Heterogeneity Affecting Outcome From Acute Stroke Therapy
Making Reperfusion Worse

Thomas A. Kent, MD; Vicki M. Soukup, PhD; Roderic H. Fabian, MD

Background—Stroke patients are heterogeneous not only with respect to etiology but also in terms of preexisting clinical conditions. Approximately one fifth of patients with acute stroke are hyperglycemic and/or have had a recent infectious or inflammatory condition.

Summary of Review—Experimental research indicates that these factors can alter and accelerate the evolution of stroke and reperfusion injury, although these effects are complex and some may have a favorable impact. Both conditions involve activation of inflammatory and reactive oxygen mechanisms. In addition, hyperglycemia has concomitant deleterious vascular and metabolic effects that worsen infarct size and encourage hemorrhagic transformation in reperfusion models. Clinical data are less extensive but in general support an adverse impact on outcome.

Conclusions—After examining these data in detail, we concluded that the presence of these clinical conditions could assist in identification of those at increased risk for complications of reperfusion therapy. Furthermore, consideration of these factors may provide a rational basis for combination therapy and improve the clinical relevance of experimental stroke models. (Stroke. 2001;32:2318-2327.)

Key Words: cytokines ■ hyperglycemia ■ reperfusion injury ■ stroke ■ tissue plasminogen activator

Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) for acute ischemia has ushered in a new era of urgent care for victims of stroke. Results from the National Institute of Neurological Disorders and Stroke (NINDS) Study Group, and more recently ANCOROD, have demonstrated treatment efficacy, despite the significant risk of hemorrhage. Yet even with the favorable benefit/risk ratio for eligible patients, rtPA remains poorly utilized due to the narrow time window as a substantial treatment barrier. Intra-arterial administration may extend the time window and has demonstrated modest benefit, but studies have confirmed that the risks of intravenous (IV) rtPA administration outweigh the benefits after the 3-hour time window. Even with suspected clinical risk factors instituted as additional exclusionary criteria for the North American IV rtPA trial (ie, severe hypertension and presence or history of intracerebral hemorrhage), results indicate an elevated risk of symptomatic cerebral hemorrhage in patients seen within 3 hours of symptom onset. The degree of benefit lessens over time even within the therapeutic window, underscoring the importance of time in the evolution of the ischemic process.

Stroke patients are heterogeneous not only with respect to the etiology of the stroke, but also, it is increasingly being recognized, with regard to their baseline status at the time of the stroke. This review will present data that support the hypothesis that 2 conditions common in acute stroke patients, hyperglycemia at the onset of stroke and a recent infection, accelerate and alter the evolution of ischemic processes. Although both deleterious and beneficial events can occur, overall the effect of these conditions is to increase the likelihood of adverse pathophysiological processes and hemorrhagic transformation within the accepted time window, hence reducing the opportunity for benefit from reperfusion.

Data from the NINDS rtPA trial have provided compelling evidence for the notion that those most susceptible to hemorrhagic transformation might have an acceleration of the “ischemic process.” A subgroup of patients treated with rtPA had evidence of ischemia by CT scan, even though it was obtained within 3 hours of the onset of the symptoms. Results showed that only 6% of subjects with a normal baseline CT scan suffered a hemorrhage compared with 31% of those with early ischemic signs on the pretreatment CT scan. Although significant hypodensity on the initial CT scan has been variously interpreted as indicative of an error in estimating the onset of the stroke, it is also conceivable that certain patients have an acceleration of the ischemic process. The relatively high risk of hemorrhagic transformation even within the therapeutic time window suggests that perhaps for some patients, 3 hours may be too long for safe thrombolysis. It is also conceivable that if the patients who are most susceptible to hemorrhagic transformation can be identified,
the therapeutic window for patients without these factors might be considerably longer than 3 hours.

A number of imaging methods have been proposed to identify the subjects at risk for hemorrhage or least likely to benefit from thrombolysis. However, these promising methods have not been established as clinically meaningful in predicting response to thrombolysis, and it seems timely to consider other factors that may be helpful in establishing a safe, therapeutic time window for specific individuals.

The current report examines how hyperglycemia and recent infection might accelerate the ischemic process prior to thrombolysis and reperfusion. First, a review of experimental data on inflammation and elaboration of reactive oxygen species during ischemia and reperfusion focuses on deleterious (but also less-appreciated beneficial) effects, along with data that preexisting hyperglycemia and activation of inflammatory mediators may tip the balance negatively. Thereafter, relevant basic and clinical data that link hyperglycemia and recent infection to worsened outcome are reviewed. The corroborative evidence suggests that these 2 factors warrant further study in terms of their ability to identify those at higher risk for thrombolytic therapy. Therapeutic implications for heterogeneity in acute stroke patients, particularly as related to rational application of combination approaches, are also discussed.

Inflammatory and Reactive Oxygen Mechanisms in Reperfusion Injury

Reperfusion can result in tissue injury in excess of that which might transpire if reperfusion does not occur. In some animal models, reperfusion is essential to produce tissue injury, with minimal injury noted under conditions of no reperfusion. This area has generated considerable interest and has been shown to be an important factor in tissue injury for other organ systems (eg, the heart).

Recent clinical trials have shown that reperfusion injury plays a role in the pathogenesis of cerebral infarction and may exacerbate tissue injury, particularly if reperfusion of the ischemic brain is accomplished through therapeutic intervention directed at thrombolysis or anticoagulation. For example, 6.4% of rtPA-treated subjects in the NINDS-sponsored trial experienced cerebral hemorrhage compared with 0.6% in the placebo group. Similarly, a 3-fold increase in hemorrhagic transformation was observed in heparinoid-treated patients in the TOAST trial for acute stroke.

Although an increased understanding of the pathogenesis of reperfusion injury has evolved, clinical application to the bedside has been less straightforward. Vascular endothelial injury results in an increase in edema and hemorrhage, with reperfusion injury occurring as an element of breakdown in the blood-brain barrier and matrix proteins. There is an increase in recruitment of inflammatory cells through expression of adhesion receptors for leukocytes and promotion of thrombosis via platelet activating factor, factor VIII/von Willebrand factor, thromboxane A2, the rapid inhibitor of tPA (PAI-1), and endothelin. It appears that for phagocytes to contribute acutely to vascular injury, reperfusion of ischemic tissue must occur. Injured endothelial cells immediately express selectins and begin to upregulate ICAM, both of which participate in the adhesion and transmigration of inflammatory cells such as neutrophils and macrophages. Activation of inflammatory cells may lead to additional vascular injury, which further exacerbates the tissue injury, possibly through the production of superoxide anion. Inhibition of neutrophil recruitment using anti-neutrophil or anti-ICAM antibodies has been shown to reduce tissue injury due to cerebral ischemia, most consistently in reperfusion models.

However, these effects of inflammation are complex. In some models of nervous system injury, stimulation of an inflammatory response by pretreatment with lipopolysaccharide reduces ischemic cerebral injury even though neutrophil recruitment is increased. Moreover, implantation of stimulated homologous macrophages improves recovery in a model of spinal cord trauma injury. Thus, the role of phagocytes and the inflammatory cascade leading to phagocyte recruitment in the pathogenesis of nervous system injury may entail both mechanisms of nervous system protection and repair, as well as injury.

These differential mechanisms that result in both beneficial and deleterious effects suggest that response to therapies may not be easily predictable, in part due to heterogeneity among stroke patients. For example, certain patients may have a more vigorous inflammatory reaction and may benefit from anti-immune therapy despite potential interference by the therapy with long-term beneficial processes such as neural repair. If such patients could be identified, anti-immune therapy could be reserved for the patients most likely to sustain the greatest benefit in the acute setting. Our experimental work has shown that neutrophil recruitment and superoxide generation are important only when ischemia duration is prolonged before reperfusion or when the ischemic tissue has been recently exposed to the inflammatory cytokine interleukin (IL)-1β. In contrast, models with a shorter duration of ischemia or relatively minimal reperfusion show negligible neutrophil recruitment and contribution to outcome. These experiments are discussed in more detail below, but their implications for patient care seem clear—patients most likely to benefit from anti-immune therapy are those whose ischemic duration is long or whose ischemic process is accelerated. Patient selection may therefore be among many factors explaining the failure of anti-inflammatory strategies in clinical stroke trials.

The role of reactive oxygen species in the pathogenesis of reperfusion injury is well known; however, certain details are emerging that have clinical implications. First, the production of toxic reactive oxygen free radicals, particularly superoxide anion, after ischemia and reperfusion is very rapid. Therefore, attempts to reduce their deleterious effects would need to occur rapidly, perhaps even before reperfusion. In lieu of being able to rapidly intervene, downstream events are potential targets. Reactive oxygen species may produce additional injury through lipid peroxidation, reaction with nucleotide bases, DNA repair enzymes, activation of other related enzymes such as poly(ADP-ribose) synthetase, and reduction of nitric oxide levels. Nitric oxide reacts with the superoxide anion to form the toxic peroxynitrite radical and is scavenged by...
hemoglobin that may be released into tissue.\textsuperscript{70} Oxygen-dependent nitric oxide synthase is activated in ischemic tissue when calcium enters ischemic neurons. Nitric oxide is reduced as peroxynitrite is generated when reperfusion floods hypoxic tissue with oxygen.\textsuperscript{71} Nitric oxide may be also be reduced by vascular endothelial damage that may occur with ischemia or a secondary inflammatory response.\textsuperscript{72} Nitric oxide reduction has the potential to lead to vascular contraction,\textsuperscript{73} and the peroxynitrite radical is potentially damaging in its own right.\textsuperscript{74}

Oxidizing conditions resulting from reperfusion up regulate nuclear factor (NF)-\textkappa, a redox-sensitive transcription factor.\textsuperscript{75} NF-\textkappa is activated when an inhibitory factor, I\textkappa-B\alpha, is degraded,\textsuperscript{76,77} thus allowing NF-\textkappa subunits to dimerize, translocate to the nucleus, and bind to several transcription promoting regions of the genome.\textsuperscript{78} I\textkappa-B\alpha is primed for degradation by phosphorylation by the kinase IKK, followed by ubiquination.\textsuperscript{79} In turn, IKK is activated by phosphorylation by several kinases, including those activated by IL-1, TNF-\alpha, IL-6, and IKK itself.\textsuperscript{80,81} NF-\textkappaB stimulates the increased transcription of inflammatory cytokine mRNAs, such as that for IL-1, IL-6, TNF-\alpha, and others.\textsuperscript{82} Thus, the oxidative stress of reperfusion increases activation of NF-\textkappaB, which results in increased expression of proinflammatory cytokines that further activate NF-\textkappaB through IKK signaling pathways.\textsuperscript{83} Moreover, proinflammatory cytokine transcription stimulates increased expression of endothelial adhesion molecules such as the selectins and ICAM-1. Inflammatory cells elaborate reactive oxygen species that increase oxidative stress and are likely to further activate NF-\textkappaB. These factors would be expected to have additional deleterious effects on vascular endothelium. Agents that block proinflammatory cytokine activity or NF-\textkappaB activation and translocation to the nucleus have been found to reduce tissue injury due to cerebral ischemia in animal models.\textsuperscript{38,84,85}

Similar to inflammatory stimulation, oxidative stress has been associated with beneficial as well as harmful intracellular events. For example, activation of NF-\textkappaB by oxidative stress promotes transcription of genes for proteins involved in reduction of apoptosis, such as nerve growth factor, Bcl-xL, and apurinic/apyrimidinic endonuclease (APE)/Ref-1, and for production of antioxidants such as manganese superoxide dismutase (MnSOD).\textsuperscript{86–89} Similarly, paradoxical exacerbation of ischemic injury was seen when the TNF receptor was knocked out in mice.\textsuperscript{90} Perhaps attention to specific downstream effects of oxidative stress (ie, activation of specific subunits of heterodimers of NF-\textkappaB, expression of proinflammatory cytokines and proapoptotic factors) may provide more promise for neuroprotective efficacy than reduction of reactive oxygen species. The interaction of these events is complex, and the outcome of therapeutic interventions aimed at these elements of cellular injury is uncertain without more rational and specific targeting of these mechanisms and knowledge of the underlying state of the organism with respect to these factors.

In animal models, agents that reduce oxygen free radical concentrations have been found to reduce tissue injury due to reversible cerebral ischemia.\textsuperscript{91–94} As yet, clinical studies of antioxidants have not borne out the promise suggested by some animal model results. Several factors may contribute to this apparent lack of consistency. Our experimental data\textsuperscript{95} confirmed previous work\textsuperscript{96} that there is a rapid burst of oxidative stress on reperfusion in animal models (Figure), yet little attention has been directed in clinical trials to address this rapid burst with properly timed antioxidant therapy. In addition, native SOD has been shown to suppress superoxide anion concentrations for only a brief period of time and effective therapy would require prolonged therapy.\textsuperscript{97} When superoxide anion levels are actually measured, large doses are required to significantly reduce these levels,\textsuperscript{98} presumably due to poor penetrability of an intact blood brain barrier. SOD conjugated to polyethylene glycol appears to have a longer duration of action and penetrates the blood-brain barrier well,\textsuperscript{98} but it has not been studied clinically in stroke patients. Other antioxidants may have either a limited scope of action or reach peak concentrations too late to significantly alter the cascade following the early oxidative stress of reperfusion.

Given this background in the pathogenesis of ischemia/reperfusion, 2 clinical conditions emerge that could potentially alter outcome. These are hyperglycemia at the time of stroke and recent infection and inflammation prior to stroke. A separate discussion of each follows.

**Hyperglycemia**

Approximately 20% of subjects enrolled in acute stroke trials are diabetic and/or have high blood sugars (eg, >60 mg/dL, but <400 mg/dL, the upper limit for rtPA therapy).\textsuperscript{1,28,10} It has long been suggested that hyperglycemia increases the morbidity and mortality of stroke, but there is controversy that this condition may simply reflect a generalized sympathetic nervous system response to a vascular event or the consequence of more extensive disease due to chronic diabetes rather than an independent risk factor influencing outcome. The retrospective analysis of Demchuk and colleagues\textsuperscript{10} of 138 patients indicated that baseline serum
glucose was an independent predictor of hemorrhage after tPA. Serum glucose was directly related to incidence of hemorrhagic transformation, with a 25% incidence of symptomatic hemorrhage among tPA-treated patients with a serum glucose >200 mg/dL compared with 5% rate for those with glucose levels <100 mg/dL. Hyperglycemia worsened outcome among the entire cohort in the TOAST trial but interacted with treatment specifically in the subgroup of patients with lacunar stroke, in which the probability of favorable outcome lessened even within what is considered only modest hyperglycemia, from 50 to 150 mg/dL. This association of hyperglycemia with worsened outcome was independent of a history of diabetes.

Animal data support the notion that preexisting hyperglycemia worsens outcome in reversible cerebral ischemia; less consistent results are obtained with permanent focal occlusion models. Obviously, vascular disease caused by chronic hyperglycemia might produce increased tissue injury in infarction by adversely affecting vessels directly and affecting collateral circulation through acceleration of atherosclerosis. Yet, adverse effects of increased tissue injury are observed even after short-term experimental hyperglycemia, before an effect on accelerated plaque formation and atherosclerosis can have occurred.

The process by which hyperglycemia worsens outcome is uncertain, but both perfusion and metabolic mechanisms have been implicated. Peri-ischemia glucose infusion, withdrawn before reperfusion, was found to increase infarct size without impairing reperfusion blood flow after a brief, 30-minute period of ischemia. Preexisting short-term hyperglycemia in the streptozocin model that was not reversed after more extended periods of occlusion (ie, 60 to 90 minutes) also significantly increased volume of infarction relative to non-hyperglycemic rats. In more severe or prolonged ischemia/reperfusion (60 minutes to 4 hours), reperfusion blood flow at the site of prior injury was decreased. Acute hyperglycemia achieved by injection of 50% D-50 glucose solution also dramatically increased the risk of hemorrhagic transformation while reducing reperfusion blood flow. These findings suggest that a vascular mechanism may be a critical component for worsened outcome during severe and prolonged ischemia, whereas metabolic impairment may be a more salient factor following brief ischemic conditions.

Potential mechanisms of impaired reperfusion blood flow include hyperglycemia-induced damage to endothelium, increased expression of adhesion molecules, and/or glycosylation of critical proteins that generate vasodilating or anti-thrombotic substances such as nitric oxide. The role of nitric oxide in mediating the deleterious effects of hyperglycemia on experimental infarct is confirmed by the observation that pretreatment with the nonselective nitric oxide synthetase inhibitor, N\(^{-}\)-nitro-L-arginine methyl ester, provides neuroprotection in experimental reversible middle cerebral artery occlusion and hyperglycemia and prevents the vascular compromise.

In addition, hyperglycemia affects recovery of metabolic function after ischemic and hypoxic injury. Several potential metabolic factors have been associated with worsened outcome: (1) deteriorating acidosis, which directly injures tissue; (2) prolongation of posts ischemic alkalosis, which interferes with mitochondrial function; (3) delayed posts ischemic hyperthermia, which promotes deleterious enzymatic reactions such as the formation of peroxynitrate; and (4) promotion of hydroxyl radical formation.

A common end point in hyperglycemic cellular changes is the production of reactive oxygen species. The formation of advanced glycation end products (AGE) (as a function of elevated nonenzymatic glycation of proteins, lipids, and nucleic acids) is accompanied by oxidative, radical-generating reactions and thus represents a major source of oxygen free radicals under chronic hyperglycemic conditions. AGE have been proposed as a potential link between the harmful effects of hyperglycemia and inflammation. AGE are formed by nonenzymatic glycosylation of proteins and protein precursors. AGE are formed at an accelerated rate in patients with hyperglycemia and have been linked to secondary complications of diabetes. Increased AGE can appear intracellularly after episodes of hyperglycemia lasting only several hours in endothelial cell cultures. The formation of AGE is accompanied by the generation of reactive oxygen species that may contribute to their damaging effects.

Additional mechanisms of injury due to AGE includes the actions of receptors for AGE (RAGE) that are found on many tissues, such as the central nervous system and in microvascular and arteriolar endothelial cells. AGE can further increase oxidative stress and inflammation through interaction with RAGE, which are linked to NF-kB expression apparently through Ras but not Rac or Cdc42. RAGE are also found on phagocytes, where they promote phagocyte activation and binding to AGE-labeled tissues. AGE-RAGE interaction greatly increases microvascular injury and AGE has been found to increase the severity of infarction due to reversible experimental cerebral ischemia, in which administration of AGE-linked albumin prior to 30 minutes of ischemia followed by partial reperfusion worsened infarct size. Interestingly, in the latter model, AGE-linked albumin administered systemically did not reduce cerebral blood flow, actions resembling those seen in the briefer ischemia/reperfusion hyperglycemic model.

There is clinical evidence that supports a rapid effect of hyperglycemia on processes that could exacerbate ischemia. For example, an increase in blood levels of free radicals and a reduction in vitamin E levels is seen in the blood of subjects after an oral glucose load. This oxidative stress may result in the activation of NF-kB and the previously described subsequent events in the inflammatory cascade to promote additional tissue injury.

In addition to effects on endothelial function and stimulation of inflammatory mediators, hyperglycemia may affect vascular tone by altering patterns of eicosanoid production. Hyperglycemia activates several signaling pathways that could have considerable effect on vascular function. For example, hyperglycemia stimulates lipoxygenase and cyclooxygenase pathways in vascular smooth muscle, leading to enhanced formation of vasoconstrictive prostaglandins such as thromboxane A2.
some animal models and may provide a target for therapeutic intervention, including cyclooxygenase inhibition. Beneficial effects of such medications on vascular tone could, however, be outweighed by their antplatelet actions. It is possible that more selective COX-2 inhibitors could minimize these hematomal effects.

To date, no prospective clinical study has unequivocally demonstrated the efficacy of treatment of hyperglycemia in the peri-infarct period, although animal studies indicate that insulin improves outcome if given before or during ischemia. Parenthetically, even in the absence of hyperglycemia, insulin appears to improve outcome in experimental stroke models, although most studies in focal ischemia involved treatment before or during ischemia. Insulin treatment has not yet been studied in large, prospective, randomized clinical trials, but preliminary results suggest it might be safe. In one experimental study, withdrawal of high glucose infusion before reperfusion did not reduce infarct size, which suggests that normalizing glucose alone without the use of exogenous insulin is not sufficient to reduce the impact of hyperglycemia. Many stroke center models recommend reduction of hyperglycemia in the acute setting, despite a lack of evidence as to therapeutic benefit, risks, and optimal glucose level target. Nevertheless, it seems reasonable to attempt to reduce hyperglycemia with insulin in a well-monitored setting. Given the interesting results that even modest (<150 mg/dL) elevations of glucose worsened outcome for some subjects in the TOAST trial, more aggressive treatment of hyperglycemia merits further investigation.

Recent Infection/Inflammation

A second common finding in acute stroke patients is a history of recent infection before the stroke. Long-term markers of infection/inflammation, such as c reactive protein and serum IL-6, predict subsequent vascular events and the severity of those events. Moreover, there is a higher incidence of myocardial infarction associated with systemic infection. Of relevance to this review, reports indicate that infection in patients in the weeks before stroke is significantly higher than that in matched controls. Researchers from the University of Heidelberg noted that infectious and inflammatory conditions occurred in 22% of cerebral ischemia patients during the preceding week compared with 8% in a neurological control group, with both bacterial and viral infections represented. Although the mechanism by which infection/inflammation influences acute arterial thrombosis is not known, upregulation of cytokines by systemic infection, which promotes phagocyte recruitment and vascular injury, has been implicated.

There is considerable interest in how recent infection/inflammation might lead to thrombosis and stroke, but the influence of these conditions on the outcome after stroke has received far less attention. Yet, both clinical and experimental data suggest that recent infection/inflammation may be an important factor in outcome. Our laboratory has studied whether administration of a specific inflammatory cytokine (IL-1β) would accelerate development of reperfusion injury in an experimental model. Results showed that pretreatment with IL-1β on the cortical surface accelerated a number of pathological processes in experimental middle cerebral arterial occlusion. These included reduced cerebral blood flow on reperfusion, increased neutrophil recruitment, and increased superoxide anion production after reperfusion. These events occurred after 60 to 90 minutes of ischemia, a time period that produces no measurable superoxide anion radical formation among non–IL-1β–pretreated rats. Exposure to IL-1β accelerated the poor-reflow phenomenon and reduced the ischemia time necessary to unleash superoxide anion radicals on reperfusion, an effect that could accelerate reactive oxygen species–mediated reperfusion damage to the vasculature and parenchyma. Thus, in the presence of upregulation of certain inflammatory cytokines such as IL-1β, infection/inflammation may be an important factor in outcome.

Conclusions and Clinical Implications

The experimental results reviewed thus far suggest that conditions common in stroke patients, hyperglycemia and...
Hyperglycemia and Recent Infection: Incidence, Mechanisms of Injury, and Potential Targets for Intervention

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recent infection, may accelerate pathological processes from ischemia, rendering reperfusion more hazardous than otherwise expected in the same time window. Clinical evidence is less extensive but generally supportive. The Table has been provided to summarize the proposed mechanisms of injury and potential targets for intervention. Specific features of these pathophysiological mechanisms that may influence therapy, such as time course of elaboration of superoxide anion, were discussed in detail. Consideration of these variables could assist in stratifying potential thrombolytic candidates and, based on proposed mechanisms of exacerbation, might be worthwhile targets for combination therapy.

There is a convergence of evidence to suggest that activation of inflammatory signaling pathways is a common mechanism shared by both conditions. If this is indeed the case, there may be an association between plasma concentrations of soluble inflammatory markers before thrombolysis and complications of thrombolysis such as a cerebral hemorrhage and edema. However, these markers may not accurately reflect prior infection, and an alternative might be to add screening questions to address potential signs and symptoms of recent infection. This information could be added to thrombolysis databases and statistically analyzed for its independent contribution to outcome.

The review of literature on potential contributory effects of hyperglycemia suggests some additional specific therapeutic strategies. Hyperglycemia activates multiple prostaglandin pathways that might produce additional vascular pathology as well as metabolic changes that cause direct tissue injury. It is possible that some of these effects of hyperglycemia are amenable to therapy, with cyclooxygenase inhibition as one possible target. Patient selection could be facilitated by a search for specific markers of the effects of hyperglycemia that may be involved in the pathogenesis of worsening. The metabolic effects of hyperglycemia might be detectable with localized MR spectroscopy sensitive to lactate. This may aid in detecting persons with accelerated metabolic derangement associated with hyperglycemia. As discussed previously, an acceleration of the ischemic process could potentially be imaged using the extent of hypodensity on CT scans, diffusion/perfusion mismatch, or sodium MRI, albeit the sensitivity and specificity of these imaging methodologies for improving outcome have not yet been established.

Sources of heterogeneity among acute stroke patients, such as the factors discussed here, may be responsible for differences in therapeutic benefit frequently seen between animal and human trials. Results from treatment trials using animal models that do not reflect this heterogeneity may be misleading when generalized to patients. For example, animal stroke models that result in a rapid increase in reactive oxygen species or inflammation (such as prolonged reversible ischemia) may only provide a relevant model of therapeutic intervention for a subgroup of stroke patients (e.g., thrombolytic candidates who are hyperglycemic or have a recent infection). A favorable outcome for such a cohort by a particular treatment might be masked within the negative outcomes of the overall group score.

Animal models have generally neglected these factors, as have clinical trials. For example, experimental animals are often fasted overnight before induction of stroke to reduce reactive hyperglycemia and avoid complications such as seizures during recovery. Many experimental studies use pathogen-free animals, failing to consider how preexisting immune response may affect the progression of ischemia. It is conceivable that consideration of such factors as discussed here may provide more clinically relevant animal models and a more rational basis for subgroup outcome analysis in therapeutic trials.

As attempts are made to extend the therapeutic window for reperfusion therapy, a heightened understanding of the specific factors that interact with reperfusion will become more important. These factors may include the kinds of clinical heterogeneity discussed here as well as potential genetic susceptibility factors. Knowledge of these factors may further enhance clinical decision making in terms of profiling the patients who will benefit from thrombolysis and identifying those who are at increased risk of complications for a given therapeutic window. At present and in the absence of prospective data, it is premature to exclude patients with modest levels of hyperglycemia or a history of recent infection from treatment if all other criteria for thrombolysis are met. On the other hand, it would seem reasonable to consider excluding...
such subjects from future clinical trials that attempt to extend the therapeutic time window.

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Stroke. 2001;32:2318-2327
doi: 10.1161/hs1001.096588

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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