Trifluoperazine Pretreatment
In Experimental CI Gerbils

To the Editor:

It has been well established that cyclic 3', 5'-adenosine monophosphate (cAMP) is elevated in the cerebral cortex following anoxia, ischemia, trauma, and decapitation, and in the cerebrospinal fluid (CSF) in experimentally induced cerebrovascular disorders, in patients with acute cerebral contusion and concussion, and in patients with stroke. Phenothiazine tranquilizers have been shown to inhibit the rise in cerebral cAMP following decapitation and injury, without altering basal levels of cAMP. (In addition, one of the phenothiazines, chlorpromazine, has been shown to protect liver cells from death due to ischemia.) Of the phenothiazines tested against a rise in cerebral cAMP, trifluoperazine most efficiently inhibited that rise, a dose of 20 mg/kg inhibiting the rise by nearly 100%. For that reason, we have tested whether trifluoperazine would also have a protective effect in gerbils with experimental cerebral infarction.

Trifluoperazine (20 mg/kg) in a buffer solution was given intraperitoneally to 31 animals 90 min before operation. Thirty control animals received an equal volume of the buffer solution and 42 control animals received no treatment. Infarction was produced by ligation of the left common carotid artery. The animals were evaluated every 8 hours for 88 hours in a double-blind manner.

In the trifluoperazine-treated group, 25.8% (8 of 31) had infarcts, a lower incidence than in the buffer-treated group, of which 63.0% (17 of 27) had infarcts and in the nontreated group of which 51.2% (21 of 41) had infarcts. Mortality was not significantly lowered in the trifluoperazine group, but the trifluoperazine-treated animals had a lower probability of dying than the nontreated animals (p < 0.05) at every 8-hour observation period and a lower probability of dying than the buffer-treated animals (p < 0.05) at 6 of the eleven 8-hour observation periods. Thus, we believe that trifluoperazine prevented the small, nonfatal infarcts that were seen in the control groups.

Since pentobarbital has been reported to inhibit elevations in cAMP and to offer a protective effect in cerebral ischemia similar to that seen with pentobarbital, and to offer a protective effect in experimental cerebral ischemia similar to that seen with pentobarbital, and to offer a protective effect against prevention of an ischemia-induced rise in cortical cAMP and the ischemia-induced rise in cortical cAMP, it provides a protective effect against stroke. Although trifluoperazine has not been used in the treatment of stroke, our results show that it provides a protective effect against cerebral ischemia similar to that seen with pentobarbital, and suggest a possible mechanism for pentobarbital protection.

John C. Sowers, B.A.
Medical Student,
Bowman Gray School of Medicine of Wake Forest University

C. Patrick McGraw, Ph.D.
Associate Professor
Department of Neurology and Section on Neurosurgery,
Department of Surgery,
Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, NC 27103

References

Non-Invasive Methods Defended as Valuable

To the Editor:

The editorial appearing in Stroke (9:427-429, 1978) by Dr. Burton A. Sandok, levels unwarranted criticisms of non-invasive procedures for evaluation of the cerebral circulation. I believe
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several of his arguments are invalid and reflect apparent lack of experience, particularly with Doppler ultrasonic imaging of the carotid bifurcation. He uses some serious and nagging clinical questions which have existed for years and lays them at the feet of the new non-invasive tests. For example, "proof is lacking that the risk of surgical treatment is less than the natural history of the disease" and that the techniques do not determine whether or not symptoms of "patients with non-hemispheric TIA's are merely coincidental or causally related." Further, he states, "in asymptomatic patients, such studies must be proven useful in determining which group of patients is at greatest risk for symptoms of cerebrovascular insufficiency and infarction." The irony of these types of criticisms is that the important questions raised may be answered by the potential of non-invasive ultrasonic techniques. While these are important questions, it is the very absence of answers to those questions that requires that all the non-invasive information obtainable must be available to physicians who make difficult decisions in the management of their patients.

His statement that, "there is more to evaluating patients with non-invasive tests than merely being able to describe the pathological anatomy of the artery," discloses his lack of understanding of the meaning of the Doppler information which is primarily physiological. Indeed, I agree that the primarily morphological information available from x-ray angiography is a limitation of angiography which Doppler provides; both functional and morphological information should be integrated in the complete evaluation of many patients. Dr. Sandok's personal experience appears to be related mostly to the use of early instrumentation for ultrasonic real-time imaging of the carotid bifurcation. We share his experience that these instruments are extremely limited in their present resolution. If these instruments are able to integrate the full capability of the Doppler probes, clearly, the combined duplex instruments may be of value, if their cost effectiveness is established.

His statement, "one must be cautious in allowing information to indicate one type of treatment over another," leaves us no alternative in our present state of ignorance than to utilize all information available so that we may indeed arrive at a cautious and a considered determination of management steps to be followed.

Dr. Sandok is misinformed, or, to say the least, not up-to-date in his conclusion that non-invasive tests cannot "differentiate severe stenosis from occlusion." This, in fact, is a great strength of continuous wave Doppler over pulse Doppler and over present real-time imaging systems. His simplistic criticism that the "clinical usefulness of the Doppler studies" is "questionable" applies equally to all information that we utilize in the clinic; including the history, physical examination, and x-ray angiography. Further, the criticism that present ultrasonic instrumentation is of little help in detecting minimal atherosclerosis with ulceration glosses over the fact that x-ray angiography frequently fails to provide this information. No claims have been made for Doppler ultrasonic detection to detect intimal ulceration.

To consider some specific applications of Doppler ultrasonic evaluation in the diagnosis-treatment process, I should like first to define the testing procedure with which I have experience. The complete Doppler CVE (developed by this Institute for the extracranial arterial circulation) consists of a pertinent history, arm pressures, pulse palpations, and auscultation over the eyes, neck, and chest, followed by Doppler audio signal recordings from the ophthalmic, peripheral, vertebral, subclavian, and brachial arteries, with Doppler (DOPSCAN) imaging of the carotid bifurcations. Both stenotic and non-stenotic plaques of the carotids are detected by objectively-defined signal abnormalities. The percentage of stenosis, or the effective diameter of the internal carotid artery, can be calculated from spectral analysis or judged by listening to the audio tape recordings.

Severe stenosis (90-95% reduction in lumen) and occlusion of the internal carotid can be differentiated. Detection of these crucial lesions is of great importance and this capability alone makes the DOPSCAN of great value in clinical management. Continuous Wave Doppler is necessary to detect these severe degrees of stenosis whose very high frequencies cannot be detected by pulse Doppler systems.

Other carotid lesions differentiated by Doppler CVE include common and external stenosis, and stenosis of the cephalic internal carotid near the base of the skull. Subclavian or innominate artery stenosis and obstruction, as well as vertebral artery steal and vertebral artery stenosis, can be diagnosed from Doppler CVE.

Our experience with the Doppler CVE is based on 5,600 patients, referred by 500 physicians, to 3 Seattle laboratories operated by the Institute of Applied Physiology and Medicine. Of all patients who are subjected to angiography, 20% are analyzed at a weekly conference at the Providence Medical Center. Through this conference and research studies, the effect of the Doppler findings on clinical decisions is continuously observed. My purpose here is to share these observations and provide examples of how the Doppler CVE is used in the greater Seattle Metropolitan area in clinical management decisions.

In the patient with asymptomatic bruits, DOPSCAN may disclose the external carotid as the source of the bruit and alleviate concern. If the Doppler signals locate the bruit source in the internal carotid, the grade of stenosis may be specified, and if found to be 80% or greater, the patient is referred for x-ray angiography which is justified by many physicians. When carotid stenosis is moderate and not of hemodynamic significance, the progress of the lesion can be non-invasively followed by repeated DOPSCAN imaging. The Doppler CVE may eliminate the carotid bifurcation as the source of the bruit and may localize it to the vertebral, subclavian, or innominate arteries, or to the aortic arch. In candidates for major surgical procedures, the hemodynamic significance of lesions of the extracranial arteries can be determined to aid the surgeon in his decision for or against relief of that lesion before proceeding with other surgical procedures.

In the patient with non-lateralizing or non-focal symptoms Doppler assists in the decision to accept the dangers and costs of x-ray angiography or may eliminate such need when no surgically approachable lesion is found. For example, the finding of an unsuspected severe stenosis provides an indication to many physicians for immediate angiography and endarterectomy without which the patient is in danger of stroke from large downstream clots. If the Doppler CVE diagnoses vertebral stenosis or a subclavian obstruction with a vertebral steal, a careful decision must be made concerning whether surgical correction will relieve the symptoms. If Doppler establishes the additional presence of a carotid lesion of hemodynamic significance, surgical relief of the carotid lesion may eliminate the symptoms and eliminate one threat of stroke. On the other hand, Doppler may clear the carotids of suspicion or implicate the vertebrals, or clear suspicion of the entire extracranial supply and direct the diagnostic search to the brain or heart.

In the patient with TIAs whose symptoms are "hard core" (amaurosis fugax, contralateral numbness, or weakness with a speech defect) angiography is usually indicated but the usefulness of the Doppler contributes in several areas. The examination itself and the findings may encourage both the patient and non-specialist physician to accept angiography as a necessary procedure. In addition, the Doppler findings are useful in planning the angiography techniques and establish the hemodynamic significance of the stenotic lesion whose functional information is not available from angiographic studies. In addition, DOPSCAN provides a baseline for post-surgical non-invasive follow up.

If in the TIA patient, no Doppler evidence of plugging at the carotid bifurcation is found, medical treatment may be a reasonable choice since x-ray, as well as the new pulse-echo ultrasonic imaging techniques, presently do not reliably identify crater evidence of intimal ulceration. In the same situation, Doppler evidence of collateralization around the orbit, accompanied by an ophthalmic
bruited, strongly suggests a stenosis in the cephalic internal carotid at the base of the skull, a lesion which is not surgically approachable. In the patient with a fresh or completed stroke angiography is not usually performed, but Doppler may disclose an unsuspected severe stenosis at the carotid artery bifurcation for which an appropriately timed endarterectomy may prevent further embolization and the extension of brain damage. We have found patients on the "stroke ward" in which Doppler detected an appropriate occlusion coinciding with the involved side to explain the stroke, but with a simultaneous severe stenosis on the opposite internal carotid artery. Appropriately timed endarterectomy of the severe stenosis may prevent additional stroke.

Many additional uses of the Doppler findings assist the clinical management decision. Of special interest is the finding of external carotid artery stenosis in the presence of an occluded internal carotid artery providing the opportunity for surgical improvement of the collateral circulation and prevention of eye/brain emboli from this source.

In summary, we believe the decision not to utilize the non-invasive information available from Doppler evaluation in patients with symptoms of cerebrovascular insufficiency is insufficient to ignore an important source of information which can assist in more rational clinical decisions.

Merrill P. Spencer, M.D.
Director, Institute of Applied Physiology and Medicine
701 Sixteenth Ave.
Seattle, WA 98122

The author replies:

There are numerous articles in many journals pointing out the value of non-invasive techniques for the diagnosis of carotid artery disease. As with many new techniques in medicine, enthusiasm for their usefulness needs to be tempered with an understanding of their limitations. The editorial in Stroke was prompted not by a desire to dampen the enthusiasm of the many investigators who have been utilizing these techniques but to balance that enthusiasm in the minds of "non-users" by pointing out some of their limitations.

In the editorial I pointed out that: "most studies to date indicate that these techniques are useful in detecting hemodynamically significant lesions, but are of little value in detecting minimal stenosis or in differentiating severe stenosis from occlusion." Doctor Spencer points out that in experienced hands utilizing continuous wave Doppler and spectral analysis some of these limitations may be overcome. I would anticipate that improvement in instrumentation and technique will yield even more satisfactory results.

I further pointed out that it was not with the studies themselves that I had concern, but rather with the way in which the information obtained from these studies was being used.

My editorial was not intended to discourage the use of non-invasive studies. On the contrary, the potential value of these studies is great and if they could be applied in a prospective manner to study the natural history of the atherosclerotic disease process, these new techniques may provide us with a rational basis for making therapeutic decisions.

None among us should ignore any new source of information about our patients. Non-invasive techniques are certainly one such source. It is reasonable to assume that these studies can help us better to select which of the many patients with asymptomatic bruit, non-hemispheric symptoms, TIA, or completed stroke may benefit from further study and treatment. In spite of the many studies already done — (and the examples provided in Doctor Spencer's letter) — the value of these studies in altering the course of disease still remains unproven. Refinement of instrumentation and improvement in technique must continue, but objectivity must be used to assess value.

While progress is being made, some will utilize the available information in the manner they deem most appropriate for the benefit of their patients ... and that seems reasonable. There must remain some among us who will utilize the data prospectively to try to prove that the assumptions being made are indeed correct ... that, too, seems reasonable. There will also remain some who will be uncertain about adding these new techniques to their practice. Given the current state of the art ... that, too, seems reasonable.

Burton A. Sandok, M.D.
Mayo Medical School and Clinical Cerebrovascular Research Center
Rochester, MN 55901

Questions of Methodology With Labelled Microspheres

To the Editor:

The interesting paper by Lin and his colleagues on the effect of dextran on cerebral function and blood flow following "cardiac arrest" in the dog raises many questions. Radioactively labelled microspheres are a powerful tool in the study of cerebral blood flow. However, there are a number of methodologic considerations which should be emphasized when using this technique.

Buckberg and others have shown that the number of microspheres in a given tissue sample is the major determinant of variability in flow measurements. No data are presented in this paper on the number of microspheres injected or, more importantly, on the number of spheres in the tissue samples. Rapid injection of the microsphere suspension may cause additional controlled variability. Increased left ventricular filling pressure/volume from the injection can cause a transient increase in cardiac output. Any beat to beat variability of cardiac output is more critical if the injection is completed rather than over a minute (>100 cardiac cycles).

 Withdrawal of the arterial reference sample from the aorta adds another potential source of error. The distribution of 15μ microspheres in large arteries is not uniform across the entire vessel cross-sectional area. Flow in the aorta is laminar, with red cells (and 15μ microspheres) preferentially distributed near the vessel wall. Thus, the number of microspheres in aortic reference samples will vary depending on position of the withdrawal catheter tip.

Some idea of the mean values and ranges of absolute blood flows for the tissues under study, in addition to the % change from baseline data presented, would be helpful in assessing the possible impact of such methodologic considerations. Although the CO2 responsibility of cerebral blood flow is blunted following global ischemia, allowing Pco2 to vary from 30 to 40 mm Hg could introduce a non-random bias into the blood flow data, especially if the Pco2 were uniformly lower in the post-ischemic period.

The statistical analysis of the data also deserves comments. When the text states that the "EEG returned to control patterns sooner" in group I and III than in II, while the tabular data show no statistically significant difference between group II and III (59.5 ± 10.8 min vs 46.9 ± 4.8 min, 𝑝 < 0.3), the meaning of such comparisons becomes difficult to interpret. It is clear that the dextran-treated group (II) had a statistically significantly higher score at 5 hours than did the untreated group (I) using the Mann-Whitney U test. Yet it is unclear why the unpaired Students’ t-test, used in all the other analyses, was not used in that analysis.

Recalculating the p value for that data using the Students’ t-test revealed 0.05 < 𝑝 < 0.10. It appears that much of the "improvement" in cortical grey matter blood flow in the post-arrest period in group III (treated dogs) is derived from the blood flow data on the 4 dogs in group III which did not develop post-arrest hypertension. Comparison of the entire treated group (11 animals) and the untreated controls revealed a "trend" toward higher flow rates in the treated animals, but with p value of 0.05 < 𝑝 < 0.10. It might be more conservative to state that the data are suggestive of a difference between the 2 groups, rather than stating unequivocally that after 5 hours, the gray matter flow was "greater" in group III than in group II. It will be important to see if the improved EEG score at 5 hours following dextran therapy is associated with im-
Non-invasive methods defended as valuable.
M P Spencer

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/10/4/478.2.citation