

trates the properties of channel state-modulated binding and frequency dependence common to all those in clinical use. The explication of its quantitative differences from lidocaine in the paper by Clarkson and Hondeghem⁶ also illustrates an important case in which the theoretic framework derived from basic research preceded the recognition of the resultant clinical problem.

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Post-Cardiac Arrest Therapy: Calcium Entry Blockade and Brain Resuscitation

IN THIS ISSUE, Steen *et al.* report improved neurologic function and a reduction in brain histopathology in monkeys treated with nimodipine following 17 min of selective cerebral circulatory arrest.¹ Their study gives further support to the hypothesis that pathologic events occurring after resuscitation from a cardiac arrest can increase neurologic damage and that therapy directed toward these events may ameliorate brain damage.²⁻⁵ While this study is of considerable practical and theoretic importance, the authors' suggestion that immediate controlled clinical trials be instituted requires further consideration, especially in view of the scientific controversy that encompassed the efficacy of barbiturate therapy after circulatory arrest.^{5,6} In that situation, clinical trials began before the initially promising results with barbiturates could be tested in other laboratories. This resulted in a negative clinical trial, which actually could have been predicted by further laboratory studies that found no role for barbiturates.⁷⁻⁹

Within the context of the neck tourniquet model for selective cerebral circulatory arrest in the primate, Steen *et al.* have shown with statistical validity that nimodipine ameliorates brain damage.¹ In fact, this study represents

a *tour de force* in bringing together an international team of neuroresuscitative scientists with extensive experience with the model and its enormous intensive care requirements. Additionally, the study was not based upon a shot in the dark, but rather upon the knowledge that postcirculatory arrest brain damage is associated with delayed hypoperfusion, which could be corrected partially by calcium entry blocking drugs.^{2,3} Based upon their neuropathologic findings of symmetric cortical lesions in arterial border zones, Steen *et al.* emphasize the importance of calcium penetration into vascular smooth muscle as a possible cause of vasospasm leading to hypoperfusion.¹ Some of the brain stem lesions described by Steen *et al.* fall outside of arterial border zones and may be caused by factors not related to recirculation deficits.¹⁰ Since these brain stem lesions apparently respond to nimodipine therapy other mechanisms, explaining its benefits in postischemic brain also may be involved.

Pathologic Calcium Cascades

As noted by Steen *et al.*, an increase in intracellular calcium ion concentration may be a triggering stimulus for a variety of pathologic reactions.¹ The central role of calcium as the putative initiator of events leading to

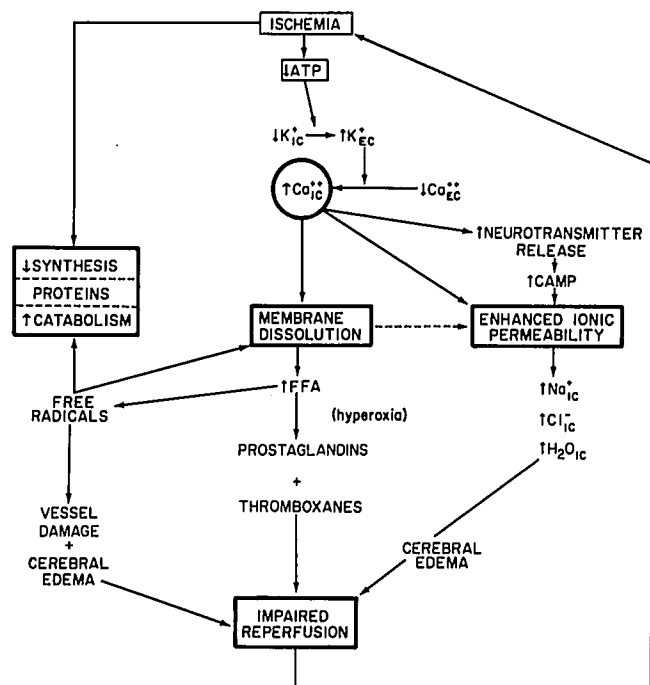


FIG. 1. Schematic representation of calcium-related pathometabolic pathways possibly activated by brain ischemia. See text for further evaluation. Abbreviations: EC = Extracellular; IC = Intracellular.

enhanced cellular ionic permeability, dissolution of lipid membrane structure, and enhanced protein catabolism, as well as impaired reperfusion, are summarized in figure 1. These events recently have been reviewed extensively by Siesjo and White *et al.* and are discussed here to emphasize the multitude of pathologic cascades in which calcium plays a role, and that may, as noted by Steen *et al.*, underly some of the nimodipine effect in his monkeys.^{2,3,*}

The immediate result of an hypoxic-ischemic insult is a dramatic reduction in ATP, leading to failure of ion-pumping activities with resultant cellular sodium intrusion and potassium extrusion. Massive calcium influx into the cell occurs after extracellular potassium concentrations reach a threshold value, around 15 $\mu\text{M}/\text{ml}$, presumably because potassium-induced cellular depolarization opens voltage-dependent calcium gates.

One of the major catabolic cascades initiated by abnormally high intracellular calcium levels involves degradation of phospholipid-rich membranes with release of fatty acid subunits. During the ischemic episode, free fatty acid levels, especially arachidonic acid, continue to increase, while high-energy metabolites, intracellular pH, and lactate levels stabilize after the initial 5 min of complete brain ischemia. Thus, arachidonic acid levels reflect the duration of ischemia. Following recirculation,

and in the presence of oxygen, cyclo-oxygenase catalyzes breakdown of arachidonic acid into thromboxanes and prostaglandins. These cyclo-oxygenase metabolites are vasoactive, and apparently the vasoconstrictor action predominates following a period of ischemia. Abnormal vasoconstrictive activity is believed, at least in part, to cause delayed hypoperfusion following cerebral circulatory arrest.

Entry of excess calcium into the cell during energy deprivation states sets up a number of other pathologic cycles that accelerate further penetration of ions into the cell. High intracellular calcium levels result in release of sequestered neurotransmitters with subsequent formation of cyclic AMP. This, combined with a direct membrane action of excessive intracellular calcium concentrations, further increases membrane leakiness to previously excluded ions. For instance, intracellular levels of sodium and chloride ions now increase and drag water into the cell. During the initial period of ischemia, this causes only cellular swelling, with no net gain in brain water content. However, with recirculation, brain water increases and the cerebral edema caused by this net gain in hydration eventually can impede cerebral blood flow. The abnormally high ionic permeability of the cellular membrane also may divert respiratory energy from ATP production to Ca^{++} pumping, thus uncoupling oxidative-phosphorylation.

Another possible mechanism for tissue destruction during and after brain ischemia involves the generation of highly reactive free radicals that can fragment membrane bound fatty acids as well as break protein cross-linkages with resultant enzyme inactivation. During ischemia, free radical generation is probably due to the lack of an electron acceptor (oxygen), and with recirculation generation of these reactive moieties is a consequence of further metabolism of arachidonic acid released by excessive calcium penetration into the cell. In the laboratory, free radicals have been shown to have a role in the formation of cerebral edema and can cause damage to cerebral vessels. Thus, besides causing direct cellular damage, they may participate in the development of late hypoperfusion and brain damage secondary to it.

Clinical Trials Now?

We currently are faced with a solid, but isolated, demonstration that nimodipine, a calcium entry blocking drug with cerebral action, can ameliorate postischemic brain damage under tightly controlled laboratory conditions.¹ The authors of the current study suggest that clinical trials should begin based upon their report and a body of supporting pathophysiologic data implicating excessive intracellular calcium levels as associated with postischemic brain damage. For a number of reasons, I would feel more secure if the results of Steen *et al.* with postischemic administration of nimodipine were repro-

* Reference citations included in these reviews are not cited herein.

duced within their own laboratory or by other investigators. Given the relatively small numbers of animals involved in this study, a different outcome in only one animal could have changed their statistical results. While statistical validity clearly is established within the context of the current report, additional studies seem warranted. Indeed, the findings of Steen *et al.* should stimulate the necessary granting agencies to provide funding required to perform these complex studies. Additionally, such studies should be performed under conditions that more closely simulate the clinical situation, *i.e.*, total circulatory arrest. Preferably, these studies should be performed in primates, however, our own experience with closed cardiac massage in monkeys resulted in very poor circulatory resuscitation yields. If improvements in monkey CPR techniques cannot be accomplished, then demonstrations of the neuroresuscitative efficacy calcium entry blockade begun after recirculation in nonprimates would validate further the need for clinical trials. We currently have no direct information that administration of calcium blockers following resuscitation from a cardiac arrest and given in the face of poor cardiovascular performance would not be deleterious in humans. While only modest hypotension and tachycardia occurred in Steen's monkeys after nimodipine, these reactions could be more severe following a cardiac arrest and actually enhance brain and/or cardiac damage.

Any discussion of risks requires an assessment of the risk of barking up the wrong tree. Excluding direct risks to the patient, this type of risk includes expenditures of clinical research time and money on projects that could have a predictable negative outcome with regard to benefiting our patients. The number of uncontrolled variables in the clinical situation of cardiac arrest are vast. Only extensive prospective well-controlled clinical trials involving a large number of institutions can hope to definitively answer a question concerning the efficacy of a drug or technique with purported value in ameliorating postcardiac arrest neurologic damage. Another negative trial, based more upon enthusiasm than scientific facts, could result in difficulties in recruiting institutions to participate in yet other trials of a different promising neuroresuscitative method. On the other hand, additional laboratory demonstrations of the efficacy of nimodipine or other calcium entry blockers might permit broadening of the current clinical trial, as other investigators express a desire to evaluate the therapy.

In a sense, the horse is already out of the barn, as a clinical trial testing the efficacy of another calcium blocker, lidoflazine, is already underway.[†] Presumably, this trial is based upon a demonstration that lidoflazine

reduced neurologic deficits when given to dogs after a 10-min period of ventricular fibrillation.¹¹ While this study seems to support their clinical trial, another report from the same group found no benefit from lidoflazine given after resuscitation from asphyxia-induced cardiac arrest of 7–10 min duration.¹² This difference may be due to different physiologic conditions imposed by asphyxia, *e.g.*, more profound acidosis with arrest preceded by an hypoxic epoch. However, since both 10 min of ventricular fibrillation and 10 min of asphyxial arrest resulted in practically the same neurologic deficit scores in this laboratory's control groups, 34% and 36%, respectively, there remains an internal inconsistency that must be explained. Furthermore, different calcium blocking drugs can have profoundly different cardiovascular and cerebral effects; laboratory and clinical results obtained with a specific agent may not simply be transferable to a different compound.

Currently a reasonable scientific compromise can be made with regard to clinical evaluation of the role of calcium blockers given after cardiac arrest. The multi-institutional clinical trial of barbiturates, spearheaded by Safar's group at the University of Pittsburgh, although finding no brain benefit, still provided us with useful information.⁹ They found that the deleterious cardiovascular side effects of barbiturates could be offset. This same group is involved in the current lidoflazine clinical trial, and in a reasonably short time they should be able to indicate whether or not the use of calcium blockers immediately following resuscitation from a cardiac arrest has dangerous cardiovascular side effects. If this practice proves safe with regard to cardiovascular stability, an additional laboratory support for a neuroresuscitative action for calcium blocking agents can be established, then an expanded clinical trial should be launched. This enlarged study should be able to evaluate expeditiously the clinical usefulness of postcardiac arrest calcium blocker therapy aimed at reducing devastating neurologic damage aftermath of cardiac arrest.

At this time I personally cannot advocate the use of calcium entry antagonists following cardiac arrest. As individual clinicians make their own choice with regard to this issue, one should not forget that rapid restoration and maintenance of normal cerebral perfusion pressure and tissue oxygenation remains the mainstay of post-cardiac-arrest neuroresuscitative therapy.

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