The following is in response:
To the Editor:

The additional information provided by Drs. Arboix and Martí-Vilalta is very helpful and the reference to their published article is appreciated since there is so little other data available on the onset times for different stroke subtypes.

Dr. Koltringer's letter summarizes data from 423 patients showing that viscoelasticity of whole blood is higher in the morning and lower in the afternoon. Although the inciting mechanism of ischemic stroke has not yet been established, the correlation observed does offer an additional mechanism to consider. He does not mention whether there could be a corresponding practical, low-risk medical intervention that might reduce the incidence or severity of stroke if his findings in fact prove to be significant.

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Effect of Induced Hypertension on Cerebral Blood Flow Following Middle Cerebral Occlusion in Rats
To the Editor:

Drummond et al. have recently reported that induced hypertension increased regional cerebral blood flow in the aftermath of middle cerebral artery occlusion in the rat. They were unable to conclude that this represented a therapeutic effect since no metabolic studies were performed, but they claim that this was a reasonable inference.

Using the same model and a comparable moderate increase in arterial pressure, we found that both cerebral lactate and water content were significantly reduced at 2 hours postocclusion. The mechanism of this apparently beneficial effect is not proven. A return to aerobic metabolism and restoration of membrane transport systems could be a direct effect of better tissue oxygenation, but it is also possible that the washout of lactate, etc., plays a role.

Once the blood-brain barrier is breached and vasogenic edema occurs, induced hypertension will cause aggravated edema and an increased risk of hemorrhage. The duration of both the "therapeutic window," when reoxygenation can save ischemic cerebral tissue, and the "safety window," before reperfusion at high pressure has adverse effects, needs to be precisely identified before these experimental data can be used as rationale for a clinical trial.

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References

The following is in reply:
To the Editor:

We are grateful for the comments of Drs. Aspey and Harrison. They draw attention to the very important question of the length of the grace period that can elapse prior to institution of hypertensive therapy in stroke patients. The concern is that clinical maneuvers designed to force reperfusion of ischemic tissue may actually be deleterious if the duration of the insult has allowed ischemic injury to the blood-brain barrier to develop. To pursue this question, our group has performed investigations in which the application of phenylephrine-induced hypertension was delayed for 2 hours following middle cerebral artery occlusion in rats. Our data (unpublished observations) indicate that 2 hours of induced hypertension instituted 2 hours after middle cerebral artery occlusion result in a reduction in the severity of edema at the periphery of the ischemic territory, with no change in the ischemic core and a reduction in the size of the histochemical injury as revealed by the stain 2,3,5-triphenyltetrazolium. We have not, as yet, studied induced hypertension instituted after longer intervals.

There is a second clinical situation which, although less common, may still arise. It is the situation in which a vascular occlusion takes place, but recanalization occurs reasonably promptly as a result of dissolution of thrombus or platelet aggregate. In this circumstance, the clinician might unwittingly expose the entire ischemic territory, from core to periphery, to a much higher pressure head than that which would occur in the periphery of an ischemic lesion in the face of a persistent vascular occlusion.

To define the risks of hypertensive therapy, the effects of reperfusion in the setting of reestablished vascular patency should also be evaluated at various intervals following the initial occlusive event. Our group has undertaken investigations to define the safe intervals. In spontaneously hypertensive rats, we performed temporary middle cerebral artery occlusions of either 2 or 3 hours' duration. Immediately after reestablishing vascular patency, phenylephrine-induced hypertension was initiated and maintained for 2 hours. Evan's blue accumulation in brain did not occur after 2 hours of vascular occlusion, but was substantially worsened by induced hypertension after 3 hours of vascular occlusion (unpublished observations).

We agree with Drs. Aspey and Harrison that additional experimental data should probably be obtained before a systematic clinical trial of this type of therapy is undertaken. The effort is probably justified, however, for with the evolution of thrombolytic therapies, there may be a renewed interest in supportive therapies for the patient with acute focal cerebral ischemia. Hemodynamic and barbiturate therapy for stroke victims has been contemplated and occasionally undertaken in the past. However, when there is no prospect for rapid recanalization or development of collateral flow, the clinician is in the position of having to apply these therapies for prolonged periods (48–72 hours). The application of such invasive and physiologically stressful procedures for prolonged periods in elderly patients is a daunting clinical undertaking and probably accounts for the limited use of and success with this type of therapy. Effective thrombolytic therapies may create a circumstance wherein the therapies needed are those that support the ischemic brain during the relatively short periods required to reestablish vascular patency.

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Effect of induced hypertension on cerebral blood flow following middle cerebral occlusion in rats.
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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/21/5/827.citation