follow-up. However, for those patients unwilling or unable to participate, carotid endarterectomy offers important advantages in selected individuals whose surgeons have demonstrated low complication rates.

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For the Participating Investigators of the VA Cooperative Trial on Asymptomatic Carotid Stenosis

References


Response

I believe the comments by Drs Hobson and Weiss are pertinent and factual, and I hope their conclusions will be supported by the ACAS study. At present, however, their study does not solve the controversy.

Their comments do not change what was stated in the Willis Lecture: “Unfortunately, in a study in which the treatment cannot be blinded, these [end points] were primarily transient events and quite likely could have been influenced by bias. The primary, hard, nonsubjective end points of stroke and death were not significantly different.”

This was true in their paper in the New England Journal of Medicine, where the hard, nonsubjective end points of stroke and death were summarized in Table 5 and were not significantly different for the surgical group (87 of 211) than for the medical group (103 of 233).

I would not argue with their conclusion that they should support the clinical follow-up of the ACAS trial. Nor would I argue that it would be wrong for surgeons with demonstrated low complication rates to perform endarterectomy on patients who are unwilling or unable to participate in the ACAS trial. But it would also not be wrong to treat them medically.

If Drs Hobson and Weiss truly believe that carotid endarterectomy offers proven advantages over medical therapy, it would be unethical to continue the ACAS study. Continuing participation must mean that they, as conscientious physicians and clinical scientists, have agreed with my conclusions that the issue still hasn't been put to rest.

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References


Pharmacologically Induced Hypothermia for Cerebral Protection in Humans

We read with interest the article by Zhang et al regarding the protective effect of hypothermia during reperfusion in a rat model of reversible middle cerebral artery ischemia. We agree that the results of this and other studies suggest that hypothermia may be a useful cerebral protective agent during postischemic reperfusion. In the accompanying editorial comment, Zivin points to the difficulty in rapidly inducing and maintaining hypothermia in humans if this therapeutic approach were to be translated into the clinical area. He suggests that this may limit the use of the technique in patients with stroke. We agree that this may be the case if conventional methods of cooling, such as those described by Zivin, are used. However, the use of pharmacological hypothermic agents may allow us to reduce body temperature in a controlled and reproducible manner. The centrally acting cholinergic agent oxotremorine can produce profound hypothermia but is associated with several undesirable peripheral cholinergic side effects such as bronchospasm. However, other more selective central nervous system cholinergic agonists can produce hypothermia with reduced peripheral effects. A recent article has shown that such drugs, when administered before induction of temporary forebrain ischemia and during reperfusion in a gerbil model, produce reduction in the amount of neuronal loss by their hypothermic effect. The temperature reduction of approximately 2°C produced in these experiments would be expected to have profound cerebral protective effects. Although application to human subjects requires further work, these data at least provide a basis for the investigation of pharmacological methods of providing hypothermic cerebral protection in patients.

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References


Response

Homeothermic animals have developed a variety of mechanisms for temperature regulation. Heat is produced predominantly by basal metabolism and muscular activity (including shivering), and is lost mainly through radiation and convection. Heat production is an active process, whereas heat loss is largely passive. The body as a whole, as well as the brain, is mostly composed of water that has a relatively high thermal capacity. Therefore, heat is readily
retained. Furthermore, intact skin is a reasonably good insulator. Humans, who have relatively low surface-to-volume ratios (compared with many common laboratory species), can defend their core body temperature much better than small animals. Therefore, when heat production stops, it takes a considerable length of time for a person to cool appreciably, whereas smaller species may become poikilothermic rapidly.

Many recent stroke investigations have shown that modest decreases in brain temperature reduce neurological damage. However, such studies are generally performed under ideal conditions in which the animal is anesthetized at the time of ischemia induction. Consequently, the muscular responses to lowered core temperature are abolished, and the central regulatory responses to hypothermia may be blunted or lost. Furthermore, in many experiments the test animals have skin removed and are otherwise manipulated to increase the rate of convective losses.

Menon and Young point out that hypothermia can be induced pharmacologically, and this may be a useful way to treat stroke victims. Such drugs are likely to act mainly by eliminating heat production. It is possible that these agents may also augment convection by, for example, increasing evaporation. However, it is probable that additional cooling techniques will be required to produce effective temperature reduction in a reasonable length of time.

I think it has already been proved that hypothermia decreases the rate of ischemic tissue damage, but that is not the key issue. Strokes generally occur with little or no warning. The patient must be transported to the hospital, a diagnosis must be made, and then treatment can be initiated. It has been shown that the time required to initiate therapy can be reduced quite remarkably to less than 90 minutes. However, if pharmacologic therapy is then started along with active cooling techniques, there will be a further delay until adequate hypothermia is attained. Most stroke patients are elderly and have concomitant medical problems, most notably cardiac disorders. Thus, treatment should be induced gently to prevent the well-established complications of hypothermia, such as cardiac arrhythmias. In addition, if surface cooling techniques are used, temperature reduction will decline more rapidly at the brain exterior than in the deeper structures. Therefore, the distribution of damage will partly determine the efficacy of this type of therapy.

The question of whether hypothermia will be useful clinically for stroke therapy remains to be answered. Although the concept is attractive, and comparatively well understood, there are formidable obstacles to be overcome before such a method of treatment becomes practical.

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Effect of Emitted Power on Waveform Intensity in Transcranial Doppler

In 1991 your journal published my comments1 on an article by Halsey2 that reported the effects of increased emitted power on the quality of transcranial Doppler (TCD) signal intensity. What could have been an important contribution to solving what is still the greatest problem of TCD examination was seriously flawed by confusing units of emitted power with those of emitted intensity. In addition, Dr Halsey failed to distinguish between the very different units of emitted intensity and in situ intensity used in his investigations.

A more recent study by Itoh and coworkers3 attempts to apply Halsey’s results to Japanese patients by comparing the failure rate of two series of TCD studies at different levels of ultrasonic output. Unfortunately, the incorrect data have been uncritically adopted to produce erroneous ultrasonic values for the series examined at higher acoustic outputs, which are then compared with results obtained at a “standard transducer power,” which is even more erroneous.

It is stated that the first series of TCD examinations was carried out with a TC2-64 instrument (Medasonics, Fremont, Calif) “at the standard transducer power of 100 mW/cm2.” These are units of intensity, not power. However, the instrument to which they refer has no such “standard transducer power” or intensity. It seems likely that the setting of the intensity control at 100% has been mistakenly assumed to be 100 mW/cm2.

The purpose of this control is to allow a percentage reduction of the acoustic output in order to use the lowest intensity required to obtain utilisable Doppler signals. It does so by regulating the amount of electrical power to the transducer crystal, which converts it to acoustic energy. But this is only one of three variables that determine the acoustic intensity, the others being the pulse repetition frequency (PRF), which is increased with the scale setting, and the configuration of the transducer itself, especially the depth of focus. A setting of acoustic intensity in mW/cm2 is therefore not possible but is only an adjustment to a percentage of the maximum at a given combination of these parameters.

Even at the lowest PRF, used to measure flow velocities within the normal range, 100% emitted intensity is of the order of 250 mW/cm2 and as high as 550 mW/cm2 at the highest PRF, which is necessary to record velocities of up to 400 cm/sec. These are, of course, measurements of spatial peak-temporal average (SPTA) made in water, and the maximum value is reduced to 240 mW/cm2 by the application of the Food and Drug Administration’s formula originally used for estimating in situ intensity for fetal isonsonation and to 51 mW/cm2 by using the unit of estimated intracranial intensity (EII) proposed by me as being more realistic for TCD applications.4

Throughout the second series of studies made with the Transpect TCD instrument (Medasonics, Fremont, Calif) repeated reference is made to results obtained at an emitted power [sic] of 400 mW/cm2. Closer examination of the methodology reveals that this is not the case, but that this is intended to mean an emitted intensity that results in an in situ intensity of 400 mW/cm2, although we are not told what this emitted value is.

Calculations based on information provided in the instrument handbook show that it would be 576 mW/cm². This means that the limit of 50 J/cm² recommended by the American Institute of Ultrasound in Medicine,5 which Dr Itoh and his colleagues sensibly sought to observe for reasons of safety by limiting periods of emission to less than 120 seconds, was in fact being exceeded by over 60%.

However, as with the instrument used for the first series, this TCD system also provides control of acoustic output only as a percentage of maximum, which is adjustable in the software and displayed on the monitor. This software provides for an “override” of the maximum output, as apparently used by Itoh and colleagues in this study, but the percentage displayed then becomes inoperative, remaining fixed at 100%. The reporting of values in mW/cm² therefore implies a precision which is by no means justified unless the two systems used were calibrated in a water bath. The unfamiliarity with the basic concepts of acoustic measurement demonstrated in this article makes it clear that this was not the case. Such calibrations require expensive equipment and are time consuming, but they are essential if we are to solve the important problems of efficacy and safety of TCD.

Although acoustic intensity obviously plays a role in the ability to obtain good Doppler signals in transcranial examination—just as it does in extracranial examination—this is not such an important factor as was first thought. The compact bone that forms the inner and outer tables of the skull has an attenuation coefficient of 5.6 dB/cm at the frequency of 2 MHz used in TCD instruments, which can therefore theoretically penetrate bone at thicknesses greater than those encountered in the temporal bones even of black subjects.6

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