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Brain Resuscitation: The Chicken Should Come before the Egg

FIVE YEARS AGO in this journal Rockoff and I speculated upon a possible benefit or Pandora's box effect that might derive from publishing an article showing a positive neuroresuscitative influence of barbiturates after a prolonged period of global cerebral ischemia.[1,2] In the current issue, another study from the same laboratory, utilizing the same selective cerebral ischemia model, "does not support the use of barbiturates for brain resuscitation."[3] Within the context of a controversial and complex model, Gisvold *et al.* have clearly rejected the earlier hypothesis that barbiturates have a primary role in postcirculatory arrest situations. This conclusion is the same as that offered recently by Todd *et al.*,[4] who employed a simpler model of global ischemia, employing ventricular fibrillation in cats, to test barbiturate therapy under intensive care support conditions similar to those employed by Gisvold. Does the current report drive the nail into Pandora's box and indicate that neuroresuscitation research is dead? The answer to that question is "no" on several counts.

Neuroresuscitation Science

The initial report by Bleyaert *et al.* stimulated a flurry of research activity into the pathogenesis of postcirculatory arrest encephalopathy, based upon a new-found enthusiasm that physicians could do something to ameliorate neurologic damage.[2] From these investigations has emerged additional hope as well as confusion. Pathophysiologic–biochemical studies indicate that the brain can survive a period of circulatory arrest two to three times longer than the old threshold for brain death, which was set at 3–4 min. More importantly, recent work indicates that events occurring *after* restoration of the cerebral circulation are associated with continued or secondary processes eventuating in neuronal death.[5] These postresuscitation events can continue for as long as 72 h and vary in their influence upon different areas of the brain.[6] In the future, we may recognize that these events may represent a continuation of a chain of therapeutically irreversible events initiated during the cerebral circulatory arrest. However, such a nihilistic approach does not appear to be warranted at this time.

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Improved CPR

Pathophysiologic studies on global brain ischemia point toward at least two valid directions for additional research activity. The first, dealing with prophylaxis against brain insult during the cardiac arrest, seems obvious, yet gets little attention. Research in this area should be directed toward better methods of providing effective CPR, which assures adequate cerebral perfusion and oxygenation. This may include improved forms of mechanically supporting the circulation as well as new drug regimens. The pathophysiologic data available today support this approach, as brain damage is a threshold phenomenon based upon the severity and duration of flow reduction.

Postresuscitation Pathophysiology

The second direction for research is based upon what we are learning about the brain following ischemic–hypoxic insults. We have gained intuitions regarding therapy that might alter the seemingly self-destructive postresuscitation events. These may be divided into functional, physiologic, metabolic, and biochemical categories. As will emerge from this discussion, overlap among these different classifications occurs.

FUNCTIONAL

Seizures occurring following cardiac arrest may be classified as a functional abnormality. They have been implicated in causing further damage to the brain and/or increasing mortality by many investigators, among them Gisvold *et al.* and Todd *et al.*[3,4] Seizures increase cerebral metabolic demand at a time when the requisite

compensatory cerebral blood flow response may be limited by intrinsic pathologic responses involving vasculature as well as by a hypodynamic systemic circulation. Sympathetic nervous system activation during seizures may add a further burden to the already stressed cardiopulmonary system and thereby increase mortality. There appears to be a consensus that seizure prophylaxis and/or prompt effective anticonvulsant therapy in the postarrest period makes sense and can be attained with minimal risk.[3,4,7]

Functional depression of the central nervous system, as well as ischemic brain damage has been reversed by administration of naloxone.[8] Presumably the mechanism for such reversal involves antagonism of pathologic accumulation of endogenous opiates. Systemic factors were controlled poorly in the initial naloxone studies, and presently brain protection with narcotic antagonists remains controversial.

Physiologic

Extrinsic and intrinsic cerebral circulatory abnormalities abound in the postcardiac arrest period.[5,9] Early cerebral hyperperfusion, associated with systemic arterial hypertension and cerebral vasomotor paralysis, has been implicated in causing blood brain barrier breakdown leading to cerebral edema formation and penetration into the brain of foreign substances with toxic and/or adverse metabolic consequences. Attempts to control cerebral hyperperfusion are of dubious merit because early (within a few hours), and late, brain hypoperfusion (brain ischemia) frequently occur following cerebral circulatory arrest. At this juncture it is probably most prudent to attempt to maintain normal to slightly elevated cerebral perfusion pressure during postcardiac arrest supportative care.

Postarrest perfusion impairment also has been ascribed to coagulation abnormalities, rheologic disorders, microvascular endothelial swelling, vascular spasm due to altered ionic balance, (K^+, Ca^{++}) or accumulation of vasoactive kinins and/or neuropeptides. Detection of these abnormalities suggests therapeutic approaches including, but not limited to, anticoagulants, improved microcirculatory function (hemodilution, dextrans, perfluorochemical oxygen transporting blood substitutes, osmotic agents, *etc.*), antivasospastic measures (Ca^{++}, K^+ blockers, direct vasodilators, maintenance of high cardiac output and perfusion pressures), and stabilization of membrane structure (steroids, anesthetics).

Metabolic

Most prominent among the metabolic theories leading to secondary brain damage is that high brain glucose levels predispose to cerebral edema and neuronal demise by supplying an overabundance of substrate resulting in an intense brain lactic acidosis.[5,10,11] There have been several demonstrations that augmented blood glucose levels in the precirculatory arrest period are associated with a worse neurologic outcome. For anesthesiologists this may translate into a simple and low-risk prophylactic regimen consisting of omission of glucose-containing solutions to patients at high risk for cerebral and/or circulatory intraoperative instability. The use of glucose metabolic inhibitors (*e.g.*, deoxyglucose) as postarrest therapy also has been suggested as a way of blocking cerebral acidosis.[12]

Biochemical

Currently the most fashionable biochemical theories of postarrest biochemical derangements include depletion of high-energy compounds, formation of reactive free radicals, abnormal fatty acid metabolism, increases in intracellular Ca^{++} levels (which may activate/modulate a number of toxic biochemical pathways), and defective protein synthesis of vital cellular subunits.[5] Restoration of high-energy phosphate levels usually occurs very quickly following recirculation, despite development of other biochemical abnormalities and neuronal death. Thus, continued energy depletion does not seem to be a pathogenetic factor following restoration of cerebral blood flow. Currently Ca^{++} entry blocking drugs are in vogue as a plausible neuroresuscitative technique.[13–15] These drugs may modify delayed hypoperfusion and/or reduce toxic intracellular Ca^{++} accumulation. To set the environment for future evaluation of calcium entry blocking drugs and other agents, a historical perspective discussing the rise and fall of the free radical scavenging agents may be helpful.

The Chicken before the Egg

After the report by Bleyaert *et al.* ascribing a neuroresuscitative value for barbiturates following cerebral circulatory arrest, investigations were initiated to find a mechanism to explain their ameliorative effects.[2] Free radicals, known to be prime suspects in postischemic pathology in other organ systems, were investigated in the brain.[5] Soon free radical scavenging by barbiturates emerged as a possible explanation for their supposed beneficial action. The only problem with this is that the cure or therapy, *i.e., the chicken,* was not viable, and therefore the theoretic explanation for its existence, *i.e.*, the *egg,* though possibly having intrinsic merit, could not explain a nonexistent phenomenon. Much confusion could be avoided, in neuroresuscitative research, if we get our chickens before the eggs. In other words, solid reproducible demonstrations of a protective effect in a relevant long-term surviving model should be required before we

search for explanatory mechanisms—the chicken should be viable and in hand.

Research in pathophysiology of brain ischemia offers neuroresuscitation scientists insights into a number of potentially fertile eggs to test. However, as can be seen from the above brief review, the number of potential eggs increases at a staggering rate as techniques in pathophysiology and biochemistry expand. Many of the changes described by pathophysiologists may represent epiphenomena and bear little direct relationship to successful neurotherapeutic approaches. How can we avoid a profusion of hard–soft boiled or scrambled eggs that waste time and money and can never hatch into the sought-after chicken?

Improved Neuroresuscitation Models

One answer to this question requires development of an inexpensive and clinically relevant animal model of global ischemia, compatible with long-term survivals, that will allow survey testing of promising neuroresuscitation techniques. A number of laboratories are approaching this goal.[6,9] Application of the proposed nonprimate model should permit early testing of emerging hypotheses that could guide further pathophysiologic work on basic mechanisms, as well as set the stage for more expensive trials in primates and eventually in humans. Such a model might also better focus multimodal therapies, which are simultaneously directed at the correction of more than one facet of postcirculatory arrest pathophysiology. This focus is crucial as a potential therapeutic window (or windows) may be highly specific with regard to the nature and timing of different therapeutic treatments. For this reason, shotgun approaches simultaneously using several modes of postcirculatory arrest treatment should be tested with caution and based upon more than a wild guess. Until we have a better understanding of the integration of the postarrest autolytic chain, there is a distinct possibility that multimodal therapeutic interventions actually may contain self-canceling elements.

Objectivity

Finally, we must be careful in interpreting "early or preliminary" encouraging results and temper our enthusiasm to apply them in our patients. The uncontrolled clinical spectrum, in which cardiac arrest and resuscitation therefore occurs, practically prohibits reasonable and efficient trials of neuroresuscitation techniques that do not have a proven laboratory track record. On this basis I strongly disagree with the concluding statement by Gisvold *et al.* that their "ongoing clinical trial of thiopental loading after cardiac arrest will hopefully provide more conclusive information" than their present negative result.[3,16] In this situation they have neither the egg nor the chicken.

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