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EDITORIAL

Title: Stroke and Extra-Cardiac Perfusion: New Vantage Points in
Brain Protection

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ABSTRACT

This report shows a new spectrum of applications of a concept of brain protection for the cardiothoracic surgeon. The underlying treatment deals with an ischemic/reperfusion injury, and novel applications of principles well known in cardiac surgery will be used to provide brain protection. Unique opportunities arise from the uncommon use of circulatory arrest in infants and adults (1-2% of procedures) to the larger areas of Sudden Death (450,000 pts/year in the U.S.), Stroke (700,000 pts/year) and carotid occlusion for peri operative endarterectomy, and neurologic problems after CPB (30% incidence).

Treatment pathways in sudden death will address the brain during CPR, the body to get a cause of arrest with use of peripheral CPB, and a controlled cardiac reperfusate to correct the underlying lesion. Circulatory arrest provides the model to treat, both this uncommon surgical process, with extension as toward treating stroke with controlled reperfusion. Novel models of pretreatment and warm brain reperfusion, that mimic warm heart reperfusion are suggested. Construction of the ultimate brain reperfusate, and its conditions of delivery will follow the valid and tested development phases of a warm cardioplegic solution, but become directed toward the brain. Old tricks that lead to new goals will become our innovative vantage points.

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Stroke, CPR, Circulatory arrest, Carotid Occlusion, Sudden Death,
Post CPB brain damage

TEXT

Cerebral damage is the most dreaded complication following a cardiac surgical procedure. Pre-occupation with this problem is evident by our prompt checking for awakening after cardiopulmonary bypass, and active limitation of deep hypothermic circulatory arrest (DHCA) intervals, when a dry field is critical in aortic arch or certain congenital heart procedures. Our current focus is directed at limiting brain ischemia intervals to reduce damage after reperfusion. Simultaneously, there is limited recognition that governing the process of controlling cerebral reperfusion may provide a unique remedy to postoperative brain damage.

This presentation will extend today's frequently used surgical cardiac reperfusion strategies toward newly proposed ways to modify reperfusion cerebral damage. The three critical steps needed to confront brain reperfusion injury include, a) accepting that this process happens, b) understanding that conventional ~one hour cold ischemic intervals are only a precursor towards injury, and c) following the established cardiac trajectory, by uncovering mechanisms that can be manipulated to avoid or correct brain reoxygenation damage.

Surgical Role in Brain Reperfusion Injury

Limitation of surgical focus to circulatory arrest in children and adults imposes a restriction to our learning potential, since only 1-2% of patients fill this category. The treatment gamut widens by addressing peri-operative patients that sustain sudden death and survive CPR, but develop brain damage. Additional arenas include neurologic events after cardiopulmonary bypass, and brain damage after carotid endarterectomy, in CABG patients undergoing cerebral revascularization. Finally, the stroke population becomes a major subset for expansion of our brain protection principles, since it includes the wide spectrum of atherosclerosis patients that develop underlying brain vessel occlusion.

Cardiac surgeons have an advantage in evaluating brain protection studies, since circulatory arrest provides a simple reproducible model for invoking brain injury, allows understanding of signs and events, thereby creating a basis for evolving methods to limit and avoid this devastating complication. Clarity comes from recognizing that replenishment of blood is not the answer, since damage persists despite reperfusion, our central surgical theme. We know that safe ischemic time periods are longer in the heart than brain, since circulatory recovery is expected, while neurologic damage is anticipated.

Brain ischemia and reperfusion after circulatory arrest differs from regional organ ischemia, because unmodified whole body reperfusion causes a global reperfusion injury, that includes the brain as the centerpiece for recognizable damage. Consequently, the door opens for treating the brain and whole body in our efforts to diminish reperfusion damage. Simultaneously, studies can be done to separate treatment of the brain and body, novel perspectives can be gleaned, and most importantly, results can be applied to the broad array of causes of brain damage previously described.

Recognition of these novel treatment possibilities allowed us to do preliminary studies that are summarized in this report, which is also amended to include future management options. Our reperfusion stimulus stems from prior success in cardiac studies (1;2) that provided a launch pad to control of the conditions and composition of reperfusion in experimental and clinical studies that produced satisfactory results after prolonged ischemia of the leg (3-5), kidney (6) and lung (7;8).

The control database of the circulatory arrest model has merits beyond its use during deep hypothermia in the surgical setting of prolonged total body ischemia. A fairly reproducible injury is made, since there is no collateral flow to camouflage results from this alternative nutrition source following carotid temporary occlusion in dogs and pigs. The major recovery end point is absence of neurologic dysfunction to correspond to our primary surgical guideline of clinical improvement. This vital end point can then be matched to other measurable goals that include biochemical testing, apoptosis and

histochemical damage. These elements of time and pathology are, critical to long term results, but we must never however lose sight of the fact that neurological recovery is the *forest*, and these measurable elements of damage are the *trees* that become disrupted by reperfusion injury.

The central themes of dealing with brain damage include the triad of a) the event, b) its cause, and c) support measures while the underlying genesis is sought. Discussion of issues of *DHCA* and sudden death will be undertaken to focus upon these interweaving factors. Certainly, brain dysfunction after DHCA fills this bill, since surgeons produce this event by turning off the pump, and can determine how to reperfuse the body and brain. Should we modify how we conduct the pump run, restore normal blood supply, or modify the conditions and composition of the reperfusate? I believe that *sudden death* in the peri-operative interval introduces an even more useful tool to understand this triad, since it makes us focus on how our currently employed cardiac reperfusion interventions can positively modify the secondary neurologic outcome of ventricular fibrillation or asystole.

Evolution of Approaches

The currently accepted mortality of sudden death is ~90 % from either in or out of hospital events. More importantly, approximately 50% of survivors have severe neurological defects. This reflects a “save the heart, lose the brain” concept, caused by treating only the arrest, but not the cardiac cause of death. A coronary event is

responsible in ~70% of patients, so that management must treat both reperfusion injury of the heart and brain. Treatment methods that address the heart have limited improvement, unless the cardiac reperfusion injury is directly addressed. Our results in 34 sudden death patients undergoing ~72 minutes of CPR, show 80% survival, with only 6% neurologic complications, a sharp contrast to prior studies **(9)**. Our prior studies showed complete cardiac functional recovery occurred, confirming that heart reperfusion injury was avoided **(10)**. The management process a) maintained brain circulation with keeping monitored blood pressure at ~60 mm Hg, b) made the cardiac diagnosis, and c) performed CABG with controlled reperfusion to the occluded vessel **(11)**.

The implications for this cardiac and brain salvage are large, since 450,000 patients in the US have sudden death, as the interface of a) aggressive maintenance of brain blood flow, b) catheterization lab diagnosis (probably using peripheral bypass support) and c) controlled cardiac reperfusion may change the approach to sudden death with introduction of a new and potentially large surgical interface. Furthermore, this concept of heart salvage by controlled reperfusion can be expanded toward the brain to a) altering the pump prime to affect other organs that had limited under perfusion during CPR, and b) applied to vascular surgery, thereby setting the groundwork for applying this regional concept to focal brain ischemia after stroke, or during carotid revascularization in patients needing carotid endarterectomy, either during CABG or as a primary procedure.

Controlled Reperfusion

Uncontrolled reperfusion uses normal unmodified blood, while controlled reperfusion alters the conditions (i.e., pressure, temperature, flow dynamics, etc) and composition (pH, platelets, wbc, complement, ionic components, osmolarity, substrate, drugs, etc.) of reperfusate blood. The spectrum of potential alterations are broad, so that my initial comments will address only the few elements we have altered to define how reperfusate modification positively determines brain recovery. This overview does not define specific treatments, but rather evolves *a concept of the value of controlled reperfusion*, to open our intellectual portals toward a new scheme of management.

Multi organ failure from post operative low output syndrome is recognizably due to poor myocardial protection. I believe that circulatory arrest causes similar multi organ failure from global reperfusion injury that may develop simultaneously with the impaired neurologic recovery after >60 minutes of cold global ischemia. We confronted this potential body/brain damage after 90 minutes of DHCA by showing that modifying the extracorporeal pump prime allows construction of a global reperfusate. We modified its composition to include WBC filtration, lowering calcium with CPD, adding Mg⁺⁺, a buffer with THAM, adding a Na⁺/H⁺ exchange inhibitor (Cariporide), hyperosmolarity, used low pressure reperfusion and applied alpha stat pH strategy.

Significant modification of reoxygenation damage followed controlling global reperfusion. Compared to untreated studies, early neurologic recovery was markedly

improved when measured by a standard score (evaluating central nerve function, respiration, motor and sensory action, consciousness, and behavior). Furthermore oxygen radical and endothelial damage was reduced, cardiac and pulmonary function improved, and less biochemical evidence of global damage was detected. These global findings are relevant to future management of circulatory arrest, and may subsequently be applied toward using temporary bypass to support sudden death patients. Clearly, the prime can be changed to add constituents that modify global reperfusion damage, since the pump becomes the heart, and actively altering the blood components that are delivered may more effectively deal with global reperfusion damage.

Concern about a *composite solution* rather than a focal mechanism is a standard response. However, reperfusion damage is an event that causes entropy which subsequently alters a spectrum of biochemical and functional components. Consequently, it will be simply impossible to define a single modifiable cause. Instead, we should build upon known factors that can positively modify reperfusion damage, rather than search for a magic bullet that is non existent. The therapeutic cocktail will grow, rather than shrink as we learn about the disrupted components. The traditional inquiry about the most important component takes me back to the concept of the search for the most important part of the cardioplegic solution. I refer the questioner to the orchestra, asking for a definition the worst instrument. The answer is the instrument that is not playing the right tune, thereby impairing the symphony by creating lack of cohesion. Reperfusion injury causes a chaotic disruption, and treatment must be harmonic and based upon input from many recognized beneficial factors.

This global view does not defeat searching for new individual components, which can subsequently strengthen any existing remedy. The critical investigative steps are to a) create a model of damage with normal blood reperfusion, b) determine if one element can completely overcome this injury, c) extend ischemic duration to define the limitations of single factors, and d) then assess if these individual elements can be added to the aforementioned global approach, with the goal of prolonging the ischemic interval by delivering a composite reperfusate that safely limits neurological damage.

Surgical Intervention Sites

Surgical access allows either pretreatment or direct reperfusate modification. To guide insight into this scheme, I will summarize two individual factors we recently tested in DHCA studies. First, reperfusion damage is closely linked to adverse calcium metabolism, whether the process is global, cardiac or cerebral **(12)**. Our ongoing studies on pretreatment with Cariporide, a sodium hydrogen exchange (NHE) inhibitor, show that positive brain reperfusion events match our recent cardiac studies **(13;14)**. NHE inhibition completely avoided neurologic damage after 90 minutes of DHCA (at 24 hour measurement), limited endothelial damage, decreased oxygen radical injury, and minimized global injury by reducing the elution of CK and SGOT **(15)**. The range of agents that can correct adverse calcium deposition is broad, but these positive findings may generate new studies, especially with testing specific roles in the reperfusion process, as we showed in prior cardiac studies **(16)**.

Second, endothelial damage is one major component of reperfusion damage, with wbc related injury causing oxygen radical production, neutrophil adherence to capillary walls and microvascular obstruction, ultimate focal areas due to ischemia from platelet deposition, and inflammatory reactions. To deal with this component, we studied reperfusate mechanical filtration after 90 minutes of DHCA by using a special CoBRA filter to deplete wbc's, platelets, and complement complex **(17)**. Consequently, the brain received a regional reperfusate via perfusion through the carotid vessels prior to global reperfusion by the extracorporeal circuit. The result was complete neurologic recovery, a finding that completely corresponded to the cardiac response we previously found after NHE inhibition after myocardial ischemia **(18)**. While isolated reperfusate filtration intervention caused prominent neurological improvement, the positive global changes of changing the pump prime with NHE inhibitors were not achieved. These limitations included more endothelin production, less limitation CK and SGOT release when the circulatory arrest experimental design failed to address the combined body/brain reperfusion damage.

Restriction of studies to only one component will limit straight forward conclusions. For example, the observed positive neurological recovery effects in untreated hearts happened after use of the alpha stat pH strategy, without our defining how pH stat management would influence effects. Prior knowledge that pH stat management causes better oxygenation during arrest induction, luxury brain perfusion, and reduced reperfusion calcium flux **(19)** was not evaluated. However, the positive brain recovery

after alpha stat sets the stage for another study, where the contrast between pH stat and alpha stat is evaluated after DHCA is extended to 2 hours. This comparison of singular strategies is simply made to show a) the benefit of either NHE inhibition or reperfusate blood filtration could potentially be similarly achieved by pH management alone after 90 minutes of DHCA, b) each positive result at short ischemic interval sets the stage for prolonging the DHCA period, and c) once a recovery limitation is encountered, the effects of combining positive effects can then be tested so that d) a brain reperfusate can be created that uses the interactive beneficial effects of many strategies.

Future Vantage Points

The stages of our search to limit brain reperfusion damage parallels the developmental process that has been so effective in cardiac studies **(20)**. The road toward brain recovery is open, and lets cardiac surgeons explore new fields that expand our therapeutic options. I think we will evolve from an initial focus upon isolated components associated with brain damage toward composite strategies. Future investigative and clinical studies that create a new vantage point, a process that extends surgical interventions far beyond the limited realm of our current brain protection interests that are now restricted to circulatory arrest in adults and children.

Word count: 2,256

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