should be adopted. No benefit would have been shown, and unless it was superior in other ways, such as side effect profile or pricing, it would be abandoned.

With this in mind, it is difficult to conceive of a cheaper or more side-effect-free treatment than nothing.

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Response

I am afraid I don’t really understand what point Dr Lewis wants to make about my editorial on CVT.1 Does he really mean that “nothing” is the treatment of choice for CVT? How many CVT patients has he treated with “nothing,” and what was the outcome? How sure is he that “it is difficult to conceive of a cheaper and more side-effect-free treatment than nothing”? Has he calculated how much it would cost if a previously healthy young person died or became disabled for life? Is he so sure that the denial of a potentially effective treatment is better than side effects of treatment, particularly in the case of CVT, in which a careful review of the literature shows the excellent tolerance for effects of treatment, particularly in the case of CVT, in which a careful review of the literature shows the excellent tolerance for effects of treatment, particularly when it is in keeping with that of others and with the results of randomized trials. After 25 years of experience with more than 180 CVT patients (including 16 in the last 12 months), I still do not know how to predict which patients are going to recover spontaneously (those who could be treated with “nothing”) and which are going to extend their thrombosis or develop pulmonary embolism (those who certainly require heparin). Given this unpredictability and given together the beneficial trend observed with heparin in the 2 randomized trials, the excellent results obtained in large open series, and heparin’s good tolerance, I do not think it is “complete nonsense” to state that heparin remains at present the first-line treatment for CVT, and I maintain that it is more urgent to concentrate our efforts on early diagnosis and treatment rather than embarking on yet another randomized trial.

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Anger Expression and Stroke Subtypes

To the Editor:

I have read with interest the article of Everson et al1 and would like to comment on a few points. First, the authors found that the subjects with an “anger-out” score in top one third had a 2-fold increased risk for subsequent stroke compared with those having a low score. The results remained significant after risk factors such as hypertension, diabetes mellitus, cigarette smoking, serum lipids, and fibrinogen were adjusted. However, the presence of coronary heart disease (CHD) was not included in their multivariate analysis. They then divided the subjects according to the presence of CHD and found that the anger-out score was a strong risk factor for stroke in the subjects having CHD but not others. I am curious whether the high anger-out score would have been a significant factor if the presence of CHD had been included in their multivariate analysis. If the result proves to be negative, the anger-out tendency cannot be regarded as a risk factor for stroke in general.

Second, I think that stroke subtype differences may be the reason that the anger-out score was a significant risk factor only in the subjects with CHD. My colleagues and I previously reported that the Tenseness dimension of Eysenck and Fulker’s type A score2 was significantly higher in stroke patients than in control subjects.3 The
subjects with a high Tenseness dimension are those who easily become irritated, nervous, and angry. The increased score remained significant even after risk factors such as hypertension, diabetes mellitus, cigarettes smoking, and habitual alcohol drinking were controlled. Thus, our results appear to agree with those of Everson et al. In our study, we further divided the strokes into large-vessel infarction (LVI), small-vessel infarction (SVI), and intracerebral hemorrhage (ICH) and found that the increased score was evident only in the patients with LVI, not in those with SVI or ICH. We therefore proposed that these behavioral characteristics are related to the pathogenesis of atherosclerotic large-vessel disease but not small-artery diseases. In the study of Everson et al, stroke subtypes were not studied in detail. However, considering that extracranial atherosclerotic carotid/vertebral diseases are closely associated with CHD, we may speculate that a majority of strokes occurring in the patients with CHD were LVI while the subjects without CHD more often developed SVI or ICH. This assumption, in concert with our own data, may explain why a high anger-out score was a risk factor for stroke only in the subjects with CHD.

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Response
We appreciate Dr Kim’s comments regarding our recent report on anger expression and incident stroke. In response, we recalculated the multivariate analyses of anger-out and incident stroke, including a dummy-coded variable for prevalent ischemic heart disease. As seen in the Table, results were little changed from our original models, with men in the top tertile of anger-out experiencing a nearly 2-fold and significant increased risk of any stroke and a 2.47-fold increased risk of ischemic stroke. In our original paper article,1 we noted that high levels of anger-out predicted excess risk only in the subgroup of men with a history of prevalent ischemic heart disease. Thus, we have demonstrated that prevalent ischemic heart disease modifies the effect of outward anger expression on stroke risk but does not confound this association.

With respect to stroke subtypes, our original report and the analyses noted above show that the effect of anger expression on stroke risk was stronger for ischemic strokes than for all strokes combined. Too few hemorrhagic strokes occurred in our population to allow reliable assessment of the association between anger-out and hemorrhagic stroke. Unfortunately, we do not currently have the information to examine large-vessel versus small-vessel infarction, as Kim and colleagues did.2 However, in our sample it is true that nearly all of the strokes that occurred in men with a history of ischemic heart disease were ischemic strokes (20 of 21 events), whereas 30% of the strokes in the men without ischemic heart disease were not ischemic (13 of 43 events). Kim’s hypothesis regarding the significance of behavioral characteristics in the pathogenesis of atherosclerotic large-vessel disease certainly is plausible and remains to be adequately tested.

Anger-Out and Increased Stroke Risk: Kuopio Ischemic Heart Disease Risk Factor Study, 1984–1996

<table>
<thead>
<tr>
<th></th>
<th>All Strokes (n=64)</th>
<th>Ischemic Strokes (n=50)</th>
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<tbody>
<tr>
<td>RH</td>
<td>95% CI</td>
<td>RH</td>
</tr>
<tr>
<td>Anger-out</td>
<td></td>
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<tr>
<td>Upper tertile</td>
<td>1.94</td>
<td>1.02</td>
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<tr>
<td></td>
<td>–3.69</td>
<td></td>
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<tr>
<td>Middle tertile</td>
<td>1.71</td>
<td>0.91</td>
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<tr>
<td></td>
<td>–3.20</td>
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<td>Lower tertile</td>
<td>Referent</td>
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There were 2,074 participants in the study. Each model includes covariates for age, resting systolic blood pressure, body mass index, low-density and high-density lipoprotein cholesterol, fibrinogen, smoking, weekly alcohol consumption, socioeconomic status, prevalent diabetes, use of antihypertensive medication, and prevalent ischemic heart disease. RH indicates relative hazard.

Trend in Outcome of Cerebral Aneurysmal Rupture Since 1985: A Proposal for Future Treatment

To the Editor:
Since 1985, we have been carrying out a population-based study of cerebral aneurysms in the Yamaguchi prefecture of Japan. The population of the area is approximately 1.5 million and has changed little over the last 15 years. The crude annual incidence rate of aneurysmal rupture has gradually increased from 1985 to 1997, from 12.9/100,000 population in 1985 (95% CI, 11.2 to 14.8) to 15.5/100,000 in 1997 (95% CI, 13.5 to 17.8).1 Any patient with cerebral aneurysmal rupture in Yamaguchi was admitted to one of 28 neurosurgical centers, where surgery was performed by well-trained neurosurgeons certified by the Japanese Neurosurgical Society. Our interest has focused on whether the overall management outcome for cerebral aneurysmal rupture, which is a severe type of intracranial hemorrhage with high mortality, has improved as a result of recent advances in surgical and management techniques.2 The 3119 patients who were admitted with cerebral aneurysmal rupture between 1985 and 1997 were enrolled in the Yamaguchi Data Bank of Cerebral Aneurysm. The outcome was estimated in terms of the Glasgow Outcome Scale3 at 6 months after aneurysmal rupture. The outcome trend is shown in the Figure. The proportion of patients with a favorable outcome (good recovery or moderate disability) relative to that of patients with an unfavourable outcome (severe disability, persistent vegetative state, or death) did not change significantly during these 13 years. Multivariate analysis was applied to these 3119 patients to determine which factors had the greatest influence on outcome. Among 11 possible factors—patient age, sex, neurological grade on admission, thickness of subarachnoid hemorrhage, side of aneurysmal rupture, aneurysmal location and size, number of aneurysms, rebleeding, symptomatic cerebral vasospasm, and hydrocephalus—the most important was the neurological grade on admission, which was assessed in terms of
Letters to the Editor

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Three-Dimensional Vector Component Analysis of Neurological Stroke Scales

To the Editor:

Neurological Stroke Scales (NSS) are impairment measurement levels of different domains essentially including consciousness/orientation, motor power, and speech/verbal communication. These domains reflect global effects of stroke and changes in specific vascular territories. Ormigo et al have advocated a Unified Form for Neurological Stroke Scales (UNSS), including the Scandinavian Neurological Stroke Scale (SNSS) and the Middle Cerebral Artery Neurological Scale (MCANS). However, monitoring patients’ progress using the UNSS involves calculating cumulative scores from each domain. Comparison of patients using scores from the UNSS is rather difficult, because similar cumulative scores may represent widely different abnormalities in different domains. Changes in a patient’s condition marked by progress in one domain but regression in another may not be reflected in the cumulative score. For example, consider 2 items on the UNSS, one measuring language, the other measuring motor power. Adding the 2 together is obviously like adding “apples and oranges.” Doing this implies that a patient who is aphasic but has minor motor deficits is comparable overall with a person who is hemiplegic but not aphasic, given similar cumulative scores. Again, the problem with simply correlating 2 sums (for example, before treatment and after treatment) is that one might lose important information in the process, and in the worst case actually “lose” the treatment effects, thereby reducing the sensitivity of the UNSS (that is, its ability “to translate meaningful clinical changes into numerical differences that are statistically significant”). The above examples show as well how cumulative scores also reduce the validity of the UNSS, that is, its ability to measure the dimension of interest. What is then required is a method to represent the magnitude and direction of change in the various domains of the UNSS.

We present here our findings in 16 patients, 10 men and 6 women of mean age 67.3±9.8 years, who suffered a stroke, as defined by WHO, of the middle cerebral artery and underwent a standardized neurological assessment with use of the UNSS on admission and at discharge, after a mean duration of hospitalization of 39.31±10.66 days. The scores for items on SNSS and MCANS reflecting global severity (consciousness/orientation), motor power, and speech/verbal communication were averaged between both scales and totaled for each domain and for each patient. The mean values for consciousness/orientation on admission and at discharge were 14.25±0.82 and 16.25±1.17, respectively (P=0.02 by t test). The motor power scores on admission and at discharge were 31.28±4.41 and 55.96±4.18, respectively (P=0.0002). The speech/verbal communication domain values on admission and discharge were 5.84±0.83 and 8.34±0.78, respectively (P=0.008).

The individual values were plotted on a 3-D scatterplot with a statistical software package (Statistica, StatSoft, Inc). Scores were plotted for consciousness/orientation on the x axis, motor power on the y axis, and speech/verbal communication on the z axis. This 3-coordinate system provided a unique placement of each case, irrespective of the cumulative score. However, 3-D rotation was applied to choose the view that best displayed the scatterplot, with minimal visual overlap of data points. The 3-D scatterplot shown in the Figure revealed the relationship between 3 domains: each point in the plot represents 1 case on admission (small open circles) and at discharge (large closed circles). The Figure revealed that the strength of the relationship between consciousness/orientation, mo-
tor power, and speech/verbal communication increased at discharge compared with that on admission. This complex (interactive) relationship between these variables would be almost impossible to identify in a numerical exploratory data analysis of the cumulative scores. The 3-D scatterplot allowed a magnitude and directional assessment of patients’ progress, hence a vector component analysis. It demonstrated the efficacy of treatment modalities in specific domains. For example, the need for continued physiotherapy and/or speech therapy in 4 patients with low scores at discharge (4 large closed circles among predominantly small open circles) is readily evident.

Therefore, we suggest the use of this approach we refer to as “3-D vector component analysis of neurological stroke scales” in further studies. However, how this approach will improve sensitivity and validity of NSS remains to be demonstrated in future stroke trials.

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Response

The rationale to quantify neurological impairments for stroke outcome research, particularly in stroke trials, is that the neurological signs and symptoms (impairments) are the most direct basis to measure the consequences of stroke for prognostic and follow-up purposes. They correlate closely with the damage to cerebral structures (face validity) on the one hand, and they are the main determinant of the functional disabilities (concurrent validity) on the other. These neurological features can be assessed in a standard manner by use of neurological scales, which assign numerical (ordinal) values to the elementary deficits and add them as a cumulative score. Several stroke scales have been produced, most of which are based on normative scaling, ie, on an empirical (based on experience) choice and weighting of items.

The United Form for Neurological Scoring of Hemispheric Stroke With Motor Impairment (UNSS)1 was made as a collective effort to help comparisons between stroke trials using either the Scandinavian Stroke Scale (SSS) or the Middle Cerebral Artery Stroke Scale (MCAS), and also to promote harmonization in the assessment of neurological impairments in stroke trials. Despite the fact that use of the UNSS as a new scale was not suggested, later independent publications showed that its items have a high interrater reliability2 and that their combination is a valid measure of clinical consequences of both ischemic and hemorrhagic strokes.3

The interesting data and comments from Njemanze and Chidi-Ebere are a helpful contribution to the use and interpretation of impairment scales in stroke. Beyond the criticism that “similar cumulative scores may represent widely different abnormalities in different domains”—a view shared by the authors of the paper under discussion1—the question of a better way to assess the usefulness of impairment scales is rarely addressed.

The responsiveness of another neurological scale (the NIHSS) was shown to be equivalent to that of disability and global scales in the only fully positive stroke trial,4 and the MCAS was found to be more responsive than the Barthel Index (disability) in the positive subgroup of another trial.5 Therefore, stroke scales seem to be valid and sensitive instruments by which to assess treatment effect in relatively large trials.

What the data of Njemanze and Chidi-Ebere show, in a limited series of 16 stroke patients, is that the UNSS is in fact a construct containing several dimensions. This was also shown in a larger series by Edwards et al,3 and also that the SSS and MCAS have
Single-Photon Emission Computed Tomography–Derived Relative Hypoperfusion Volume After Ischemic Stroke

To the Editor:

I read with interest the recent article by Barber and colleagues.1 In this report, repeated studies with 99Tc-hexamethylpropyleneamine oxime (99Tc-HMPAO) single-photon emission computed tomography (SPECT) were applied to 41 patients at acute, subacute, and/or chronic phase of ischemic stroke. Barber and colleagues concluded that the benefit of spontaneous “reperfusion” after ischemic stroke was established and that SPECT-derived hypoperfusion volume carried a prognostic value. In addition, the authors proposed the use of 99Tc-HMPAO SPECT in screening and grouping patients in therapeutic trials on acute ischemic stroke. I would raise the following comments.

First, time is a critical factor in therapeutic trials on acute ischemic stroke, and symptomatic hemorrhagic transformation is the major complication of acute thrombolytic therapy.2,3 Before clinicians would consider SPECT in screening and grouping patients in therapeutic trials on acute ischemic stroke, we need to know the extra time required for performing SPECT and obtaining the relative hypoperfusion volume. In addition, SPECT studies may not identify patients at risk of symptomatic hemorrhagic transformation, because SPECT provides no information on the integrity of the blood-brain barrier and SPECT cannot delineate the infarcted core at the acute stage.

Second, SPECT-derived relative hypoperfusion volume at the acute, subacute, or chronic phase of ischemic stroke was found to be significantly correlated with clinical outcome measures and final infarct size.1 The significant association between the latter parameters and “early reperfusion” or “nutritional reperfusion” is not unexpected, because “early reperfusion” was defined as the difference in the SPECT-derived relative hypoperfusion volumes between the acute and subacute studies and because “nutritional reperfusion” was the difference between the acute and chronic SPECT studies. While I agree with the authors that SPECT-derived relative hypoperfusion volume at different times after stroke onset carries a prognostic value, the benefit of spontaneous “reperfusion” after ischemic stroke has not been established by the results of the study. Multivariate analysis may be useful in identifying independent predictors of the clinical and radiological outcome measures.

Third, I am concerned about the use of physiological terms such as “reperfusion,” “nutritional,” and “nonnutritional” in the article.1 Although SPECT can assess perfusion and predict prognosis for recovery,1,4 SPECT provides only a relative index of cerebral perfusion. The formula used in the paper for deriving the relative hypoperfusion volume introduces 2 factors other than the actual perfusion in the region of the infarct: the overall perfusion of the brain and the perfusion of the so-regarded normal brain tissue over the mirror-image region of the infarct. Table 1 of the article illustrates an inconsistent relationship between the SPECT-derived relative hypoperfusion volume detected at the chronic phase and the CT-derived final infarct size: the SPECT-derived volume can be quite similar to or may be much smaller or larger than the CT-derived volume.

Fourth, the timing of some of the acute SPECT studies was rather close to the 24-hour limit, whereas some of the subacute SPECT studies were done shortly after this time limit.1 Given the dramatic but variable changes in the SPECT-derived relative hypoperfusion volume over time, the acute studies should be performed within a short time after stroke onset, and the interval between the acute and subacute studies should be fairly constant.

Finally, 4 patterns of change in the SPECT-derived relative hypoperfusion volume were found by the authors.1 Early “reperfusion” followed by late “expansion” can be explained by the presence of mainly “nonnutritional reperfusion.” I wonder whether the authors can postulate any explanation for the very delayed “reperfusion” 24 hours after stroke onset that persisted into the chronic stable phase. Concerning the delayed “expansion” of the hypoperfusion volume between the subacute and chronic SPECT studies in the 4 patients, the explanations proposed by the authors failed to explain the clinical course, since the patients either remained stable or improved during this interval.

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do not suggest that SPECT should replace other imaging modalities. CT remains the investigation of choice in the triage of stroke patients. The aim of our study1 was not to find the best imaging technique but to clarify the individual effects of “nutritional” and “nonnutritional” reperfusion on stroke outcome.

Thus, our major interest was in the change in the measured hypoperfusion volumes between studies. The volumetric analysis algorithm we used has been validated,2 and as the same protocol was used for all studies in each patient, we believe that changes in hypoperfusion volumes reflect true changes in perfusion. As such, we feel justified in using physiological terms such as “reperfusion” to describe a contraction of the hypoperfusion volume between acute and subacute studies as well as further division into “nutritional” (if maintained) or “nonnutritional” (if not maintained) at outcome.

We found clear correlations between hypoperfusion volume measures and stroke outcome, and although multivariate analysis was not performed, we would like to point out an earlier study by Baird et al.3 They found that the percentage “perfusion change” between SPECT studies at a mean of 8 and 33 hours after stroke onset provided independent prognostic information by multiple linear regression analysis.

Although the results of recent thrombolytic drug trials have focused interest on the first 3 to 6 hours after the onset of stroke, there is evidence from PET and combined MR perfusion- and diffusion-weighted imaging that potentially viable tissue may persist well beyond this time.4,5 As a result, we chose a 24-hour cutoff point for the acute studies. Despite this, 34 of 41 patients (83%) had acute SPECT studies performed within 12 hours of stroke onset. The prolonged persistence of potentially viable cerebral tissue may also explain the delayed reperfusion that was maintained at outcome in some patients.

In 3 of the 4 patients with early and late expansion of the hypoperfusion volumes, the late hypoperfusion volume expansion was <20%. We were therefore not surprised by the finding that these patients remained clinically stable. In the remaining patient, the late expansion of the hypoperfusion volume was 47%. Because there was no late deterioration, we can only surmise that the expansion of the hypoperfusion deficit may have been into noneloquent cerebral tissue.

We would disagree with the contention that there is an inconsistent relationship between the outcome hypoperfusion volumes and eventual infarct size. In most patients these 2 volumes are roughly similar, with a mean difference of 3 cm³ and a median of 11.1 cm³. One possible explanation for the larger outcome hypoperfusion volume seen in some individuals is peri-infarct diaschisis.

Our study has shown that SPECT can be performed in the acute setting. Despite a 24-hour acute study window, we were able to image almost one third of patients with CT and SPECT within 6 hours. Analysis of the acquired images is straightforward and rapid. SPECT may be a useful tool in the screening of acute stroke patients before thrombolytic therapy. If a small hypoperfusion deficit is seen, we would hypothesize that there is less potential benefit to find from such therapy, whereas severe hypoperfusion deficits may predict a greater risk of hemorrhagic transformation.6 SPECT may also allow the grouping of patients in therapeutic drug trials. Like others,7 we suggest that the time is right for the investigation of these hypotheses with randomized multicenter trials.

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Memory Dysfunction and Caudate Stroke
To the Editor:
We read with great interest the recent article by Kumral et al1 on caudate vascular lesions and functional outcome. We agree with the authors that it is indeed important to take into account behavioral abnormalities after subcortical stroke. However, we would like to comment on the authors’ suggestion of the role of the caudate nucleus in the integration of verbal and visual memory, especially on the interpretation and the conclusion drawn from the neuropsychological test results.

Verbal memory function was assessed by means of the Rey Auditory Verbal Learning Test (AVLT), originally developed by Rey.2 This widely used task consists of a list of 15 words that has to be remembered in 5 consecutive learning trials. After each presentation, the patient is prompted to recall as many words as he or she can remember from that list, thus providing information on immediate recall and verbal learning.

To determine whether a patient is verbally amnesic, Kumral et al used a cutoff score of ≤9 on the first of 5 trials. This seems rather arbitrary, because the normal performance of healthy subjects runs from 5.8 to 7.8 words on this first trial of the AVLT.3,4 In addition, we recommend against use of only the initial trial to assess verbal amnesia, as this gives only an indication of immediate recall or supraspan learning. For example, patients with cerebral damage may perform equal to healthy subjects on the first trial, but the impairment presents particularly on the consecutive trials.4 Moreover, others5 have suggested that memory impairment after caudate infarction might be the result of a retrieval problem. This can be studied effectively with use of the recognition list of the AVLT, the results of which were not reported.

Unfortunately, no essential information is provided about the administration and scoring procedure of Form F of the Benton Visual Retention Test (BVRT). As this form is to the best of our knowledge not part of the standard BVRT, which consists of 5 parallel forms (A, B, C, D, and E), we cannot comment on the reported findings on visual memory.

In summary, the AVLT is a widely used neuropsychological test for the assessment of verbal memory function. However, when a cutoff is used to determine memory dysfunction, a score of 9 or lower on the initial trial is too high and results in too many false-positives. Because verbal memory is not a unitary concept, the scoring of consecutive learning trials and delayed and recognition test performance yields the most valid and reliable test results.

Cognitive research that focuses on the role of the caudate nucleus in memory function is extremely important, but the conclusions of Kumral et al inferred from the neuropsychological findings are somewhat overstated.
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Response

We thank Drs Kessels, van Zandvoort, de Haan, and Kappelle for their interest in our work on the clinical profiles and behavioral abnormalities of acute caudate stroke. It is well known that the caudate nuclei have a primary role in behavioral and cognitive functions, in processing information, and probably in conceptually integrating information. Although the role of caudate nuclei in mnemonic functions is not well established, Bokura and Robinson observed that lesions in caudate nuclei led to chronic cognitive decline, which was assessed at follow-up by the Mini-Mental State Examination. In a previous study by Mendez et al., patients with caudate lesions showed impaired immediate and delayed recall memory scores on a word list learning test (California Verbal Learning Test) and had poor recall of a complex figure drawing on a visual learning test (Rey Complex Figure Test). The Rey AVLT is a brief, easily administered test that assess immediate memory span, new learning, and recognition memory. It consists of 5 presentations with recall of a 15-word list, 1 presentation of a second 15-word list, and a sixth recall trial. Retention may be examined after 30 minutes, or 1 hours and days later. Trial I may be considered an indication of immediate recall; on average, our normal older adults (65 to 80 years) may recall 8±2 words. In our study, we measured only immediate verbal recall. We agree that other subtests are also necessary to measure long-term learning and retrieval efficiency. In our study, we used Form F of the BVRT to assess immediate visual recall and recognition. Form F is an additional form that is available to test the subject’s visual recognition and recall. This form consists of 15 stimulus cards, each exposed for 10 seconds, and corresponding 4-choice response card. We used a cutoff score of ≤9 on this form. In our study, we only analyzed immediate verbal and visual recall, which are parts of memory function. Memory function has many aspects, including acquisition, retention, and retrieval. Future studies will further clarify the abilities of learning, holding, and storing information in relation to caudate subnuclei.

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To the Editor:

In their recent article, Mäurer and colleagues concluded that (1) transcranial color-coded sonography (TCCS) identified stroke complications and differentiated between intracerebral hemorrhage and ischemic stroke with reasonable sensitivity and specificity when compared to computed tomography (CT) of the brain, (2) TCCS may substitute for CT if CT service is not available, and (3) TCCS may be used to monitor stroke complications. I would raise the following comments.

The differentiation between intracerebral hemorrhage and ischemic stroke has critical implications for stroke management because of the recent breakthrough in acute therapy of ischemic stroke with tissue plasminogen activator. A prior neuroimaging with CT or MRI is mandatory, because thrombolysis in intracerebral hemorrhage is definitely contraindicated and inappropriate. Differentiation between subtypes of ischemic stroke and determination of the underlying pathogenic mechanisms are not indicated in the acute stage because precious time should not be wasted. Signs of extensive infarction on neuroimaging would exclude the patient from receiving tissue plasminogen activator, since the risk of symptomatic hemorrhagic transformation would outweigh the potential benefit of revascularization. On the other hand, ongoing major clinical trials on neuroprotective therapy in acute stroke permit inclusion of patients with intracerebral hemorrhage. The rationale is to test whether the neuroprotectants are safe and/or effective in intracerebral hemorrhage and whether these drugs can be given by the staff of the emergency medical services before arrival to the hospital. Thus, acute thrombolysis cannot be advised if CT or MRI is not available, and neuroprotectants (if efficacy is proved by clinical trials) may be considered without CT and MRI. In either situation, TCCS has no added value. In addition, TCCS cannot detect signs of early infarction.

Time is another critical factor in acute stroke therapy. The authors recommended examination of both hemispheres by TCCS and noted that poor acoustic bone windows may preclude TCCS examination in about 20% of stroke patients. I am interested in knowing the time required to finish the TCCS examination. It is important to note that the TCCS examination was done at least 24 hours after admission and that CT was done before the TCCS examination in 85 patients. I would like to know the time interval between CT and TCCS, since hematoma enlargement with time could facilitate the detection of hematoma.

Finally, it is a shame to have the CT facility and not have 24-hour access to the CT service. In Hong Kong, radiologists are not immediately available during nonoffice hours. Nevertheless, 24-hour CT service is available because a technician is available to operate the CT machine. Physicians who provide frontline service to stroke patients should not take any compromise, such as TCCS. They should insist on 24-hour access to the CT service to provide appropriate treatment and improve the outcome for all stroke patients.


Differentiation Between Intracerebral Hemorrhage and Ischemic Stroke by Transcranial Duplex Sonography

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Response

We thank Dr Cheung for his interest in our work. We agree with him that in most instances CT is unequivocally the method of choice in acute stroke because of its high sensitivity in the detection of intracerebral hemorrhages. Its ability to identify early signs of cerebral infarction is important when thrombolytic therapy is under consideration and is surpassed only by MRI. Therefore, as outlined in our article, we recommend CT or MRI examination whenever possible in the acute stage of stroke. However, large stroke trials like the International Stroke Trial or the Oxfordshire Community Stroke Project have shown that only two thirds of the patients actually received a CT scan before admission CT was performed, and it was previously shown that hyperacute intracerebral hemorrhages could be accurately detected by TCCS. In contrast, clinical examination was shown to have a low sensitivity in the differentiation between intracerebral hemorrhage and ischemic stroke. Thus, the additional use of ultrasound performed by a trained and experienced sonographer would provide essential clues for further therapeutic and diagnostic considerations. This includes referral to a secondary care center with a neurosurgery department or a neurological intensive care unit.

In addition, the ability to detect stroke complications and the real-time depiction of intracerebral hemodynamics makes ultrasound an important monitoring tool in acute stroke that would be desirable in all stroke units.

In our article we outlined the facts that TCCS is highly operator dependent and that intracerebral hemorrhages are not seen as easily with ultrasound as with CT. Also, small parieto- and infratentorial bleedings may be missed in a significant number of patients, and approximately 15% of the patients have no suitable acoustic window. Thus, at present TCCS cannot be substituted for CT scan in stroke patients. It does, however, provide critical information in addition to the clinical judgment if CT is not readily available. Ongoing technical developments will substantially improve the quality and applicability of ultrasound systems as well as the diagnostic yield of TCCS.

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Cerebral Venous Thrombosis: Nothing, Heparin, or Local Thrombolysis?
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