Studies of isolated global brain ischaemia: I. Overview of irreversible brain injury and evolution of a new concept – redefining the time of brain death

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Summary

Despite advanced cardiac life support (ACLS), the mortality from sudden death after cardiac arrest is 85–95%, and becomes nearly 100% if ischaemia is prolonged, as occurs following unwitnessed arrest. Moreover, 33–50% of survivors following ACLS after witnessed arrest develop significant neurological dysfunction, and this rises to nearly 100% in the rare survivors of unwitnessed arrest. Although, white body (cardiac) survival improves to 30% following recent use of emergency cardiopulmonary bypass, sustained neurological dysfunction remains a devastating and unresolved problem.

Our studies suggest that both brain and whole body damage reflect an ischaemic/reperfusion injury that follows the present reperfusion methods that use normal blood, which we term ‘uncontrolled reperfusion’. In contrast, we have previously introduced the term ‘controlled reperfusion’, which denotes controlling both the conditions (pressure, flow and temperature) as well as the composition (solution) of the reperfusate. Following prolonged ischaemia of the heart, lung and lower extremity, controlled reperfusion resulted in tissue recovery after ischaemic intervals previously thought to produce irreversible cellular injury. These observations underline the current hypothesis that controlled reperfusion will become an effective treatment of the otherwise lethal injury of prolonged brain ischaemia, such as with unwitnessed arrest, and we tested this after 30 min of normothermic global brain ischaemia. This review, and the subsequent three studies will describe the evolution of the concept that controlled reperfusion will restore neurological function to the brain following prolonged (30 min) ischaemia. To provide a familiarity and rationale for these studies, this overview reviews the background and current treatment of sudden death, the concepts of controlled reperfusion, recent studies in the brain during whole body ischaemia, and then summarizes the three papers in this series on a new brain ischaemia model that endorses our hypothesis that controlled reperfusion allows complete neurological recovery following 30 min of normothermic global brain ischaemia. These findings may introduce innovative management approaches for sudden death, and perhaps stroke, because the brain is completely salvageable following ischaemic times thought previously to produce infarction.

Keywords: Brain ischaemia • Sudden death • Controlled reperfusion • Pressure • Ischaemia/reperfusion • CPR

BACKGROUND

Almost half a million US citizens per year develop sudden death, with a cardiac event being the primary cause in most patients. Survival to discharge is only 5–15% for a ‘witnessed’ arrest, [1–4] despite cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS), and becomes almost 0% if ischaemia is prolonged by either delayed CPR following an ‘unwitnessed’ arrest (time delay before CPR and ACLS are initiated) or following CPR in a witnessed arrest by persons without training [2, 5–12]. Moreover, 33–50% of witnessed arrest survivors develop significant neurological dysfunction, and this injury becomes nearly 100% in the rare survivors of an unwitnessed arrest. Recent employment of emergency percutaneous cardiopulmonary bypass (CPB) improves cardiac survival to 30%, [3, 13–19] but neurological damage remains unaffected, so that brain salvage remains the major obstacle to current sudden death approaches.

Ischaemia/Reperfusion Concept: The underlying hypothesis is that brain and whole body impairment are secondary to an ischaemic/reperfusion injury, resulting in cellular damage and organ dysfunction following reperfusion after prolonged ischaemia [20–28]. Ischaemia introduces a susceptibility to damage that may either be quickened by reperfusion with normal blood or ‘uncontrolled reperfusion’, or reduced by ‘controlled reperfusion’ where control of the conditions and composition of the reperfusate have established experimental and clinical benefits in the heart, lung and lower extremity [27–31], and will now be tested in the brain. The current overriding clinical concern seems to be how quickly to restore blood flow, and not the method or the quality of reperfusion, so that there is an absence of the conventional use of the controlled reperfusion approaches that have
successfully offset reperfusion damage. Rapid reperfusion may work when the ischaemia has been short, and the cellular changes are mild, but not after prolonged ischaemia, where the consequences of uncontrolled reperfusion are usually severe and irreversible.

Controlled reperfusion studies on the heart, lung and lower extremities that have stemmed from our laboratory experience over the past 30 years [24, 25, 27–29, 32, 33] have documented the avoidance of cellular damage following ischaemic times thought to produce irreversible injury, and have resulted in the clinical use of this therapy in heart attacks, cardiac surgery, lung transplantation and limb salvage [25, 27–31, 34, 35]. Conversely, uncontrolled reperfusion following prolonged ischaemia results in metabolic, structural and functional alterations to ischaemic organs, accentuates dysfunction of remote non-ischaemic organs, and raises morbidity and mortality [20, 21, 25, 27–29, 32, 35–41]. These problems also follow strategies directed at only isolated reperfusion components, [24, 25, 27, 29, 42, 43] whereas successful use of controlled reperfusion integrates many factors, such as buffers, pH, calcium, WBCs, magnesium, pressure, temperature, nutrients, etc., [24, 25, 27–29, 32–34, 44–49] and various other factors may be subsequently modified as more experience is gained.

**Witnessed arrest**

In a witnessed arrest, the high mortality rate and neurological damage are secondary to (i) the belief that irreversible brain damage follows after only 4 min of ischaemia, (ii) the suboptimal delivery of CPR and the inability of CPR alone to always restore cardiac function and (iii) that negligible brain blood flow follows both CPR and resumption of cardiac activity because (iv) the underlying cardiac lesion causing arrest, is not corrected.

A key component approach involving three steps was developed to address these problems following witnessed arrest with immediate CPR, and it has been successful [3, 50]. First, CPR is considered adequate only if the monitored blood pressure is 60 mmHg to ensure adequate brain perfusion, since hypotension may otherwise occur in unmonitored situations. Second, rapid conversion to CPB to supplement brain and total body perfusion if CPR and ACLS in the first few minutes do not restore satisfactory cardiac rhythm and haemodynamics. Third, prompt cardiac catheterization and analysis of angiograms for proper diagnosis of the underlying cause, followed by coronary revascularization with established controlled reperfusion myocardial protection techniques that successfully restore regional and global cardiac function [3, 24, 27, 29, 51].

Experimental studies demonstrate that this strategy leads to 100% cardiac survival [50]. Subsequent clinical application in four different medical centres resulted in 80% survival among 34 patients who underwent CPR for 72 ± 43 min (range 20–150 min) before CPB, and 95% of survivors had complete neurological recovery [3]. In this series, every patient failed to respond to CPR with ACLS and defibrillation, and no witnessed arrest patient receiving CPR was excluded. These findings contrast to conventional conclusions, where 66% of patients are excluded from cardiac arrest studies that examine new CPR therapies because 33% cannot be defibrillated, and another 33% never return to adequate blood pressure [2, 5–11]. Moreover, interventions that improve survival to 50% of ‘resuscitated’ patients (involving only 33% of presenting patients) must be more realistically compared with the entire 100% cohort that were treated after they underwent arrest, since only 15% obtain overall survival.

**Unwitnessed arrest**

Although the witnessed arrest problem may be solved by applying this three-step approach, the unwitnessed arrest dilemma persists. Current clinical mortality is essentially 100% if >10 min elapse before starting CPR [2, 5–12]; brain damage is severe in the rare survivors, and prolonged warm ischaemia can lead to significant organ (heart, lung, liver, kidney and small bowel) injury [1, 3, 8–11, 28, 29, 32, 35, 40, 44, 52, 53]. CPR provides uncontrolled reperfusion so that abandonment of conventional CPR must be considered as controlled reperfusion strategies are developed to improve survival of this otherwise lethal injury.

The success of controlled reperfusion in individual organs led to the present consideration of using this modality for brain reperfusion, and towards developing a whole body approach to treat prolonged cardiac death as occurs during an unwitnessed arrest. The concept was first tested following 90 min of deep hypothermic circulatory arrest (DHCA) [54, 55]. As in individual organs, controlled reperfusion of the entire body following prolonged DHCA led to recovery of the heart, lung, liver and most importantly, the brain [54, 55]. This led to subsequent studies [1, 4] detailed below, that applied CPR and ACLS following 15 min of normothermic sudden death induced by ventricular fibrillation (simulating an unwitnessed cardiac arrest with 15 min delay), followed by testing the effectiveness of CPB if CPR and ACLS were ineffective.

(i) **CPR and ACLS Alone**: 80% mortality due to cardiac causes, and severe brain damage occurred in the surviving 20% of pigs [1]. These findings reinforced the ineffectiveness of only applying conventional approaches without supplementation of extracorporeal circulation.

(ii) **CPR plus cardiopulmonary bypass**: CPR was started following 15 min of cardiac arrest, but if ineffective for 10 min, percutaneous femoral artery and vein cannula were inserted to initiate CPB. This time interval was selected to mirror the reported interval required for patient cannula placement in clinical studies [3, 10–17]. Whole body survival increased to 80% following CPB, but severe neurological injury persisted, [1] to mirror clinical studies of CPB after sudden death from Japan, Korea and Taiwan [13–17].

(iii) **CPR plus CPB Controlled Body Reperfusion in CPB prime**: To address the problem of cerebral damage, the composition of the entire bypass priming fluid was altered in six pigs (B. Allen and G. D. Buckberg, unpublished data) to make it a controlled reperfusion, mirroring our success in individual organs, [24, 25, 27–30, 32, 35, 44, 53] and to parallel prior findings following prolonged DHCA [54, 55]. Neurological function improved only minimally, despite 95% cardiac survival following CPR + CPB controlled reperfusion. This neurological finding differed from prolonged DHCA because CPR delivered uncontrolled reperfusion as it perfused the brain with normal blood before CPB containing the controlled reperfusion was initiated. This observation implies that CPR was detrimental and contributed to this damage.

(iv) **CPB plus Controlled Reperfusion in CPB prime, WITHOUT CPR**: This study excluded CPR, and initiated CPB with a controlled reperfusion after 15 min of an unwitnessed arrest.
Trummer and associates reported on this novel approach, and showed (100%) heart and brain recovery after 48 h [4]. This observation implies that an extended unwitnessed arrest can be corrected if (a) we abandon conventional CPR treatment because of damage caused by ‘uncontrolled’ normal blood reperfusion, and (b) adopt a counterintuitive approach that requires a ‘delay in initiating reperfusion’ (to provide time to insert percutaneous cannula) so that only the controlled reperfusion can be delivered as CPB is started, [3, 10-17, 54, 55] because (c) the ‘point of no return’ for successful resuscitation from cardiac arrest must thereby exist beyond the reported outcomes that follow conventional CPR and ACLS approaches.

This thinking parallels how studies of controlled reperfusion after acute myocardial infarction (MI) changed the accepted doctrine concerning the time interval required for the heart to develop irreversible damage, since necrosis was thought to become transmural by 6 h [21, 26, 27, 29, 56, 57]. Experimental and clinical studies contradicted this conclusion, since controlled reperfusion restored regional contractility in 100% of hearts following 6 h of left anterior descending coronary artery ligation, and similar results were achieved in 87% of 156 patients receiving this treatment 6.3 h after MI [27, 29, 56]. Conversely, normal blood or uncontrolled reperfusion did not restore regional myocardial contractility despite only 2 h of experimental ischaemia, or in MI patients undergoing significantly shorter ischaemic intervals [27, 29, 56]. These observations established the importance of accepting the inherent delay (and thus longer ischaemic times) needed for cannulation to deliver the controlled reperfusion. Consequently, the ischaemic period for attaining brain recovery needed to be extended to 30 min in our initial studies, in order to provide the added ~15 min clinically acceptable interval required for cannula insertion to initiate controlled reperfusion [13-17].

**NEW STUDIES**

**Prolonged brain ischaemia**

Prevention of reperfusion damage in the brain parallels prior findings in other organs following prolonged ischaemia, and thus formulates our hypothesis that controlled reperfusion is a unifying treatment principle for a biological process. If correct, novel treatments for longer intervals of brain ischaemia from sudden death, as well as stroke may evolve, as the two injuries are probably similar. The impact may address the annual 450 000 patients with sudden deaths, as well as 731 000 stroke patients, since neurological damage is the No. 1 cause of adult disability in 4 million stroke survivors [1-3, 58, 59].

The three papers that follow this overview reflect how we tested this hypothesis [60-62]. The framework required an improved understanding of only brain ischaemia, since whole body ischaemia during sudden death introduces (i) the confounding outcome of washout of inflammatory mediators by remote (other ischaemic) organs that exist during sudden death models of whole body ischaemia, [32, 37-41, 52, 55, 63] (ii) multi-system remote organ dysfunction (i.e. low cardiac output) that can impair brain recovery, (iii) inflammatory and other factors related to the use of CBP, [20, 64, 65] while an isolated brain model (iv) mirrors our prior studies of single organ models of heart, lung and lower extremities, [24, 25, 27-32, 44, 53] which further improved understanding of reperfusion delivery.

The first priority was to develop a new large animal model of isolated normothermic global brain ischaemia that simulates the brain in sudden death, parallels the models used to investigate controlled reperfusion in the heart and lung, and avoids the limitations of whole body sudden death models in analysing resuscitation methods on the brain [60]. Once done, the next phase was to determine the normal baseline flows and oxygen uptake in this model, especially since it was necessary to study brain reperfusion in the context of prior studies showing that low flow reperfusion was essential to avoid reperfusion injury in organs such as the heart and lung [24, 25, 27, 32, 33, 45, 46]. Recognizing the limitations of this model was an important factor, since the use of isolated brain ischaemia offsets the problems of CBP, yet we will subsequently describe that some of the perfusate flow supplies non-brain tissue via the external carotid vessels which are not readily occluded due to their anatomical position [60]. Moreover, experimental studies required some anaesthesia, and its effect on this model is separately reported [66].

Second, the perfusate needed to be tested following 30 min of normothermic global brain ischaemia in a fashion that determined if neurological recovery occurred. Initial studies employed the low pressure method applicable in other organs, yet results demonstrated neurological damage at low flows, and thereby defined the requirement to increase the flow rate to try to simulate the normal baseline flow rates that raised the controlled perfusate pressure [61]. Moreover, results will show that delivery of normal flow at lower pressures also resulted in impaired neurological recovery, so that both pressure and flow were major variables that were addressed in the third component listed below.

Construction of the perfusate composition was also a key consideration, since modification was needed to reduce the glutamate and glucose that may increase brain injury [23, 43, 67-74]. Data analysis will show that our brain findings demonstrating neurological recovery only occurred with high-pressure reperfusion, and thereby contradict the importance with low flow and pressure reperfusion in the lung and heart [24, 25, 27, 28, 32, 33, 45, 46, 61]. This observation regarding employment of higher pressure simultaneously introduced concerns about the potential of high pressure accentuating brain oedema, which may secondarily markedly impair recovery as such water accumulation has done in prior heart and lung studies [24, 25, 28, 29, 32, 33, 45, 46].

The third study explores mechanisms to deliver the requisite higher pressure while still potentially offsetting oedema formation, and thus involves comparative analysis between non-pulsatile and pulsatile perfusion delivery of a mean or phasic pressure for reinitiating brain reperfusion, as pulsatile perfusion has been shown to have potential advantages in both the heart and brain [62, 75-81]. The initial phase compares these perfusion modalities (pulsatile and non-pulsatile) at baseline and after transient (30 s) brain ischaemia, and simultaneously investigates pressure, total brain oxygen uptake and IN Vivo Optical Spectroscopy (INVOS) oximeter measurements with each modality to determine cerebral flow distribution and pressure components [62]. This comparison was undertaken because INVOS only measures brain surface oxygenation, and a discrepancy between its measurements and total brain oxygen uptake could reflect abnormal flow distribution with under-perfusion of deeper brain tissues [82, 83]. These comparisons were made at both normal and lower flows and demonstrated that pulsatile flow maintained higher intermittent (systolic) pressures, while reducing mean pressure and improving oxygen metabolism at lower delivery flows, presumably by achieving greater deep brain perfusion. These findings were then
synthesized into the second component involving studies of pulsatile flow-controlled reperfusion following 30 min of total brain ischemia. Although mean pressure was lower during pulsatile flow than with non-pulsatile perfusion, the peak pressure was higher. Results documented that pulsatile perfusion-controlled reperfusion delivery consistently avoided anatomical and functional brain damage, and thereby completely avoided the inconsistent neurological recovery previously followed non-pulsatile normal flow which delivered a variable mean pressure [62].

These studies support our hypothesis that controlled reperfusion is a unifying concept for ischemia/reperfusion damage, and open the door to using controlled reperfusion as a new modality for treating brain ischemia. Many subsequent investigations are needed to better define the optimal conditions for reperfusion of the brain, as well as the composition of the modified reperfusate solution. For instance, would adding glutamate and glucose, which are both beneficial in the heart and lung, [24, 25, 32, 47, 53, 84] be effective in the brain if combined with glutamate blockers to avoid neuro-excitatory toxicity? [23, 25, 32, 36, 47, 53, 84]. What perfusion temperature is ideal, as hypothermia has been shown to help neurological recovery in sudden death patients? [42, 88–91]. How long should the controlled reperfusate be delivered to provide maximal recovery? These and many other questions need to be answered in order to optimize this new therapy in patients.

Nevertheless, this series of studies document that controlled reperfusion is an effective therapy for prolonged brain ischemia, by permitting neurological recovery after times thought previously to produce irreversible cellular injury [4, 61, 62]. These observations suggest correction of extended (unwitnessed cardiac arrest and stroke) brain ischemia (beyond the traditional 4 min time frame) as a lethal condition is only possible by (i) revising the conventional therapy which currently provides normal blood supply (uncontrolled reperfusion) as soon as possible, and adopting a counterintuitive approach that (ii) delays the initiation of reperfusion until a controlled process (integrating conditions and composition of the reperfusate) can be enacted, and (iii) recognizes that such time delay is essential to achieve the end point of restored neurological function. This observation thus contradicts the assumption that the primary goal should be restricted to only rapidly achieving an open vessel following prolonged brain ischemia, since delivery of uncontrolled reflow introduces a reperfusion condition that does not result in satisfactory functional neurological recovery.

Conflict of interest: none declared.

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