Which Targets Are Relevant for Therapy of Acute Ischemic Stroke?

Wolf-Dieter Heiss, MD; Alexander Thiel, MD; Martin Grond, MD; Rudolf Graf, PhD

Background—The efficiency of various strategies of neuroprotection is well documented in animal experiments but is thus far disappointing in ischemic stroke, for which only early reperfusion induced by thrombolysis has improved clinical outcome. This discrepancy between expectation from experimental research and clinical reality may be related to differences in the pathogenetic factors contributing to infarction.

Summary of Comment—Positron emission tomography cerebral blood flow studies within 3 hours of onset were used to identify the various compartments of the infarct outlined on MRI 2 to 3 weeks after a hemispheric stroke in 10 patients. Critical hypoperfusion below the viability threshold accounted for the largest proportion (mean, 70%) of the final infarct, whereas penumbral tissue (18%) and initially sufficiently perfused tissue (12%) were responsible for considerably smaller portions of the final infarct.

Conclusions—These results indicate that early critical flow disturbance leading to rapid cell damage is the predominant cause of infarction, while secondary and delayed pathobiochemical processes in borderline or initially sufficiently perfused regions contribute only little to the final infarct. Therefore, emerging therapeutic strategies should be targeted to the initially critically perfused tissue subcompartments. Clinical drug trials might benefit from stratification of patients for target tissue compartments applying functional imaging. (Stroke. 1999;30:1486-1489.)

Key Words: cerebral blood flow ■ cerebral infarction ■ neuroprotection ■ penumbra ■ reperfusion ■ treatment

In the treatment of acute ischemic stroke, 2 primary strategies can be followed: limitation of the ischemic insult by early reperfusion (the vascular approach) and interference with the pathobiochemical cascade leading to ischemic neuronal damage (the cellular approach). A necessary prerequisite for either strategy is the existence of functionally impaired but viable and potentially salvageable tissue. Most likely, the time windows for those treatments to be efficacious are different: rather short for effective reperfusion, of longer duration for neuroprotection, and particularly prolonged for anti-inflammatory and antiapoptotic approaches. Reperfusion induced by thrombolysis has been shown to be effective when initiated within 3 hours of onset of symptoms. In contrast, neuroprotective strategies thus far have been disappointing clinically and were unsuccessful with respect to improving stroke outcome, although significant reductions of infarct size (up to >50%) were demonstrated in animal models with the use of strategies to antagonize the various steps in the excitotoxic cascade or free radical toxicity, to inhibit harmful secondary inflammatory mechanisms, or to attenuate cell death by apoptosis. That discrepancy between experimental results and clinical efficacy of neuroprotective drugs is in part due to the limits of animal models concerning the complexity of clinical stroke. It may also be attributed to differences in the outcome end points chosen for evaluation of therapeutic effects: certain reductions of infarct size in a particular experimental setting may in fact be poor predictions of the functional outcome of stroke patients. Therefore, it must be questioned whether the infarct volume in animal experiments is a target relevant for the development of stroke therapy, since the relative impact of the various mechanisms contributing to the size of the final infarct has never been determined in human stroke.

If the target of acute stroke therapy is the core of ischemia, in which neurons most severely affected by oxygen starvation die rapidly, only fast and effective reperfusion strategies can reverse the block of blood supply and potentially increase the flow above the critical threshold, before the time is reached when cells are irreversibly damaged. Bordering the core of ischemia is the penumbra zone, where blood flow is gradually decreased below the functional threshold but still at a level sufficient to maintain morphological integrity for a certain time, which in turn depends on the degree of the residual perfusion. This penumbra zone is usually considered the most promising target for acute stroke therapy because the therapeutic window is extended to several hours and because these areas can be defined by functional neuroimaging modalities. The penumbra again would benefit mainly from sufficient reperfusion before irreversible cell damage has occurred, but additional neuroprotective agents targeted at various steps in the pathobiochemical cascade could help, or might even be necessary, to prevent or mitigate...
Figure 1. Subcompartments of the final infarct (T2-weighted MRI, 14 days after ischemic stroke, top row) as identified by $[^{15}\text{O}]\text{H}_2\text{O}$ PET flow measurement 120 minutes after onset of symptoms in a 64-year-old male stroke patient. Most of the finally infarcted gray matter is perfused below the critical threshold (<50% of contralateral mean); only small subcompartments show early perfusion in the penumbral range (50% to 70% of contralateral mean) or at an almost normal level (>70% of contralateral mean).
secondary ischemic cell damage. Beyond those acute and early mechanisms leading to necrosis, animal experiments suggest a role for delayed effects triggered by injury to cells outside the critically hypoperfused region comprising ischemic core and penumbra. The delayed damage and prolonged growth of the infarct could be prevented by anti-inflammatory drugs and/or inhibition of apoptotic proteases, probably within an extended therapeutic window. Because of the existence of those different mechanisms leading to infarction, it would appear mandatory to stratify the target compartments of ischemically compromised tissue before specific therapeutic strategies can be sensibly tested in clinical trials.

To spark the discussion and to support our hypothesis that mainly differences in pathophysiological mechanisms account for the differential efficacy of therapeutic approaches in animal models and human stroke, we present an analysis of distinct subcompartments of the final infarct, which were classified according to their degree of residual perfusion on early measurement.

Subjects and Methods

In 10 patients with acute hemispheric stroke (5 male, 5 female, aged 48 to 76 [mean, 66.6] years), regional cerebral blood flow was studied by positron emission tomography (PET) within 3 hours of onset of symptoms. The PET studies were performed on an ECAT EXACT HR scanner (Siemens/CTI) in 3-dimensional data acquisition mode providing 47 contiguous 3-mm slices at 5-mm full width at half maximum in-plane reconstructed resolution. 

Cerebral blood flow was measured according to the [15]O H2O intravenous bolus method20 with 60 mCi used for each study. Regional tracer uptake was determined voxel by voxel in gray matter structures of the affected hemisphere, and the respective ratio to the mean of the contralateral hemisphere, expressed as a percentage, was used as relative measure of perfusion. The morphological outcome was assessed on T1-weighted MRI scans acquired 2 to 3 weeks after the stroke as 64 transaxial, 2.5-mm-thick slices with the use of a 1.0-T Magnetom impact scanner (Siemens) and a 3-dimensional sequence.

With the use of an interactive program,21 the [15]O H2O PET images were coregistered to the individual MRI volume along the anterior commissure–posterior commissure line, and gray matter regions were defined by individually thresholding the MRI data of the affected hemisphere. The cerebral hemispheres, gray matter infarct, and noninfarcted gray matter then were segmented from the MRI volumes by means of Interactive Data Language (Research Systems, Inc) and C-based image analysis system operating at a spatial resolution of 1 mm2. The threshold of severe hypoperfusion in gray matter was operationally set to 50% [15]O H2O uptake relative to the mean of the contralateral hemisphere. This perfusion level was chosen because in a previous quantitative cerebral blood flow PET study of acute ischemic stroke, it had been shown to correspond to a gray matter blood flow of <12 mL/100 g per minute,23 which represents the widely accepted viability threshold.24,25 The range between 50% and 70% [15]O H2O uptake corresponding to 12 to 18 mL/100 g per minute was used to identify penumbra tissue. 26 Within the boundaries of the final infarcts outlined on the 3-dimensional coregistered MR images 2 to 3 weeks after the stroke, 3 compartments were identified according to their perfusional state early after symptoms onset: critically hypoperfused tissue, penumbral tissue, and tissue with sufficient perfusion (Figure 1).

Results

As shown in the Table, the final gray matter infarcts varied considerably in size (1.5 to 138.4 cm3). All of the 3 pre-defined ranges of initial flow were found in each of the infarcts (Figure 1). However, despite large variability among individuals, in 9 patients the largest proportion by far was the subcompartment of critical hypoperfusion (51% to 92% of the final infarct), followed by penumbral tissue (8% to 34%), whereas the subcompartment initially perfused at a sufficient level was relatively small (2% to 25%) (Table). In only 1 case, with a final infarct of 15.6 cm³, was the subcompartment of sufficient initial flow large (41%) and the critically hypoperfused volume relatively small (31%).

These data indicate that, except for 1 case, the final infarcts were caused mainly by severe initial ischemia leading to rapid tissue damage, while other mechanisms played only a minor role.

Discussion

Our hypothesis and its impact on stroke therapy are reflected in Figure 2. Compared with the amount of tissue destroyed rapidly by lack of blood supply, secondary and delayed effects are responsible for relatively small additional damage in most cases. Since the subcompartment with sufficient perfusion where the infarct is caused by delayed damage is rather small as a promising target of therapy, the benefit from treatment directed against those postprimary mechanisms is necessarily limited, and the disappointing results of corresponding clinical trials27 are not surprising. In the penumbral tissue, another rather small fraction of the final infarct will profit from reperfusion in due time, while neuroprotective drugs alone probably do not salvage enough tissue to improve clinical outcome. When given early enough and in combinations interrupting >1 step in the complex neurotoxic cascade, those drugs may extend the therapeutic...
window in the penumbra, thus enhancing the effect of reperfusion therapy; such combinations may very well form the basis of any therapeutic strategy for stroke in the future. For the development of new treatments, it would be important to develop techniques by which the various ischemically compromised tissue subcompartments can be identified. On the basis of our hypothesis, such procedures appear to be better suited to stratify patients who will benefit from a rational therapeutic approach.

References

2. Grotta J. The current status of neuronal protective therapy: why have all neuronal protective drugs worked in animals but none so far in stroke patients? Cerebrovasc Dis. 1994;4:115–120.
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