Cerebral resuscitation potentials for cardiac arrest

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Permanent brain damage after cardiac arrest and resuscitation is determined by many factors, predominantly arrest (no-flow) time, cardiopulmonary resuscitation (low-flow) time, and temperature. Research since around 1970 into cardiopulmonary-cerebral resuscitation has attempted to mitigate the postischemic-anoxic encephalopathy. These efforts' results have recently shown outcome benefits as documented in clinically relevant outcome models in dogs and in clinical trials. Pharmacologic strategies have so far yielded relatively disappointing results. In a recent exploration of 14 drugs in dogs, only the antioxidant tempol administered at the start of prolonged cardiac arrest improved functional outcome in dogs. Cerebral blood flow promotion by hypertensive reperfusion and hemodilution has resulted in improved outcome in dogs, and brief hypertension after restoration of spontaneous circulation is associated with improved outcome in patients. Postarrest hypercoagulability of blood seems to yield to therapeutic thrombolysis, which is associated with improved cerebral outcome in animals and patients. In a clinically relevant dog outcome model, mild postarrest cerebral hypothermia (34°C), initiated with reperfusion and continued for 12 hrs, combined with cerebral blood-flow promotion increased from 5 to >10 mins the previously longest normothermic no-flow time that could be reversed to complete cerebral recovery. Mild hypothermia by surface cooling after prolonged cardiac arrest in patients has been found effective in recent clinical studies in Australia and Europe. Preliminary data on the recent randomized study in Europe have been reported. For presently unresuscitable cardiac arrests, research since the 1980s in dog outcome models of prolonged exsanguination cardiac arrest has culminated in brain and organism preservation during cardiac arrest (no-flow) durations of up to 90 mins, perhaps 120 mins, at a tympanic temperature of 10°C and complete recovery of function and normal histology. This "suspended animation for delayed resuscitation" strategy includes use of an aortic flush of cold saline (or preservation solution) within the first 5 mins of no flow. This strategy should also be explored for the larger number of patients with unresuscitable out-of-hospital cardiac arrests. Suspended animation for prolonged preservation of viability could buy time for transport and repair during hypothermic no flow followed by resuscitation, or it could serve as a bridge to prolonged cardiopulmonary bypass. (Crit Care Med 2002; 30[Suppl.]:S140–S144)

KEY WORDS: cardiopulmonary bypass; cardiopulmonary-cerebral resuscitation; cerebral blood flow; cerebral ischemia; clinical trials; hemorrhage; hypothermia; reperfusion injury; suspended animation; thrombolysis

Current resuscitation attempts from cardiac arrest (CA) yield suboptimal results (1). Restoration of spontaneous circulation (ROSC) is not enough. Cardiopulmonary-cerebral resuscitation is needed to prevent brain damage. The goals are to minimize normothermic no-flow time with immediate bystander-initiated life-support (2) and earliest ROSC and to mitigate the secondary postischemic-anoxic encephalopathy (1, 3). Results with use of outcome models in monkeys and dogs (1) have been clinically important, whereas rodent models have been used to explore the complex mechanisms of the encephalopathy (1, 3). Beneficial results in rodents could not be consistently reproduced in large animals or human patients. Interventions that were effective for protection-preservation were not typically effective for resuscitation. Interventions that seemed effective after brain trauma or focal brain ischemia in rats were not consistently effective after global brain ischemia (CA) in monkeys, dogs, or human patients. Whereas pharmacologic strategies have been disappointing, hypothermic strategies have been promising.

PATHOPHYSIOLOGY

In sudden normothermic CA, brain oxygen stores and consciousness are lost within 20 secs, and glucose and adenosine triphosphate stores are lost within 5 mins. CA no-flow times of ≥5 mins and ROSC are followed by impaired cerebral blood flow (4–9). Transient cerebral hyperemia is followed by protracted global and multifocal hypoperfusion. Impaired reperfusion may be prevented with hypertensive reperfusion (4, 7, 9), which improved outcome in dogs (8) and is associated with good cerebral outcome in human patients (1, 7). Complex chemical derangements (1) account for the death of vulnerable neurons in selectively vulnerable regions (10). During no blood flow, there are membrane depolarization, calcium influx, glutamate release, acidosis, and activation of lipases, proteases, and nucleases, which set the stage for reoxygenation injury with cascades that involve iron, free radicals, nitric oxide, catecholamines, renewed excitatory amino acid release, and renewed calcium shifts, leading to mitochondrial damage, DNA fragmentation, and scattered cell

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death (1, 3). The post-ROSC encephalopathy matures over 3 days or longer (1, 10). For animal studies, a reproducible whole-brain histologic damage scoring mechanism was evolved in 1978 (1, 10). Post-CA coma in patients may be evaluated with the Glasgow Coma Score and Pittsburgh Brain Stem Score (11–14).

PHARMACOLOGIC CEREBRAL RESUSCITATION

After normothermic CA in animal models, barbiturates and calcium channel blockers improved cerebral outcomes (1, 3). Clinical trials, however, did not prove statistically significant better neurologic outcomes (11–14). Unfavorable cardiovascular side effects may have contributed to the overall negative results. Benefits might also come from inhibitors of neuronal apoptosis, excitatory amino acid receptor blockers, and free radical scavengers, together with improvements in the microcirculation, by inhibiting vasoconstrictive mediators, leukocytes, and coagulation (15). To date, no specific pharmacologic treatment option is available for clinical use.

Circulatory arrest induces selective and delayed neuronal cell damage, primarily in the CA1 sector of the hippocampus, in the thalamic reticular nucleus, and in specific areas of the neocortex (16, 17). In CA models in rats (16, 18), DNA fragmentation in neurons was seen in selectively vulnerable areas. Anti-apoptotic proteins like Bcl-2 and Bcl-X_L, and synthetic and viral caspase inhibitors, have shown positive effects in different models of global cerebral ischemia (19, 20). The blockade of the neurotoxic effects of glutamate with N-methyl-D-aspartate receptor antagonists was ineffective after global cerebral ischemia in rats. The use of AMPA receptor antagonists is being investigated (21). Experimental evidence suggests beneficial effects of transgenic expression of the free radical scavenger superoxide dismutase (22). Because the blood-brain barrier is preserved after cardiac resuscitation, antioxidant drugs may not be active. Tempol, an antioxidant that crosses into the brain tissue, is beneficial in conjunction with hypothermia.

When cerebral reperfusion is delayed or inadequate, blood cell sludging with increased blood viscosity is observed. Endothelial cell swelling; leukocyte-endothelial interactions; dysbalance among nitric oxide, adenosine, and endothelin; vasoactive mediators; and disseminated intravascular coagulation impede microcirculation (1, 4, 7, 15). Improvement in neurologic outcome was achieved in animals with heparin, dextran, and fluids containing fibrinolytic agents (1, 6–9, 23–25). In cats, the administration of hyperoncotic-hypertonic solutions improved cerebral microcirculation (23). The number of leukocytes is increased in the brain after CA (16), but reducing the number of polymorphonucleic cells failed to improve outcomes. The administration of an endothelin(A) receptor antagonist does improve cerebral blood flow, functional activity, and neurologic outcome after CA in rats (7, 24). Tissue-type plasminogen activator (rt-PA) combined with heparin significantly reduced the cerebral no-reflow phenomenon of the forebrain in cats (25). Microthrombi have been found in cerebral microvessels 5–10 mins after onset of CA (15, 25, 26). Fibrinolysis during CPR improved outcomes in patients (27).

HYPOTHERMIC CEREBRAL RESUSCITATION

Therapeutic hypothermia was introduced in the 1950s (28, 29). Benson et al. (30) reported then on moderate hypothermia (28–32°C) in patients after CA, yielding promising but inconclusive outcomes. Concerns about arrhythmias, coagulopathy, and pulmonary infection delayed further clinical use. In the early 1980s, the Pittsburgh group resumed research on resuscitative hypothermia (31). Until then, it was believed that moderate hypothermia levels, which are risky, are needed to be beneficial. In 1987 (32, 33), a brain-damage mitigating effect was discovered for mild hypothermia (tympanic membrane temperature [Tty] 33–36°C), which was accidentally present during CA in dogs. Mild hypothermia seems simple to induce and safe. This led to the first recommendation of resuscitative mild hypothermia after prolonged normothermic CA in clinically relevant dog outcome models (34–38). When temperature was reduced to 20°C, outcome was compromised (36). Delays of 15 mins after ROSC reduced the benefit of hypothermia (37). Induced hypertension and hemodilution enhanced the benefits of mild hypothermia and restored near normal function and brain histology in dogs after 11 mins of normothermic CA (38). In rats, mild hypothermia markedly reduced hippocampal injury after forebrain ischemia (1, 3, 39). Mild hypothermia is beneficial not primarily because of a reduction in oxygen demand but by mitigating excitotoxicity, free radical reactions, edema, intracranial pressure, cell destructive enzymes, and other deleterious cascades (1).

In patients, Bernard et al. (40) and Yanagawa et al. (41) may have improved outcomes in comatose survivors of out-of-hospital CA with surface cooling for 12 hrs (40) or 48 hrs (41). Studies in Japan (41–43) included cardiopulmonary bypass (CPB) in the emergency department (43) in patients who had out-of-hospital CA and did not respond to conventional cardiopulmonary-cerebral resuscitation, plus mild hypothermia for 2 days or more. The European study of 1996–2001 began with a feasibility trial in Vienna (44) and concluded with a multicenter international randomized clinical trial (45). The feasibility trial (44) showed that it was safe and feasible to mildly cool patients with ventricular fibrillation CA. Surface cooling with cold air was initiated within 62 mins (range, 41–75 mins) after ROSC. The target temperature (33 ± 1°C) was reached after 287 mins (range, 242–401 mins) and was maintained for an additional 24 hrs. Thereafter, patients passively rewarmed and reached >35°C after 7 hrs. After 6 months, good cerebral outcome (cerebral performance category 1 or 2) was achieved by 14 (52%) patients; two patients (7%) had poor recovery (cerebral performance category 3 or 4), and 11 (41%) died. Compared to historic controls in the same department, this represents a two-fold improvement of outcome. There were no major complications that could be directly related to hypothermia. Therefore, a definitive multicenter European trial was conducted (45) that ended in 2001. Preliminary results were presented at the Wolf Creek VI conference.

SUSPENDED ANIMATION

In trauma victims who rapidly exsanguinate to CA (no flow) as a result of uncontrollable intrathoracic or intraabdominal injury (e.g., combat casualties), conventional resuscitation attempts are futile, and mortality is near 100% at this time (46, 47). In searching for new approaches, Bellamy et al. (47) recommended research into "suspended animation for delayed resuscitation" to preserve the organism during CA of up to 2 hrs for

transport and surgical hemostasis and then to resuscitate to survival without brain damage. This would require emergency (portable) CPB (33). In dog outcome models, profound hypothermia (Tty, 5–10°C) induced and reversed with CPB, could fully preserve brain viability in CA to 60 mins of no-flow time (48, 49). In the field, CPB is not yet available, and in trauma victims who exsanguinate to CA, hypothermia must be induced before the brain loses its viability (i.e., within 5 mins of no flow). Therefore, an aortic cold flush was introduced to rapidly induce preservative hypothermia; CPB was used only for resuscitation and rewarming (50). Dogs were exsanguinated over 5 mins to a CA no flow of 15 to 120 mins (51–55). At 2 mins of CA, the dogs received the aortic flush via a balloon-tipped catheter, advanced via the femoral artery. CA of 15–120 mins was reversed with CPB, followed by ROSC, assisted circulation (with CPB) for 2 hrs, mild hypothermia for 12 hrs, controlled ventilation for 24 hrs, and intensive care to 72 hrs. Final outcome evaluation at 72 hrs was in terms of overall performance categories, neurologic deficit score, and total and regional histologic damage scores in 19 different brain regions (10). Results depended on flush volume and flush temperature. Results for CA of 15 mins (51), 20 mins (52), and 30 mins (53) have been reported. For CA of 30 mins or longer (54, 55), the flush had to include the spinal cord. For CA of 60 mins (54), aortic flush at the start of CA with around 3 L of saline at 2°C, to a Tty of 20°C, resulted in good cerebral outcome but with some disabilities in the hind legs. Aortic flush with around 6 L of saline at 2°C to a Tty of 15°C resulted in all dogs having normal outcome and only mild or zero histologic damage, as did a flush with around 2°C saline to a Tty of 10°C. For CA of 90 mins (55), aortic flush at the start of CA with around 10 L of saline at 2°C, decreasing Tty to 10°C, resulted in normal outcome and zero or minimal brain histologic damage. For CA of 120 mins (55), saline flush to a Tty of 10°C resulted in a mixed outcome. Delay of the aortic flush to 5 mins after the start of CA still resulted in a good neurologic outcome, whereas delays of 8 mins resulted in a poor neurologic outcome. Flush volumes required were large and impractical for field use. When using a small volume (25 mL/kg) for aortic arch saline flush at an ambient temperature (24°C) at the start of exsanguination CA of 20 mins of no flow, decreasing Tty to 36°C, 14 pharmacologic cerebral preservation potentials, according to six pharmacologic strategies, gave disappointing outcomes (56, 57). Only the antioxidant tempol, given in high doses by aortic flush at the start of CA of 20 or 40 mins, improved functional outcome, although histologic damage was the same as in controls (58).

Suspended animation for delayed resuscitation in patients with normovolemic sudden cardiac death who are resistant to CPR and advanced life support should be explored. About 50% of out-of-hospital CPR attempts fail to achieve ROSC. The decision would have to be made very early during ROSC attempts to preserve viability of vital organs with cold flush until long-term CPB can be initiated in the emergency department. This approach would have to be compared with continued conventional normothermic CPR low flow and with continued mild hypothermic CPR low flow, with external CPR steps A-B-C (airway control—breathing control—circulation support [chest compressions]) continued until start of prolonged CPB to let (or help) the heart recover, while evaluating the brain.

PERSPECTIVES

Preventing post-CA brain damage requires minimizing normothermic no-flow times (2) through early (automatic) defibrillation and early initiation of cooling. Rapid induction of mild cerebral hypothermia requires novel cooling methods for use by paramedics and emergency physicians. Surface cooling is too slow. Future pharmacologic combinations might reinforce the proven beneficial effects of hypothermia. Thrombolysis plus heparin and antiapoptotic strategies currently appear to be most promising. Portable CPB should become available for initiation outside hospitals. Suspended animation for delayed resuscitation should be tried on comatose trauma victims in trauma hospitals' emergency departments, using thoracotomy (on onset of pulselessness) and aortic cold flush (on apnea). Future breakthroughs might depend on a combination of: 1) basic science—elucidating why (and how), after CA and ROSC, only selectively vulnerable neurons die in a delayed manner; b) serendipity—having an open mind on potential breakthrough effects of new strategies; and c) implementation—minimizing arrest times and optimizing prevention of the cerebral postresuscitation disease (1, 59, 60).

Preventing postcardiac arrest brain damage requires minimizing normothermic no-flow times through early (automatic) defibrillation and early initiation of cooling.

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