

Urgent intervention to reduce functional deficits after postoperative stroke

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SUMMARY

Background A 67-year-old right-handed man with a history of atrial fibrillation developed sudden aphasia after urological surgery. Initial diffusion-weighted and perfusion-weighted MRI demonstrated an area of hypoperfusion in Broca's area, with minimal infarction.

Investigations Neurological examination, language testing and brain MRI scans with diffusion-weighted and perfusion-weighted imaging.

Diagnosis Acute cardioembolic stroke with minimal infarction in Broca's area and a surrounding region of potentially salvageable, hypoperfused cortex.

Management Saline-induced hypertension resulting in rapid restoration of cortical perfusion and a resolution of the initial speech and language deficits. The utility of perfusion-weighted imaging in selecting appropriate candidates for urgent treatment of stroke when thrombolysis is contraindicated is discussed.

KEYWORDS aphasia, cortical hypoperfusion, induced hypertension, ischemic stroke, perfusion-weighted MRI

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THE CASE

A 67-year-old right-handed man with atrial fibrillation who underwent urological surgery was found to have become mute several hours after the procedure. The patient had been receiving prophylactic warfarin therapy for several years, and this had been discontinued a week before his operation to prevent any bleeding complications related to surgery. He was otherwise healthy with no evidence of heart failure or hypovolemia, and he had normal serum biochemistry. Although he had atrial fibrillation, his heart rate was normal. A postoperative neurological examination, undertaken 34 minutes after the onset of his symptoms, revealed that within the first hour after onset he had achieved a partial recovery of motor speech function. His speech was characterized by self-corrected errors in articulation and numerous semantic paraphasias. Although he was able to follow simple commands, he had difficulty understanding syntactically complex sentences. There were no cranial nerve deficits. The patient's pyramidal function was normal, and he demonstrated normal mass and tone with 5/5 power in all muscle groups in the upper and lower limbs. He was unable to form or copy letters when attempting to write, although he had no other significant apraxia. He had symmetric tendon reflexes and flexor plantar responses. His sensation was intact in all primary modalities.

As the patient's only neurological deficit was aphasia, his language functions were assessed further. A previously described battery of single word and sentence processing tests¹ revealed that he had normal performance on oral reading and repetition of words when self-corrected errors in articulation were not penalized, and normal comprehension of syntactically simple questions, for example, "Do tigers have stripes?" When describing a complex picture, however,

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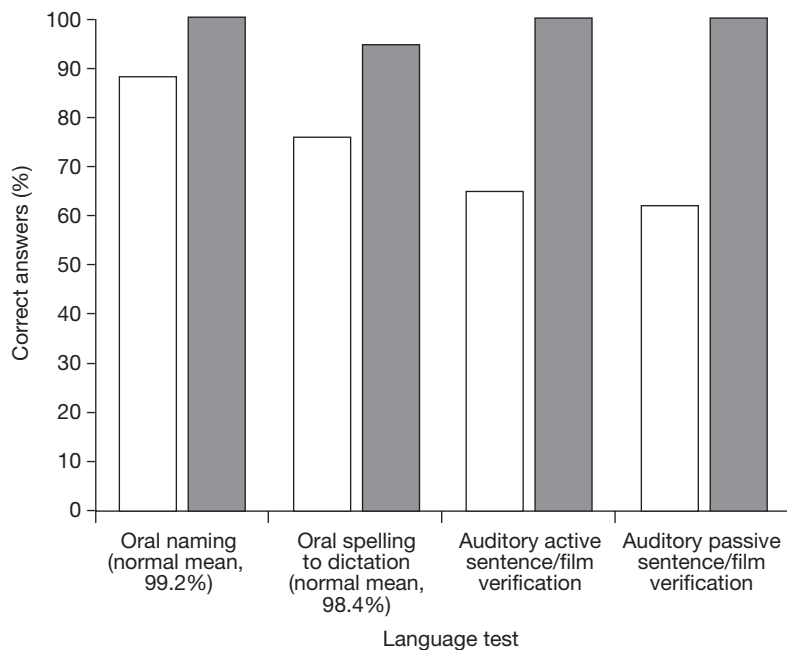


Figure 1 Improvement of the patient's performance to a normal level on four language tests after induced hypertension treatment to restore blood flow. White bars are day 1 (5 h after onset; before intervention); black bars are day 2 (32 h after onset; after intervention).

he demonstrated agrammatic speech. He also demonstrated a mild impairment in his ability to carry out oral naming (when self-corrected articulatory errors were not penalized), and poor comprehension of semantically reversible questions and sentences, for example, "Is a horse larger than a dog?" and "The boy was chased by the girl." He was also unable to form letters for writing and he had a moderate impairment in oral spelling to dictation. The patient's language test accuracy rates are shown in Figure 1.

A CT brain scan taken immediately after the patient's symptoms commenced was found to be normal. An MRI scan taken 3 hours after symptom onset, however, showed a tiny cortical abnormality on diffusion-weighted imaging (DWI) that was consistent with acute ischemia, and a much larger area of hypoperfusion involving Broca's area on dynamic contrast perfusion-weighted imaging (PWI; Figure 2A). No occlusion was seen on initial magnetic resonance angiography, perhaps because the middle cerebral artery branch supplying the focal area would have been relatively small. Although the onset of the patient's symptoms was within the 3-hour time window for intravenous thrombolysis, his very recent surgery was a contraindication for this intervention.

As a result of the presumed cardioembolic etiology of the patient's aphasia, a decision was made to treat him with anticoagulatory intravenous heparin with the aim of achieving an activated partial thromboplastin ratio of 1.5–2.0 to prevent recurrent stroke. Although there had been a small daily risk of stroke associated with the patient's atrial fibrillation, it is possible that heparin treatment had not been started earlier because of the risks of bleeding at the surgical site. As the patient's MRI scan showed only a very small diffusion abnormality, the risk associated with potential hemorrhagic conversion was felt to be minimal. In an effort to restore blood flow to the noninfarcted tissue that was hypoperfused, the patient underwent induced hypertension with intravenous saline at 200 ml/h, which raised his blood pressure from a mean arterial pressure of 111 mmHg to a mean arterial pressure in the range 130–144 mmHg.

A neurological examination carried out shortly after the patient's mean arterial pressure had been increased was found to be entirely normal. Repeat language testing was commenced on the day after intervention, when his mean arterial pressure remained at approximately 130 mmHg. The patient demonstrated recovery of all speech and language functions to the level of normal age-matched controls (Figure 1). A postintervention MRI brain scan obtained 36 hours after symptom onset demonstrated complete reperfusion on PWI, and minor DWI abnormalities within Broca's area (Figure 2B).

DISCUSSION OF DIAGNOSIS

It has long been known that there is an area of dysfunctional but potentially viable ischemic tissue surrounding a region of acute brain infarction, which can contribute to observed clinical deficits. Early experiments in primates undertaken by Astrup and co-workers^{2,3} identified a threshold of cerebral blood flow (20–30% of normal blood flow) below which neuronal electrical transmission failed to occur. In some of the experimental animals, electrical activity could be restored using reperfusion, provided that it occurred in a timely manner. These studies also identified a lower threshold (10% of normal blood flow) below which cell death occurred; this was indicated by a rise in extracellular potassium resulting from a failure of the Na⁺/K⁺ ATPase pump. The neural tissue receiving between 10% and 30% of normal

blood flow was considered dysfunctional but potentially viable. This 'ischemic penumbra'—brain tissue receiving just sufficient blood flow to survive, but not to function—has become the target of nearly all interventions for stroke. The identification of patients who have a large ischemic penumbra is thus considered an important step in the selection of patients who might benefit most from the restoration of blood flow to this region.

The combination of DWI, to provide a marker of irreversibly damaged tissue, and PWI, to provide a marker of hypoperfused tissue, has been used to achieve a rough estimate of the ischemic penumbra.⁴ There are, however, several caveats to its use. First, when blood flow is restored rapidly, the abnormality on DWI can reverse or shrink, indicating that it does not represent purely irreversible tissue. This rapid reperfusion, however, often leads to delayed reperfusion injury, so the abnormality on DWI does reflect densely ischemic tissue that is unlikely to survive. Likewise, dynamic contrast (so-called 'bolus tracking') PWI does not easily provide a quantitative measure of cerebral blood flow, and can overestimate the tissue 'at risk' of infarction. Nevertheless, the volumes of abnormality on at least two hemodynamic maps derived from PWI (time to peak maps, which show time to peak arrival of contrast to each voxel, and mean transit time maps, which show the mean time to transit across the voxels) have been shown to correlate with neurological dysfunction.^{5–7} These studies have indicated that a threshold of a 4 second delay in time to peak relative to the homologous region in the normal hemisphere corresponds to dysfunctional tissue, although areas with this delay do not inevitably progress to infarct in the absence of reperfusion. CT perfusion, PET and arterial spin-labeling perfusion imaging are all techniques that can provide quantitative measures of perfusion and are at least equally as useful as dynamic contrast PWI; PET and arterial spin-labeling are in practice, however, less often available for the evaluation of acute stroke.

In the present case, initial DWI showed only a tiny abnormality that could not account for the patient's severe aphasia. PWI, however, revealed a substantial area of cortical hypoperfusion in Broca's area, which could account for his deficits. There was little doubt that the hypoperfused area was responsible for the patient's language deficits—possibly in addition

to remote areas functionally disconnected from this area because of the hypoperfusion. Reperfusion was, therefore, deemed critical for restoration of language function, and our group has previously shown that in similar cases of cortical hypoperfusion associated with aphasia or neglect, reperfusion is associated with recovery.^{1,8}

TREATMENT AND MANAGEMENT

In the experiment by Astrup *et al.* that first demonstrated the existence of the ischemic penumbra, cortical evoked potentials were restored either by releasing the occlusion of the involved carotid artery, or by increasing cortical perfusion via aramine-induced hypertension.² Their study also showed that, in ischemic tissue, increased mean arterial pressure is associated with a linear increase in regional cerebral blood flow, indicating a loss of autoregulation of blood flow in the ischemic penumbra. Reopening of the artery or increasing blood pressure to ischemic tissue remain the only reported methods of improving blood flow in the penumbra. Recanalization, with thrombolysis, mechanical embolectomy, angioplasty or stenting, has been the mainstay of reperfusion in acute stroke, although induced hypertension can provide an alternative means of improving perfusion.

Several studies have indicated that, by using phenylephrine to temporarily increase blood pressure in acute stroke, it is possible to bring about an improvement in function. A number of case series of transient induced hypertension have reported restoration of cortical and motor function in humans.^{9–11} A pilot randomized trial that compared the outcome of acute stroke patients who received conventional management with that of patients treated with induced hypertension found that patients in whom blood pressure was raised showed more neurological and cognitive improvement, better absolute outcomes, and greater improvement in the volume of hypoperfusion on PWI than the conventionally managed patients.⁸ Marzan and colleagues also showed that norepinephrine-induced hypertension could be used safely in conjunction with other standard stroke therapies, such as systemic thrombolysis.¹² The mortality and morbidity rates described in their study—in particular the rate of intraparenchymal hemorrhage—were no different to those found in larger trials of systemic thrombolysis monotherapy. Although most

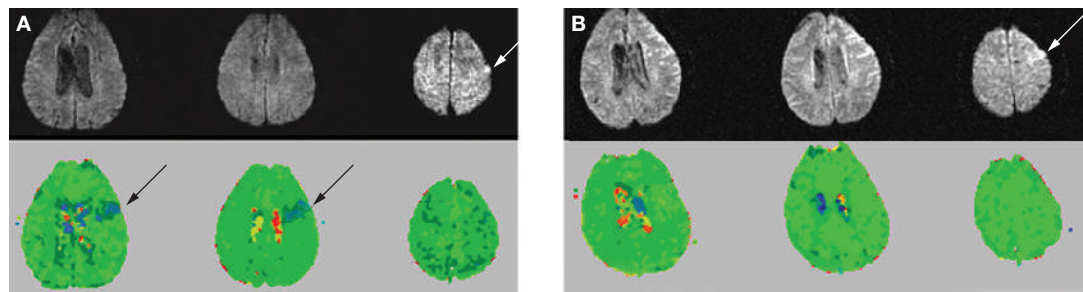


Figure 2 Diffusion-weighted and perfusion-weighted images of the patient (A) before and (B) after intervention with induced hypertension. Top rows show axial diffusion-weighted images (DWIs) and bottom rows show axial perfusion-weighted images (PWIs). Blue areas demonstrate hypoperfused regions. White arrows point to DWI abnormalities in Broca's area and black arrows point to PWI abnormalities in Broca's area. After induced hypertension, the DWI shows minor petechial abnormalities in Broca's area, and the PWI is normal, indicating reperfusion.

previous studies have used pressors when investigating the efficacy of increasing the patient's blood pressure to treat acute stroke,^{13,14} the present case indicates that intravenous saline can also be effective.

The mechanism underlying the effect of induced hypertension in acute stroke is presumed to be an increase in the level of perfusion to ischemic brain in the absence of autoregulation. The monitoring of norepinephrine-induced hypertension *in vivo* has revealed that elevation of the mean arterial pressure results in a rise in cerebral perfusion pressure in addition to a selective increase in the peak mean flow velocities of the middle cerebral artery on the affected side.¹⁵

Critics of induced hypertension as a means of achieving reperfusion would argue that because hypertension is a major risk factor for ischemic and hemorrhagic stroke, its induction during the acute phase is counterintuitive. The primary risk from high blood pressure, however, derives from chronic hypertension that leads to an increase in atherosclerosis over a period of years, with stroke being a major consequence. No major adverse effects have been reported in studies of induced hypertension in acute stroke that have excluded patients with excessive baseline blood pressures, recent cardiac ischemia or congestive heart failure. To date, no large randomized controlled trials have been conducted to determine the optimum blood pressure during the acute phase of stroke.¹⁶

It seems likely that induced hypertension, and perhaps any treatment to restore blood flow, is only appropriate for a subset of patients who show evidence of hypoperfusion beyond the

infarct, as indicated by MRI or CT perfusion. Conversely, the pharmacological reduction of blood pressure early in acute stroke in patients with ischemic penumbra could be associated with a worse functional outcome.¹⁷ The routine use of pharmacological augmentation of blood pressure cannot be recommended until the completion of further large randomized trials;^{18,19} this does not detract, however, from the importance of volume expansion in the presence of hypovolemia.²⁰

It is possible that this patient's improvement was caused by spontaneous reperfusion; however, the immediate improvement in his deficits coincided with a rise in blood pressure, indicating that his recovery was probably the result of the intervention rather than a spontaneous improvement (which is often more gradual).

CONCLUSION

Stroke should be considered as an evolving crisis in which there is an opportunity to limit the damage and restore neurological function. Neuroimaging that defines not only structural abnormality, but also hemodynamic or metabolic compromise of brain tissue, can identify patients who require urgent intervention to accomplish these goals. Induced hypertension in a controlled setting, using either volume expansion or pressors, provides a means of maintaining efficient collateral blood flow and can be a useful alternative to systemic thrombolysis when thrombolysis is contraindicated. Further clinical trials are required, however, to evaluate the risks and efficacies of induced hypertension, and other alternatives to intravenous thrombolysis, for restoration of blood flow.

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Competing interests

The authors declared they have no competing interests.